ONE-TO-ONE

CANCER PREVENTION

Since 2014 Jack Cuzick has been in the top 1% of cited researchers: *p.16*

TRANSFUSION SCIENCE

BLOOD GROUP SYSTEMS

The Lewis blood group system and secretor status: *p.26*

THE BIG STORY

THE DOUBLE HELIX

The history of the discovery of DNA and its structure: *p.30*

THE BIOMEDICAL SCIENTIST

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JANUARY 2019

THE TEN PLAGUES OF EGYPT

An ecological domino effect or divine intervention?

IBMS Institute of Biomedical Science

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Plesiomonas shigelloides	
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Shiga-like toxin producing E.coli (STEC) O157:H7	*Cyclospora cayetanensis*
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Vibrio vulnificus	
Yersinia enterocolitica	

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Sample to Insight

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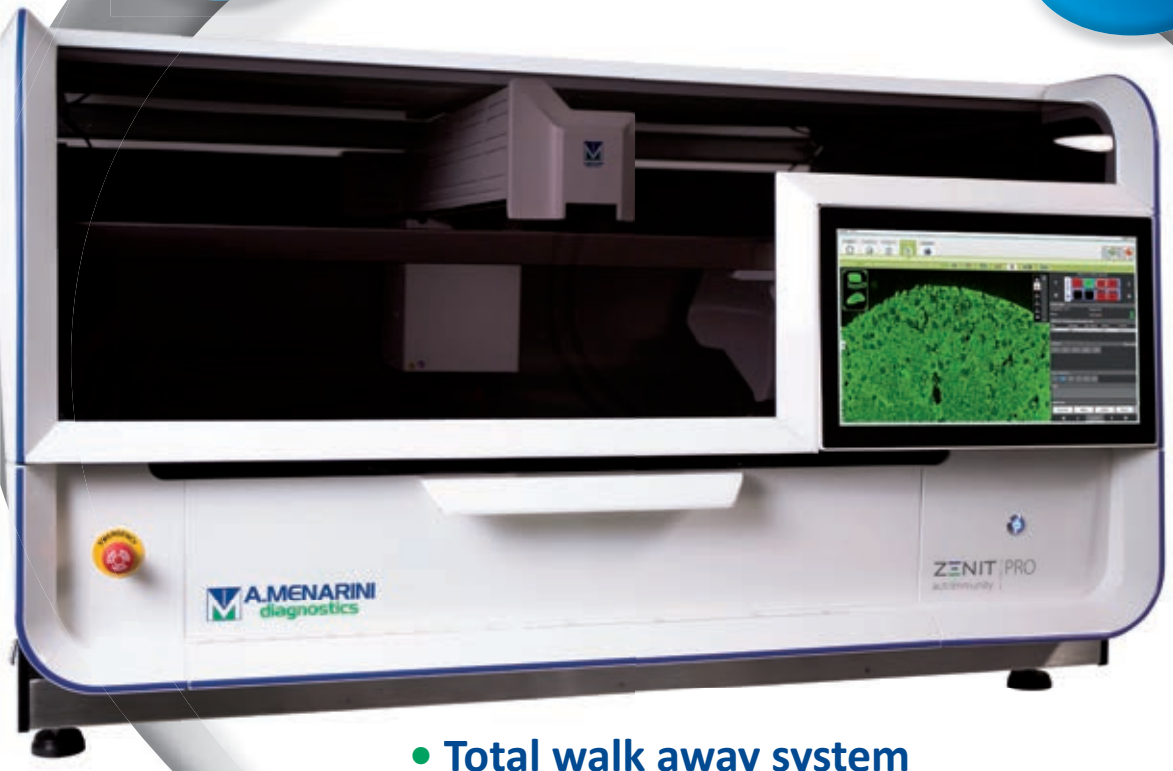

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A.MENARINI diagnostics

WHO CARES?

Sarah May, IBMS Deputy Chief Executive, asks if enough is done for those with complex care needs.

I had wanted to start 2019 with a nice cheerful and optimistic article to set us up for the year ahead, but I have just seen the excellent, but devastating, drama *Care*, which is about an elderly, but very active lady who has a severe stroke, leaving her both physically and mentally impaired. I know this will have struck a chord with a large number of us who will have someone close, whether parent, sibling, or child, who has significant and complex care needs.

There is a very scary and unpleasant reality facing us that is played out on our television screens every week in the various "fly-on-the-wall" programmes about our emergency services.

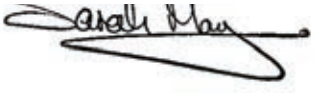
The sheer volume of distressed, frail and helpless people calling for help, and the overstretched services that provide the equivalent of an emergency sticking plaster before rushing to the next call is both frightening and appalling.

I have, and always will be, a great proponent of self-sufficiency and independence, but with the expectation that if I, or one of my loved ones, needs help it will be there for them. The sad reality is that is no longer the case. For years we have seen the erosion of our multiple support services, while simultaneously experiencing an increasing need for those very same services that are contracting or disappearing altogether. And according to all the projections, it is only going to get worse as our ageing population, with multiple complex care needs, increases.

In parallel with the shrinking availability of community care services is the almost universal norm of working mothers; there is little other option for most households. So where does that leave us as we try to juggle the competing demands of work, children, elderly parents and all their associated needs? It leaves us in a very sorry position for the 5th largest economy in the world.

Watching *Care* brought to my mind a variously quoted phrase, and the version that struck the most powerful chord with me was that of Hubert H. Humphrey, the 38th vice president of the United States. He said "...the moral test of government is how that government treats those who are in the dawn of life, the children; those who are in the twilight of life, the elderly; those who are in the shadows of life; the sick, the needy and the handicapped".

Anyone who has ever experienced our 21st century care system would probably say we have failed. All I can say is how very sad; how very wrong.



Sarah May
Deputy Chief Executive

Institute of Biomedical Science is the professional body for the biomedical science profession.

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SCIENCE NEWS IN NUMBERS

At least 548

people who visited a US zipline destination were taken ill with gastrointestinal sickness.

Investigators have been working to determine the exact cause of a suspected ***E.coli* outbreak** at a zipline canopy tour in Gatlinburg, Tennessee. **The park has since closed a well, which investigators believe may have been contaminated with the *E.coli* bacterium.** However, at the time of going to press, the cause had not been confirmed.

400

Norwegian heroin addicts will trial an experimental scheme in 2020 and be given free heroin in a bid to combat the country's high overdose rate.

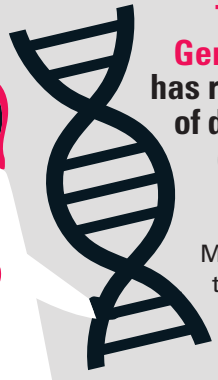
It is unclear whether patients will be selected or how much of the drug will be prescribed. Norway has the highest rate of overdose mortality in Europe – **80 per million people in 2015**.

WINTER DEATHS

There were more than 5,000 extra deaths last winter, after the flu vaccine failed to protect against some key strains.

It was the worst winter on record for more than 40 years. The figures come from a new report by the Office for National Statistics.

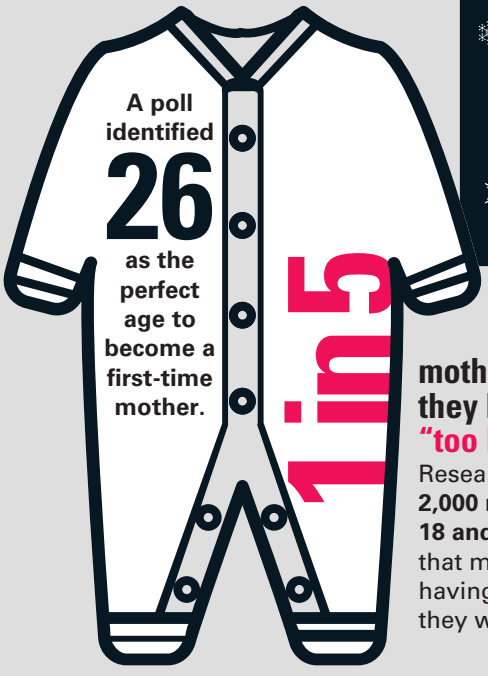
100,000 genomes



The 100,000 Genomes Project has reached its goal of decoding 100,000 genomes from NHS patients.

Health Secretary Matt Hancock made the announcement. The **2013** project took **five years** to complete.

The **first human genome** to be fully sequenced was in **2003** – it took **10 years** and cost **£2bn**. Thanks to next-generation sequencing, it now takes less than **one day** and the cost is closer to **£700**.

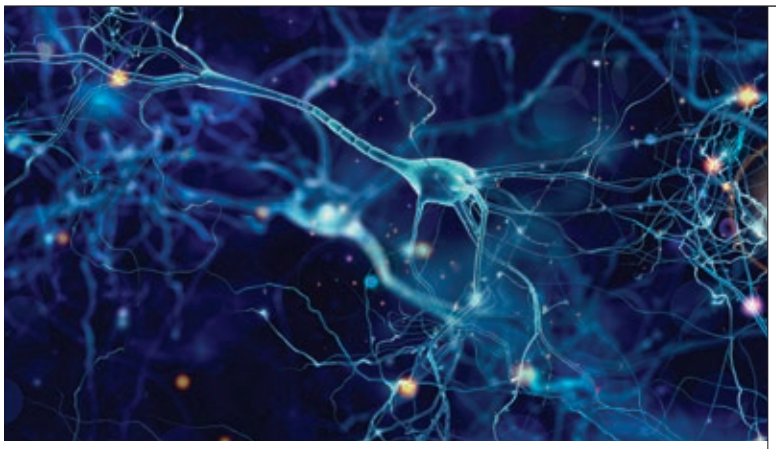


A poll identified 26 as the perfect age to become a first-time mother.

1 in 5

mothers believe they had a baby "too late" in life

Researchers **surveying 2,000 mums aged 18 and upwards** found that many regret not having a child when they were younger.



SCIENCE NEWS

ARTIFICIAL INTELLIGENCE

AI system can identify different cancer cells

Researchers in Japan have shown that an artificial intelligence (AI)-based system can identify different types of cancer cells simply by scanning microscopic images.

They claim it is able to achieve higher accuracy than humans and could play a role in the future of oncology.

The system is based on a convolutional neural network, a form of AI modelled on the human visual system. It was applied to distinguish cancer cells from mice and humans, as well as equivalent cells that had also been selected for resistance to radiation.

Hideshi Ishii, lead author of the study published in *Cancer Research*, said: "We first trained our system on 8,000 images of cells obtained from a phase-contrast microscope.

"We then tested its accuracy on another 2,000 images, to see whether it had learned the features that distinguish mouse cancer cells from human ones, and radioresistant cancer cells from radiosensitive ones."

On a 2D plot of the findings, the clustering of cell types together showed that, after training, the system could correctly identify cells based on the microscopic images of them alone.

→ **bit.ly/BS_JanNews01**

FIGHTING BACTERIA

WASP VENOM AS AN ANTIBIOTIC

The venom of insects such as wasps and bees is full of compounds that can kill bacteria.

However, many of these compounds are also toxic for humans, making it impossible to use them as antibiotics.

After performing a systematic study of the antimicrobial properties of a toxin normally found in a South American wasp, researchers at the Massachusetts Institute for Technology (MIT) have created variants of the peptide that are potent against bacteria, but nontoxic to human cells.

In of mice, the researchers found that their strongest peptide could completely eliminate *Pseudomonas aeruginosa* – a strain of bacteria that causes respiratory and other infections and is resistant to most antibiotics.

Cesar de la Fuente-Nunez, an MIT postdoc, said: "We've repurposed a toxic molecule into one that is a viable molecule to treat infections.

"By systematically analysing the structure and function of these peptides, we've been able to tune their properties and activity."

→ **go.nature.com/2RUEHjg**

EXHIBITION

THE UNSEEN SIDE OF SCIENCE

The Francis Crick Institute's new exhibition, Craft & Graft: Making Science Happen, will showcase the surprising roles of the people who work around the clock to make its life-changing research possible.

The free exhibition runs from March until December 2019 and takes visitors behind the scenes to meet the technicians, engineers and specialists supporting science at the Crick.

These technical teams prepare, process, make, mend, analyse and innovate.

From fixing faults in complex cutting-edge technology to feeding fruit flies and operating robots, technical staff are essential to keep the labs running and science happening.

The exhibition shines a spotlight on five specialist teams who have opened their doors for the first time:

- The technicians feeding and breeding over 15,000 families of fruit flies.

- The "librarians of life-forms" responsible for nurturing billions of cells in thousands of flasks, plates and vials.
- The people who meticulously clean the Crick's essential glassware to allow re-use and prevent any contamination.
- The mechanical and electronic engineers who race against time to fix, adapt or invent vital equipment for use in the labs.
- The specialists preparing biological samples, from fruit flies to cancer cells, for study using powerful microscopes.

The exhibition is part of the Crick's wider commitment to support technical staff working in research and to highlight their vital work.

→ **bit.ly/BS_JanNews02**

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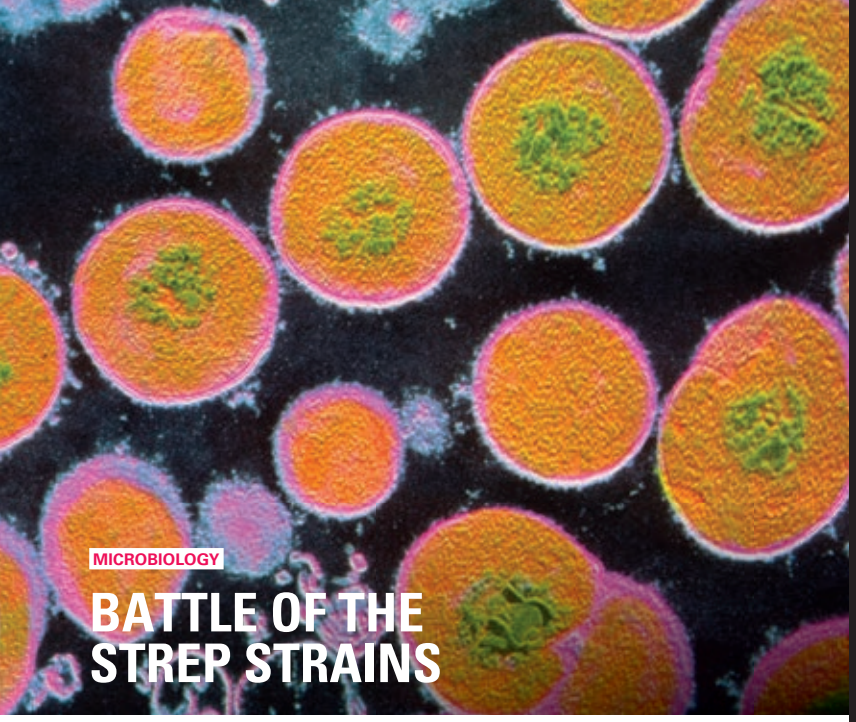


MICROBIOLOGY

BATTLE OF THE STREP STRAINS

Results of a new US study indicate that whichever strain of *Streptococcus pneumoniae* is in place in a mammal's tissues first is more likely to thrive than Strep "latecomers".

Senior study author Jeffrey Weiser, MD, Chair of the Department of Microbiology at NYU Langone Health, said: "With Strep infections costing the lives of nearly a million children under five each year globally, we are urgently seeking new ways to defeat bacteria by learning more about how they compete with each other."

Previous studies have established that bacteria engage certain mechanisms only when bugs have multiplied beyond a population density threshold, known as a "quorum".

The new study suggests that among the mechanisms initiated by a Strep quorum is release of two toxins – choline binding protein D (CbpD) and the competence-induced bacteriocins (CibAB). These toxins kill intruding, competing strains. The owners, however, also release other factors that protect them from their own toxins. Their newly arriving relatives, not yet having a quorum, do not yet have their defenses in place.

→ **go.nature.com/2PBkjBA**

INFLAMMATORY BOWEL DISEASE

IBD LINKED TO PROSTATE CANCER

Men with inflammatory bowel disease have a four to five times higher risk of being diagnosed with prostate cancer, reports a 20-year US study.

This is the first report to show men with inflammatory bowel disease have higher than average PSA (prostate-specific antigen) values, and a significantly higher risk of prostate cancer.

Lead study author Dr. Shilajit Kundu said: "These patients may need to be screened more carefully than a man without inflammatory bowel disease.

Researchers looked at 1,033 men with inflammatory bowel disease and a control group of 9,306 men without the disease.

They followed the two groups of men for 18 years and found those with inflammatory bowel disease were much more likely to have prostate cancer and higher PSA levels.

→ **bit.ly/BS_JanNews03**

WHAT'S HOT AND WHAT'S NOT

HOT

WEIGHING SCALES

Trials show that people who have regular weigh-ins and information are less likely to put on weight than those who are just given healthy lifestyle information.

HOT

PLACENTA

The world's first lab-grown placenta has now survived for a full year, remaining stable in its Petri dish. The organoid was cultivated by Cambridge University doctors.

HOT

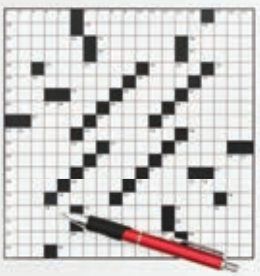
REDHEADS

In the biggest ever genetic study of hair colour, scientists have discovered the eight genes that are linked to red hair.

NOT

SURGERY

Better drugs, vaccination and genomics will help to make some operations obsolete, says a report commissioned by the Royal College of Surgeons of England.



NOT

CROSSWORDS

Doing crossword puzzles and Sudoku does not appear to protect against mental decline, according to a new study in the *BMJ*.

NOT

FAX MACHINES

The NHS has been banned from buying fax machines and told to phase them out completely by 31 March 2020.

BIOBANK

Genetic changes associated with physical activity

The time we spend sitting, sleeping and moving is determined in part by our genes, University of Oxford researchers have shown.

In one of the most detailed projects of its kind, the scientists studied the activity of 91,105 UK Biobank participants who had previously worn an activity monitor on their wrist for a week.

The scientists taught machines to automatically identify active and sedentary life from the huge amounts of activity monitor data.

They then combined this data with UK Biobank genetic information to reveal 14 genetic regions related to activity, seven new to science, they report in *Nature Communications*.

The work paves the way for better understanding of sleep, physical activity, and their health consequences.

Further analysis of the human genetic data showed for the first time that increased physical activity causally lowers blood pressure.

Physical inactivity is a global public health threat estimated to cost healthcare systems $50bn a year. It is associated with a range of common diseases including obesity, diabetes and heart disease. Changes in sleep duration are linked to heart and metabolic diseases and psychiatric disorders.

The genetic analysis also showed overlap with neurodegenerative diseases, mental health wellbeing and brain structure, showing an important role for the central nervous system with respect to physical activity and sleep.

Dr Aiden Doherty, who led the work and is based at the Big Data Institute, University of Oxford, said: "How and why we move isn't all about genes, but understanding the role genes play will help improve our understanding of the causes and consequences of physical inactivity."

→ **go.nature.com/2Gc7XQV**

DENDRITIC CELLS

REPROGRAMMING IMMUNE SENTINELS

In a world first, a research team has successfully reprogrammed mouse and human skin cells into immune cells called dendritic cells.

The process is quick and effective, representing a pioneering contribution to applying direct reprogramming for inducing immunity.

The finding, by researchers at Lund University in Sweden, opens up the possibility of developing novel dendritic cell-based immunotherapies against cancer.

Our dendritic cells function as the immune system's sentinels. Their task is to scan our tissues for foreign particles, such as bacteria, viruses or cancer cells, and to devour them.

They subsequently break down the particles into smaller pieces, known as antigens, and present them on the surface to the immune system's killer cells (T-cells). In this way, the killer cells learn which infectious agents and cancer cells they are to search for and kill.

Due to these key features, dendritic cell-based strategies have been tested to treat cancer patients.

However, cancer can affect the dendritic cells in such a way that they get lost or become dysfunctional.

Now, for the first time, the research team in Lund has succeeded in obtaining dendritic cells by a process called "direct reprogramming".

They have identified three essential proteins (PU.1, IRF8 and BATF3) that are required and sufficient to change the identity of mouse cells to make them become dendritic cells nstead.

They have also confirmed that the same protein cocktail reprograms human skin-derived cells to dendritic cells.

→ **bit.ly/BS_JanNews04**

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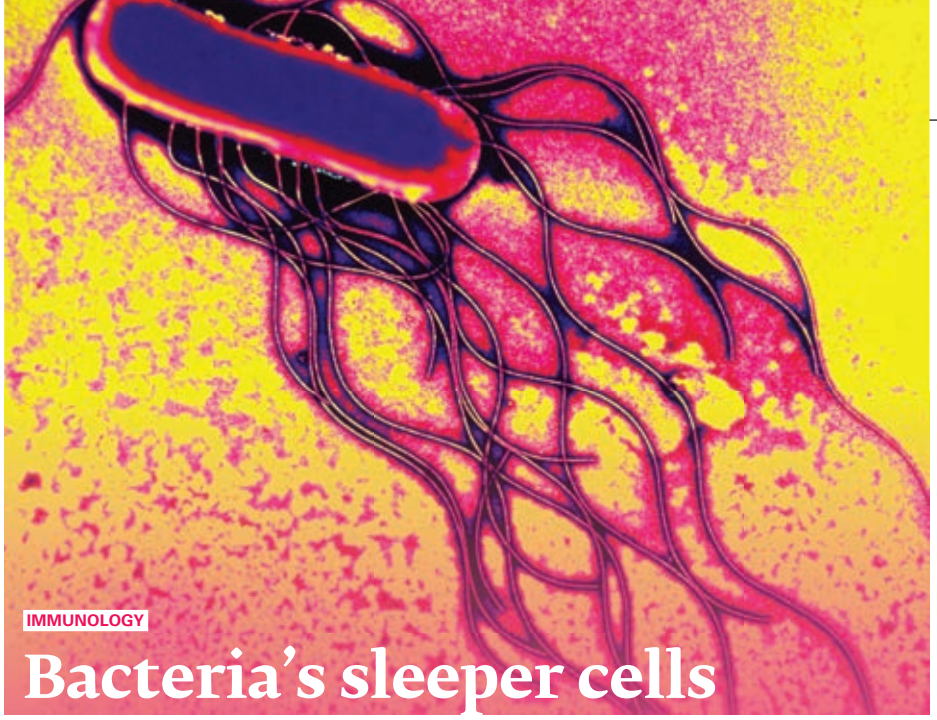


IMMUNOLOGY

Bacteria's sleeper cells

New research, from scientists at Imperial College London, unravels how so-called bacterial persister cells manipulate our immune cells.

This can potentially open new avenues to finding ways of clearing these bacterial cells from the body, and stopping recurrence of infection.

The findings may help explain why some people suffer from repeated bouts of an illness, despite taking antibiotics.

The scientists studied bacterial cells of Salmonella called persisters.

Whenever bacteria such as Salmonella invade the body, many of the bugs enter a type of stand-by mode in response to attack by the body immune system, which means they are not killed by antibiotics.

These persister cells stop replicating and can remain in this dormant, "sleeper-cell" state for days, weeks or even months.

When antibiotic treatment has been stopped, if some of these bacterial cells spring back to life, they can trigger another infection.

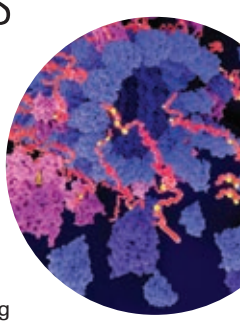
Dr Sophie Helaine, senior author of the research explained: "Persisters are often the culprit for repeat or hard-to-treat infections. The classic scenario is a person suffers some type of illness – such as a urinary tract infection or ear infection, and takes antibiotics that stop the symptoms, only for infection to return a few weeks later."

The scientists are now investigating if they can turn the tables against the bacteria by targeting the mechanism by which the persisters weaken our immune cells.

→ **bit.ly/BS_JanNews05**

POINT-OF-CARE TESTING

BLOOD TEST FOR ALZHEIMER'S



Investigators at Brigham and Women's Hospital in the US are working to develop a blood test that could accurately diagnose or even predict Alzheimer's disease before symptoms appear.

The tau protein has long been implicated in Alzheimer's; however, tau occurs as a family of related molecules with subtly different properties. The Brigham team took advantage of the complexity of tau and built assays to measure its different forms. They identified tau proteins specifically elevated in the disease.

Co-author Dominic Walsh said: "A blood test for Alzheimer's could be administered easily and repeatedly, with patients going to their primary care office rather than having to go into a hospital.

"Ultimately, a blood-based test could replace cerebrospinal fluid testing and/or brain imaging. Our new test has the potential to do just that. Our test will need further validation in many more people, but if it performs as in the initial two cohorts, it would be a transformative breakthrough."

The test was carried out on two small sets of patients from two different demographics, numbering 65 and 85 participants.

→ **bit.ly/BS_JanNews06**

UNDER THE MICROSCOPE

This month: Self-experimentation

This looks like quite a self-explanatory one.
Yes, it does exactly what it says on the tin – self-experimentation is when people experiment on themselves.

Has it been in the news recently?
There have been a couple of stories. First, a team of six doctors from the UK and Australia swallowed Lego and timed how long it took to pass through their systems.

Why on earth did they do that?
They said it was to provide reassurance for concerned parents whose children have swallowed Lego and they published their findings in the Christmas edition of the *Journal of Paediatrics and Child Health*.

And how long did it take?
It ranged from 1.1 days to three days, with an average of 1.7 days. They also noted that there was no correlation between a looser stool and a quicker retrieval time.

You mentioned that there were a couple of stories...
That's right – the other piece is a feature entitled "Adventures in self-experimentation" in the *BMJ*. It explores the history of scientists using themselves as guinea pigs, including a 71-year-old emeritus neurologist who indulged in inadvertent (and subsequently deliberate) self-experimentation with *Urtica ferox*, a stinging nettle endemic to New Zealand. His notes of the neurological manifestations after exposure provide clues to the toxin's mechanism of action.

What about a historic example?
In 1901, Nicholas Senn investigated whether cancer was contagious by surgically inserting under his skin a piece of cancerous lymph node from a patient with cancer of the lip.

SHIMADZU
Excellence in Science

Professor Paolo Brambilla Desio Hospital, Milan

Professor Brambilla is one of the first adopters of the CLAM system, who worked with Shimadzu to develop a number of applications at Desio Hospital, including immunosuppressants, steroids and vitamin D determination.

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"The CLAM system did exactly what Shimadzu described it would do. It is exactly the instrument that we need."

www.shimadzu.co.uk/CLAM-2k

TECH NEWS

ANTIBODY LIBRARIES

ANTIBODY DISCOVERY

Carterra continued its popular seminar series on accelerating antibody discovery in December.

Industry leaders gathered in Cambridge, Massachusetts to listen to a range of speeches and presentations on the topic and instruments. The Carterra LSA array SPR instrument enables the rapid and detailed screening and characterisation of large antibody libraries at the earliest stage.

By performing both kinetic studies and epitope binning on all members of a library, unique candidates can be identified to provide epitope diversity and IP coverage.

The result is a streamlined selection process and researchers are now able to see greater detail within their antibody library, minimising the risk of missing potentially high-value antibodies.

→ **carterra-bio.com**

TRISOMY

NON-INVASIVE PRENATAL TESTING

PerkinElmer has received CE-IVD mark in Europe for its Vanadis fully automated non-invasive prenatal testing system for commercialisation and distribution to laboratories and obstetricians throughout Europe.

The system is the first of its kind designed to simplify screening for trisomies 21 (Down syndrome), 18 (Edwards syndrome) and 13 (Patau syndrome).

It measures fetal chromosomal trisomies in maternal plasma by labelling and counting specific cell-free DNA fragments using imaging – removing data-intensive steps required for gene sequencing.

→ **perkinelmer.com**

CANCER

NEW GENOMICS CENTRE TO OPEN

Cancer Research UK and AstraZeneca have announced that they are opening a new centre in the UK, dedicated to realising the full potential of functional genomics in the discovery and development of new drugs for patients with cancer.

This partnership will explore in more detail the function and interaction of genes and proteins in cancer, and apply new genome-altering technologies, such as CRISPR, to create sophisticated models of the disease for research.

The centre will be a dedicated world-class resource for AstraZeneca and Cancer Research UK's academics and alliance partners working at all stages of translational research, from target discovery and validation, to assessing novel drug combinations.

→ **discoverylabs.cancerresearchuk.org**

THE BIG QUESTION

THIS MONTH WE ASK

"What are your professional 2019 New Year resolutions?"

Jill Rodney

Chief Executive
Institute of Biomedical Science

I am resolved to focus on four key themes during 2019 to help advance our profession.

The progress in the development of consultant biomedical scientists in cellular pathology has been a key achievement of the Institute. However, I passionately believe that consultant biomedical scientists can, and should, be developed in all disciplines and I will be working hard this year encouraging employers and health departments to recognise this and to get on board with our vision for professional development.

I want to continue to raise our voice and strengthen our Institute's influence. We are the experts in biomedical science and we will take every opportunity to play a leading role in shaping healthcare across our four nations.

Equally, I will be encouraging all members who feel they could help shape the future of the Institute to consider standing for Council. I understand that for some this may appear quite daunting but we are a truly supportive organisation and welcome member engagement in all aspects of our work.

Our strategy to make us an even stronger and more relevant organisation is very ambitious and cannot be delivered overnight, or even within one year, but it is most definitely achievable. I believe that working together towards our goals we will make it happen.

Finally, I would like to wish you a healthy, happy and professionally successful new year and look forward to seeing you at Congress 2019.

IMAGE: ISTOCK PHOTO

Rob Dabrowski

Editor
The Biomedical Scientist

I first became a journalist because I want to know things. I'm nosey. I find nothing more intriguing than trying to decipher a whispered conversation. It doesn't matter of it's a couple of colleagues talking by the water cooler, or a pair of strangers sitting behind me on a bus – if there's something being talked about, then I want to know what it is.

The best way to find out about things isn't sitting behind a desk looking at a computer screen and bashing away at a keyboard. The best way is by getting out there and meeting people face-to-face.

This brings me to my professional resolution for 2019: to get out from behind my desk and talk to as many biomedical scientists as I can.

Some of the best articles published in the magazine (and the most valued professional relationships I've formed) have been from conversations, meetings or discussions at events.

Over the next 12 months, I want to get out of the office and into the lab (or lecture theatre). It's the best way to see what is happening on the frontline.

It's also the best way of finding out what people think of the magazine. I want to know what we are doing right and what we are doing wrong. My aim is to produce the best, most relevant and stimulating magazine that I can. If people think there are areas that can be improved, or disciplines that are under represented, I'd like to know.

If any members have comments, thoughts or upcoming events, please get in touch – editor@thebiomedicalscientist.net

Hayley Pincott

Associate Practitioner
University Dental Hospital, Cardiff

In May, I was awarded the Mary Macdonald bursary to complete my Certificate of Achievement II, so my main goal is to finish the portfolio, or be close to completing it. This will then allow me to become a registered scientist with the Science Council. I'm really excited to become a registered scientist, as it demonstrates a level of skill and knowledge and will also give me a small confidence boost, as we often get other healthcare professionals visiting the lab and it will help with any discussions involving our role in patient care.

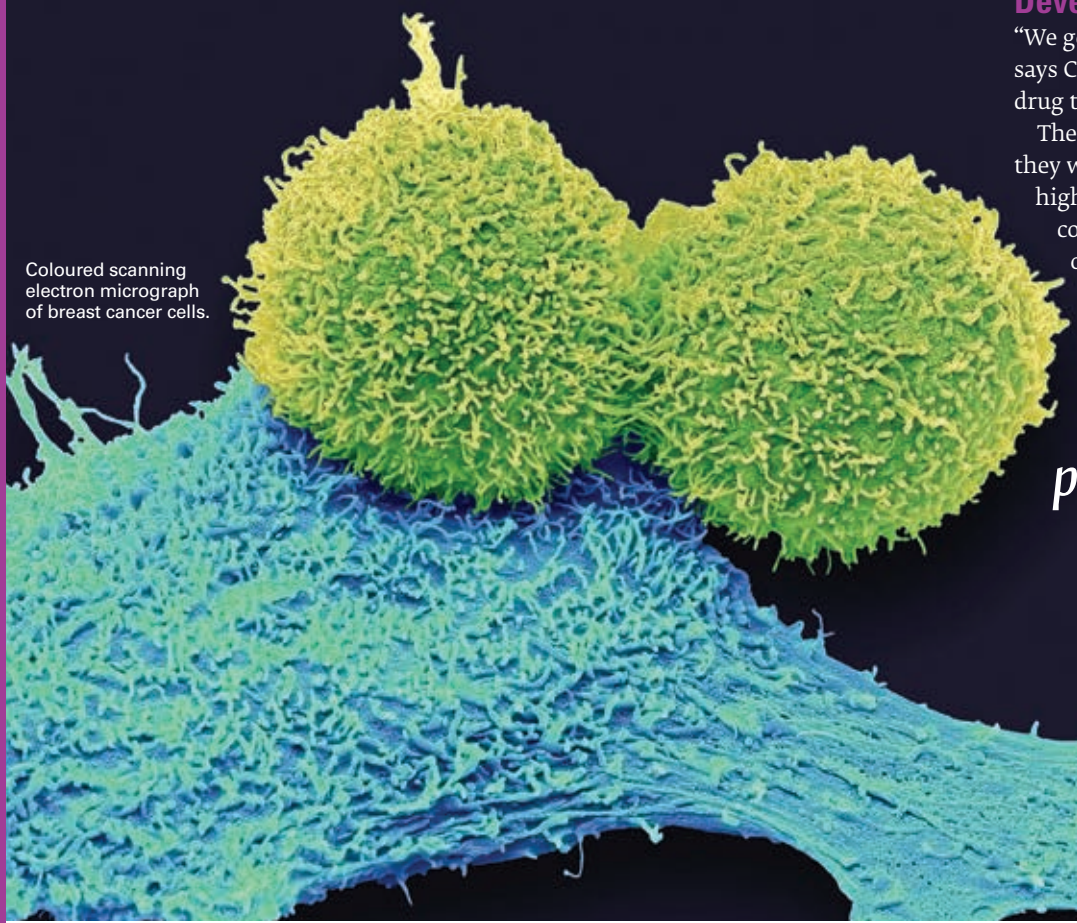
I really enjoy going out to schools to work with primary school children, however, I haven't done much work with secondary school pupils, so I'd like to expand a bit on what I deliver and the audience I work with.

I feel that at Year 10-11 pupils start to think about careers and the qualifications they might need and this age group is ideal for showcasing biomedical science as a possible career choice. I've also been lucky enough to be a co-applicant on a Wellcome Trust grant for public engagement, which we have recently been awarded, so it would be great to start the work with the team.

Anyone who knows me is very aware that I'd like to become a biomedical scientist, however, I'm in quite a unique situation and I'm finding it really difficult to complete my degree, so my last resolution is in relation to this. I'm going to be more determined and more driven to find a solution. I think it would help if I approached more people for advice.

ONE STEP AHEAD OF CANCER

In the UK, one in two of us can expect to get cancer in our lifetimes. With such a high disease burden, efforts to prevent cancer are at least as important as efforts to treat it.



Coloured scanning electron micrograph of breast cancer cells.

Jack Cuzick, a scientist at Cancer Research UK and Queen Mary University of London, has been working on cancer prevention for nearly 40 years. He was first counted among the top 1% of highly cited researchers in the world in 2007. Since 2014 he has been in the top 1% every year, including 2018.

His work on prevention and screening started out in the 1980s with the discovery that certain drugs that were used to treat breast cancer, such as tamoxifen, also appeared to have a preventative effect. Patients who took the drug to treat a cancer in one breast were less likely to develop cancer in the other breast after a course of this treatment. There were other drugs too that appeared to have an even bigger effect on reducing the occurrence of new tumours.

Developing a model

"We got pretty excited about these drugs," says Cuzick. "We thought they could be a drug to prevent breast cancer."

These drugs still have side effects, so they would only be a viable option among high-risk populations. Cuzick and his colleagues developed a model to find out who was at high risk of breast cancer, to guide who should be

"We think most people between the ages of 50 and 70 should take a low dose of aspirin for 10 years"

considered for more screening and preventative therapy. Lower-risk patients need less screening than the average interval of three years, whereas higher-risk patients need it more frequently.

This became known as the Tyrer-Cuzick model and was widely adopted throughout the field. Cuzick is still working on ways to hone the model further. "We're finding better ways of predicting risk. Genetic scores are turning out to be very useful, for example," he says.

Recently, Cuzick's work has turned to other drugs that could have a preventative effect against cancer. In one influential piece of research, Cuzick found that aspirin has a dramatic effect on reducing the incidence of cancers of the colon, stomach and oesophagus by up to 30%.

"It was a very striking effect," says Cuzick. Aspirin also had an effect, albeit a more modest one, on other cancers, including lung, breast and prostate cancer. "It looks like the second most important thing you can do to prevent cancer, second only to stopping smoking."

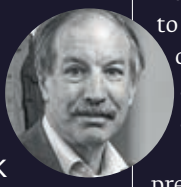
The effect of aspirin is about equal in magnitude to exercising and avoiding obesity. There are some people, of course, for whom taking aspirin is not wise. People who have bleeding in the stomach, for example, would be best to avoid it, as aspirin can worsen the problem. But for people who can tolerate aspirin, Cuzick believes it could be an excellent – and very cheap – effective cancer preventative.

"We think most people between the ages of 50 and 70 should take a low dose of aspirin for 10 years," says Cuzick. "That may have a bigger impact on cancer rates than anything other than those lifestyle factors. That's why we're so excited."

After taking aspirin for about three to five years, patients see the preventative benefits for about 20 years, according to Cuzick's research. But there are several more hurdles to overcome before this recommendation goes mainstream. Cuzick and his colleagues still don't know why aspirin has this protective effect.

IMAGE: SCIENCE PHOTO LIBRARY

CUZICK'S HONOURS AND AWARDS



- ✔ **2003** – Fellow of the Academy of Medical Sciences
- ✔ **2014** – Cancer Research UK Translational Cancer Research Team Prize
- ✔ **2015** –The American Cancer Society Medal of Honour
- ✔ **2016** – Elected Fellow of the Royal Society
- ✔ **2017** – Cancer Research UK Lifetime Achievement in Cancer Research Prize
- ✔ **2017** – CBE for services to cancer prevention and screening.

Understand the mechanisms

"Our work now is to try to understand better who is going to benefit more from aspirin, and who is more likely to have side effects," says Cuzick. "If we understand the mechanisms we can design drugs that could be even better than aspirin for cancer prevention."

Some of the most exciting other compounds that could be useful cancer prevention drugs are also widely accessible. This has the double benefit of being less expensive and often having to go through a less-intensive clinical trial process, as they are already known to be safe to consume. Cuzick's team is interested in the properties of commonly available food ingredients like curcumin (which is found in turmeric), pomegranate juice and green tea.

Another tack Cuzick is pursuing is to see what existing drugs could be re-purposed for cancer prevention. For example, metformin, which is used to treat diabetes, is thought to have a degree of anti-cancer effects. Bisphosphonates, which are often used to treat osteoporosis to combat the loss of bone density, are also thought to be a good candidate for investigating as a cancer preventative.

In many cases with cancer prevention, there are the issues of effectiveness and toxicity. If a drug is an excellent preventative but has severe side effects – such as Cuzick's early discovery with tamoxifen – it is not going to be a promising drug to roll out to broad patient groups or healthy people. As a result, it may save lives, but it won't necessarily make a dent in cancer cases on a population level. On the other hand, more innocuous treatments, such as aspirin, are particularly exciting as there is the potential to give them to all but the people most sensitive to the drug. If it does prove effective, it could lead to preventing a great many more cancers in the long run.

The next challenge

For Cuzick, being among the top 1% of highly cited scientists is a welcome award, but he says that he measures the impact of his science in more immediate terms: "Reduced incidence [of cancer] and ultimately mortality in those taking [these drugs]."

With this aim in mind, the next challenges are to improve the uptake of drugs that are well-established as effective cancer preventatives. These include anti-oestrogenic compounds for breast cancer and "aspirin for all", says Cuzick.

After a long and impactful career, Cuzick still has some of his own goals to pursue. Hopefully they might include a few more anti-cancer compound discoveries. "Discovery and validation of new agents is key," he says. "But given the time scale, I may just be able to initiate some projects that others carry on to a conclusion." BMS

THE TEN PLAGUES OF EGYPT

Stephen Mortlock asks if the 10 plagues of Egypt were the result of an ecological domino effect or divine intervention?

As children, many of us will have read how the Hebrew people living in Egypt were suffering under the cruel rule of the Pharaoh. Moses asked the Pharaoh to let them return to their homelands in Canaan, but he refused. As a consequence, 10 plagues were inflicted on the Egyptians in a divine demonstration of power and displeasure designed to persuade the Pharaoh to reverse his decision. But were the plagues historical events or, as some historians have suggested, simply passed-down accounts of several natural disasters? Some scholars concede that from an historical standpoint, the first nine plagues resemble natural events and while some are disconnected, others appear to be part of a chain reaction with set patterns and a rapid succession. The Egyptians were renowned for recording every event, whether temporal or religious in nature, but there are few references to plagues in ancient Egyptian literature. What if the plagues, however, involved villages and the countryside around Goshen, these might not have been referred to the royal court for insertion in official chronicles.

Recording history

When did the plagues occur and who was the tyrannical Pharaoh? The Greek historian Herodotus put the dates around 1570-1550 BC when Egypt was under the rule of the Hyksos (an Asiatic tribe), but there was no Pharaoh, until Ahmose I (1550-1525 BC) raised rebellion and overthrew the invaders. During this time apocalyptic rainstorms, devastated much of Egypt, and were described on the Tempest Stele of Ahmose I, these have been attributed to short-term climatic changes caused by the Thera volcanic eruption on the island of Santorini around 1630 BC (although it has also been suggested that the storm reference is merely a metaphor for the chaos caused during the war). Trevisanato (in his 2005 book *The Plagues of Egypt: Archaeology, History, and Science Look at the Bible*), suggested this eruption was also the trigger event for the plagues. There are indications that the environmental effects of this

Right. A volcano erupting on the Greek island of Santorini (Thera, Thira), thought by some to be the location of Atlantis. Date: 1866

eruption were felt around the globe – some scholars have also linked this eruption to the legend of Atlantis. Trevisanato believes that volcanic ash tainted the Nile causing it to become acidic and sediments found at the bottom of lakes along the Nile Delta seem to suggest that there was deposit of volcanic ash sometime during the Middle Bronze Age, which would be in line with the eruption on the Greek volcanic island. In a pre-industrial ancient Egypt, sulphates from a massive volcanic fall out would provide the simplest and most plausible scientific explanation for this contamination. A red, acidic Nile would have killed the fish, kept people from drinking from the river and, according to contemporary records, caused burns which later became infected with 'larvae'.

However, Alfred Edersheim proposed in his *Old Testament Bible History* that Thutmose II (1509-1479 BC) may have been the protagonist. In 1886 when the mummy of Thutmose II was unwrapped by Gaston Maspero there were scars from some type of infection which were still visible even after being embalmed. Maspero described the mummy as being "scabrous in patches, and covered with scars". Lesions covered the back, waist, arms and legs of the body and there was a mixture of papules, scabs and scars. Had Thutmose II died of a disease spreading through the region at that time? Evidence exists that the Queen's nanny, Sitre In, suffered from a similar condition. The details are very similar to descriptions of the 6th plague where "boils burst forth upon man and beast throughout the land of Egypt!" (Exodus 9.9).

A red river

Another candidate for the Pharaoh is Ramesses II (1303 - 1213 BC), made popular by the Hollywood epic *The Ten Commandments*. At this time the climate of the capital city Pi-Ramesses was wet and tropical, but towards the end of his reign the climate became dry and more desert-like. This change has been confirmed by a study of the stalagmites in local Egyptian caves, which have provided a record of the weather patterns of the time. It is possible that the Nile turned from a swiftly flowing river into a sluggish, muddy watercourse due to the rising temperatures and arid conditions. This was the basis of the 1950s naturalistic theory by Greta Hort, who proposed that certain algae in particular, *Haematococcus pluvialis* and *Euglena sanguinea*, were able to flourish in these conditions. The red colour is due to the presence of astaxanthin and under the right conditions the cells can be populous enough to turn water red. *Euglena sanguinea* is also known to produce the potent icthyotoxin euglenophycin. The idea of an algal bloom is also proposed by Dr Stephan Pflugmacher, who believes that when the Nile changed it allowed the toxic algae *Planktothrix rubescens* to thrive in the warm slow moving water. When the algae died it turned the water red causing a phenomenon called "Burgundy blood". Dr JoAnn Burkholder has cited a similar condition in North Carolina in 1996 but caused by *Pfiesteria piscidia*. So there is recorded evidence for this type of event. The ancient historian Josephus Flavius reported that the blood red water was

"A massive volcanic fall out would provide the simplest and most plausible scientific explanation for this contamination"

undrinkable, the fish died and the air was filled with a horrid stench. Algal blooms can be harmful to wildlife, as the algae contain a toxin that can accumulate in shellfish and poison the animals that feed on them. Fumes from densely-concentrated algal blooms can also disperse toxins in the air, causing breathing problems for people. More importantly, a bloom in the water would have the killed the fish, allowing amphibians to breed unchecked, as fish eat their eggs. Studies have also shown that tadpoles, when stressed because of a change in their environment, quickly develop into frogs. The toxic water would have caused the amphibians to leave and swarm over the land in overwhelming numbers. The amphibians would have stayed away from the deadly river and many would have died, leading to the third plague – lice (this could mean lice, fleas or gnats, based on the Hebrew word kînnîm).

IMAGES: ALAMY

If toxic algal led to the first plague and dead frogs followed, it is not surprising that a swarm of insects would also follow.

The plagues continue

The lack of frogs in the river would have let insect populations, normally kept in check by the frogs, increase massively. The rotting corpses of fish and frogs would have attracted significantly more insects to the areas near the Nile. If so, an infestation with certain insects could have set the stage for the later plagues. Scientists have theorised that the sickness that killed the beasts of the field for Egyptians in later plagues might have been Bluetongue or African horse sickness (AHS), these are *Orbiviruses*, of the Reoviridae family, both of which can be spread by insects of the *Culicoides* species. Marr and Malloy argued that the fourth plague represents a swarm of flies, such as the stable fly (*Stomoxys calcitrans*). Studies have shown that cattle heavily infested with stable flies can become anaemic and have lower milk yields. The stable fly also bites humans and could have led to the boils that occurred as part of the sixth plague. In many parts of the world, the species is a carrier of trypanosomid parasites including *Trypanosoma evansi* and *Trypanosoma brucei*. There would have also been an increase in the common house fly (*Musca domestica*), which belongs to a group of flies often referred to as "filth flies". The house fly has been in existence since the origin of human life, is well adapted to life in human habitations and acts as a potential vector of diseases. A recent study found that over 100 pathogens including bacteria such as *E. coli* and *S. aureus*, viruses, fungi and parasites have been associated with this prolific insect, so it is not surprising that people would have been suffering from increased illnesses. Could the boils have been caused by *S.aureus*?

The fifth plague, which killed off the Egyptian livestock, has similarities of rinderpest, a member of the genus

THE 10 PLAGUES IN THE BOOK OF EXODUS

01 Blood
The waters were turned to blood – the fish in the river died and the Egyptians couldn't drink the foul water.

02 Frogs
Frogs swarmed forth, covering every inch of land and entering houses and bedrooms.

03 Lice
All over Egypt, bugs crawled forth from the dust to cover the land.

04 Wild animals
Hordes of wild animals destroyed everything in their path.

05 Pestilence
A fatal pestilence killed most of the domestic animals of the Egyptians.

06 Boils
The Pharaoh, his servants, the Egyptians and even their animals developed painful boils all over their bodies.

07 Fiery hail
Hail struck down all the crops in the fields and shattered every tree.

08 Locusts
The locusts covered the face of the land and swallowed up every crop and all the fruits of the trees.

09 Darkness
A thick darkness over the land of Egypt, so total that the Egyptians had to feel their way around.

10 Death of the first-born
All firstborn Egyptian sons (and firstborn cattle) died. Israelites marked lamb's blood above their door and were passed over.

Below. Death of the firstborn of Egypt – last of the ten plagues. Exodus, chapter XII

Morbillivirus, a member of the *Paramyxoviridae* family. This causes high fever, diarrhoea and ulcers in the mouths and noses. Rinderpest is spread between animals by direct contact and possibly aerosol over limited distances. The virus can be spread via secretions from the eyes, nose, or mouth, and the faeces, urine, blood, milk, or reproductive fluids of infected animals.

Then, around 1600 BC, the plume of another Santorini eruption may have been responsible for the seventh, eighth and ninth plagues – the fiery hail, the locusts and the days of darkness. According to the archaeologist Charles Pellegrino, the Santorini eruptions would have been comparable with the Mount St Helens eruption of 1980 and this volcanic plume coupled with high velocity dust storms could have rained down in Egypt, thereby turning days into nights and causing weather anomalies with increased precipitations and higher humidity. It is possible that when the volcanic ash mixed with thunderstorms above Egypt, it led to dramatic hailstorms. This could have created the conditions which caused the infamous desert locust (*Schistocerca gregaria*) to change from the solitary to the more gregarious form, not only are they more sociable they change in appearance, becoming stronger, darker in colour and more mobile. They can swarm over long distances and, according to the United Nations Food and Agricultural Organization, when they get hungry, a one-tonne horde of locusts can eat the same amount of food in one day as 2,500 humans. Such a pestilence would devour all the remaining plants that the hail did not destroy.

Archaeologists have always believed that the last plague, the death of the firstborn male, was caused by wheat infected with a fungus. But this seems unlikely, since infants died also and they would probably not have been eating grain. Also, why were some children spared? There is a similar historical precedent where ergot fungi (*Claviceps purpurea*), infected rye grain, and is believed to have precipitated the Salem witch trials in the winter of 1692 where it may have been the cause for the hallucinations, trances, seizures, and violent behaviours that were the supposed signs of being a witch. Although ergot did not cause death in the settlers, it is unclear why it affected some people and not others. A similar fungus could have infected the Egyptian grain.

"It is very easy to dismiss the plagues as a fable when confronted with natural events"

Conclusions

Were the plagues an ecological domino effect or divine intervention? It is very easy to dismiss the plagues as a fable when confronted with natural events such as volcanic eruptions, thunder, and desert sandstorms driving locusts into Egypt. But there are many problems with trying to analyse historical events from contemporary records. Often it is difficult to work out where or when they happened. In this instance, the period for the plagues of Egypt is sometime between the years 1570 and 1440 BC, depending on who was writing about them. Eusebius Pamphili (263-339 AD), the first Church historian, believed the specific date to be 1446 BC. And yes, there were the Thera volcanic eruptions in around 1630-1600 BC, one of which is described as the largest on record, but it was 1,050 kilometres (650 miles) away from the northwest part of Egypt. And the eruption was many years before the Exodus took place; the eruption would only have caused some of the plagues, if one or other of the dates is wrong. I am not a theologian and rely on empirical evidence to make decisions, but occasionally there is a question where you ask: "What if?" BMS

Dr Stephen Mortlock is Pathology Manager at the Nuffield Health Guildford Hospital. He would like to thank the matron and all the staff at Nuffield Health, Guildford Hospital for their continued support. To see the article with full references, visit **thebiomedicalscientist.net**

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CLOPIDOGREL AND *CYP2C19* GENOTYPING: A GENOMIC PERSPECTIVE

Ibrahim Nakibingé looks into one of the first generation of adenosine diphosphate receptor antagonists.

Plavix, commonly known as clopidogrel, is widely used as the gold standard dual antiplatelet therapy when combined with aspirin. However, the pharmacogenetic variability of the liver drug metabolising enzyme cytochrome-P450 isoenzyme CYP2C19 has been shown to be associated with reduced platelet inhibition as well as major adverse effects in a selected number of acute coronary syndrome (ACS) and myocardial infarction (MI) patients.

In the US, the Food and Drug Administration (FDA) recommends genotyping before prescribing clopidogrel to cardiovascular disease patients; however, several organisations, including the American College of Cardiology, have opposed this view, citing insufficient evidence. This paper briefly reviews the literature on *CYP2C19* genotyping and responsiveness to clopidogrel to decide whether the drug is suitable for patient treatment or if there are alternatives better suited from a genomic perspective.

Background

Clopidogrel, along with ticlopidine, is considered among the first generation of adenosine diphosphate (ADP) receptor antagonists, or more conventionally referred to as P2Y12 inhibitors, as they block ADP binding to P2Y12 receptors on platelets.

The metabolism of the drug is associated with several genes including *ABCB1, CES1 CYPA2, CYPB6, CYP2C9, CYP3A4, CYP3A5, P2PY12* and indeed *CYP2C19*. As with other *CYP450* superfamily members, *CYP2C19* is highly polymorphic, more than 25 known variants have been reported with subgroups being associated the enzymatic activity in clopidogrel metabolism. The technology (next generation sequencing [NGS]) to identify these variants in patients is now available to clinicians with some drug regulatory bodies sanctioning their use in tailoring patient treatment.

CYP2C19 GENOTYPING

Early *CYP2C19* genotyping was based on traditional methods such as qPCR, which are heavily time-consuming and therefore unsuitable; for example, in determining the patient's treatment course. Furthermore, due to the mutations that may occur during product amplification, the method did not yield adequate accuracy until the advent of AmpliChip CYP450 GeneChip microarrary technology which evolved from Affymetric GeneChip platform.

Based on the genotype obtained, the AmpliChip CYP450 test for *CYP2C19* is able to predict the patients as poor metaboliser (PM), intermediate metabolisers (IM), extensive metaboliser (EM) or ultra-rapid metabolisers (UM). Furthermore, in a *CYP2D6* study using the AmpliChip CYP450 test, 33 variants were detected that included those associated with

dysfunctional enzyme activity, while compared to traditional techniques. Depending on the NGS platform used, the application employed to identify SNPs is likely to be superior and, unlike array methods, is less likely to suffer from biased missingness that lead to false associations. Additionally, NGS technologies offer the superior targeted sequencing of exomes. Nonetheless, it is evident the genotyping technologies are sufficient enough in their ability to detect variants, and indeed the problem faced is that of interpreting the results correctly so as to allow the planning of a suitable treatment course.

Interpretation, indications and contradictions

Clopidogrel has been reported in a number of clinical studies along with other antiplatelet agents. For example, the Joint Utilisation of Medications to Block Platelets Optimally (JUMBO-TIMI26) and successively the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation (PRINCIPLE) studies, both found prasugrel to significantly enhance inhibition of platelet aggregation when compared to clopidogrel. Furthermore, prasugrel's duration of onset was faster (peak plasma concentration at 30 minutes) as it only required one CYP450 enzyme for activation, whereas clopidogrel requires two. Such differences in drug responses may or may not be associated with the gene's polymorphic variants. A meta-analysis of *CYP2C19* genotyping found that overall there is no significant association between genotype and clopidogrel responsiveness in relation to cardiovascular events. However, between certain genotypes the difference observed was significant as found between PM (*CYP2C19* *2-*8) and UM (*CYP2C19* *1,*17). Therefore, depending on the patient's genotype, the dose prescribed by a clinician can vary, and it is further complicated by heterozygous patients.

The figure below summarises the recommended algorithm for clinicians when planning a patient's treatment course. In the clinical studies stated left, where some patients were subject to increased bleeding from clopidogrel, with genotyping data, it was evident that these were most likely individuals carrying *1 (wild type) or *17 (UM) allele, whereas those with *2-*8 alleles, a lower risk of bleeding would be observed, since they are poor metabolisers but a higher dose would be needed to confer any significant biological antiplatelet activity. For these reasons, the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on *CYP2C19* genotyping for clopidogrel recommend alternative antiplatelet therapies, such as prasugrel, ticagrelor or indeed PAR-1 and $\alpha_{II}b\beta_3$ inhibitors are considered when not clinically contraindicated. Although patients are genotyped, the benefits of prescribing clopidogrel should be carefully weighed against major adverse effects such as bleeding, in which case a potential antiplatelet benefit would be counterbalanced by the bleeding and other factors that contraindicate. For example, it has been reported that *CYP2C19**17 (rs12248560) status confers significant enhanced clopidogrel metabolism but also increases risk of bleeding. Additionally, the presence of a novel *CYP2C19* variant in a patient annotated as "probably damaging" or "pathogenic" without further investigations should be cautiously reported as its biological interaction with clopidogrel would be unknown. Likewise for variant identified as "benign" or "tolerated", it should not be assumed, for example, to mimic the biological behaviour of known loss of function variants in response to clopidogrel. As for the IM phenotypes that have genotypes such as *1/*2 or *2/*17, it is recommended that alternative antiplatelet therapies are prescribed due to the high risk of adverse cardiovascular outcomes. Finally, clinicians should always remember that the aim of personalised medicine is ultimately to minimise disease risk and associated adverse effects. BMS

Ibrahim Nakibingé is a Biomedical Scientist and IT Transition Analyst working in North West London Pathology.

ALGORITHM FOR TREATMENT PLAN DEPENDING ON PATIENT'S *CYP2C19* GENOTYPE (Figure adapted from Scott *et al*, 2013)

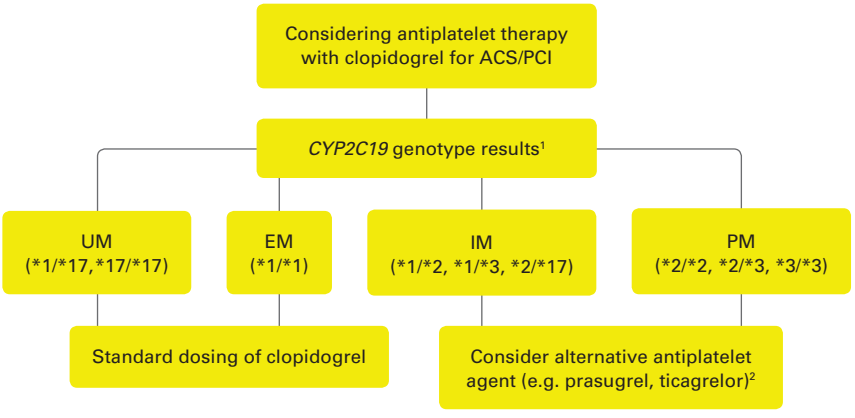
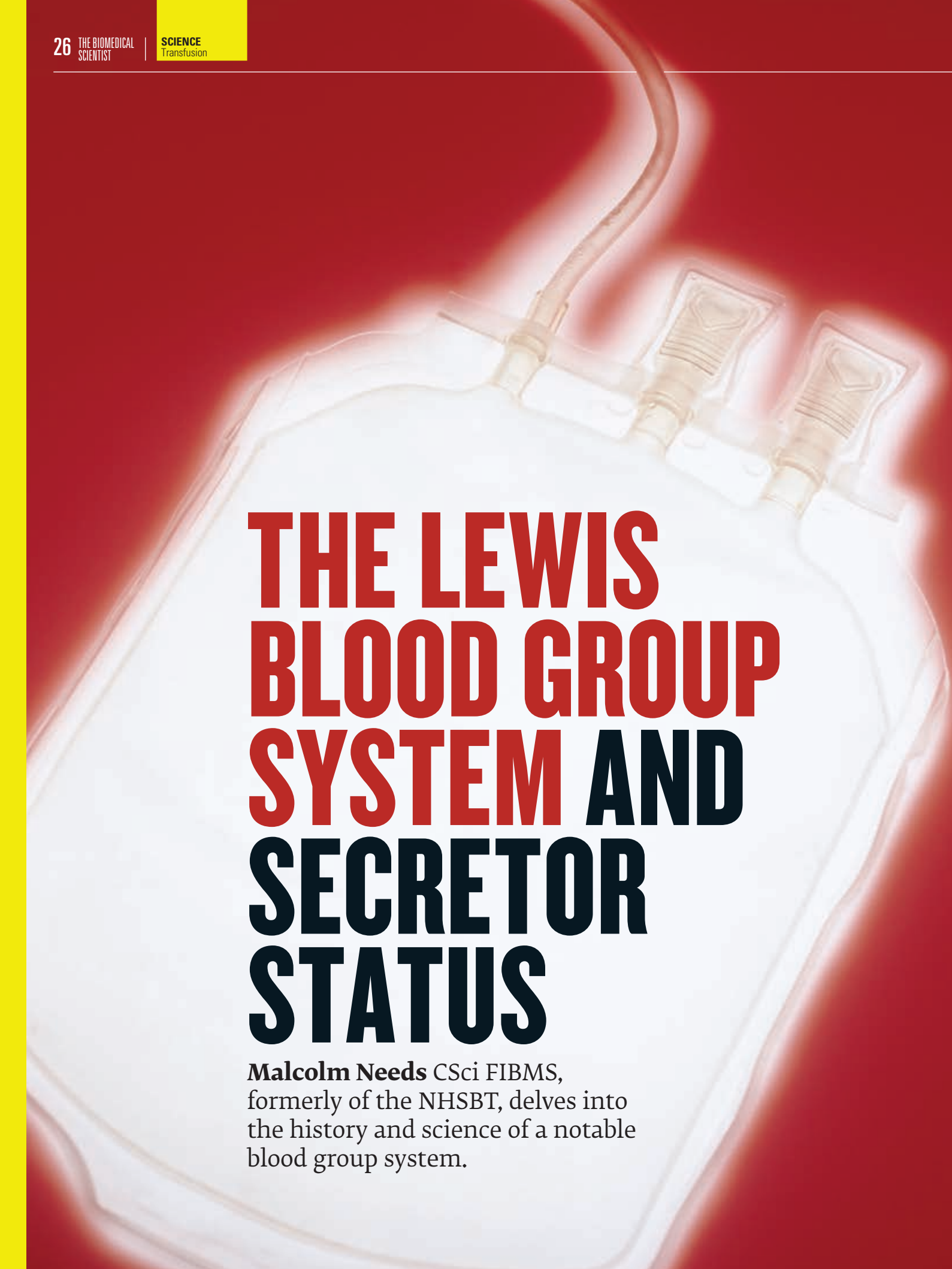


IMAGE: SCIENCE PHOTO LIBRARY



THE LEWIS BLOOD GROUP SYSTEM AND SECRETOR STATUS

Malcolm Needs CSci FIBMS, formerly of the NHSBT, delves into the history and science of a notable blood group system.

Le^a was first described in 1946 by Mourant, when it was named L.

Le^b was first described in 1948 by Andresen.

In 1955, Sneath and Sneath observed that red cells lacking Le^a and Le^b will take up these antigens from plasma containing them. Equally, red cells expressing either Le^a or Le^b will give these up to plasma lacking them. In other words, the antigens were found to be soluble.

Between 1948 and 1951, Grubb and Brendemoen independently observed that the saliva of Le(a+b-) individuals strongly inhibited anti-Le^a, and that the saliva of the majority of Le(a-b+) individuals also inhibited anti-Le^a, but did so less strongly.

In 1963, Mollison *et al* demonstrated that this phenomenon also occurred *in vivo*.

From this it can be seen that:

- Lewis antigens are not intrinsic to red cells.
- They are located on type 1 glycosphingolipids that are adsorbed onto the red cells from the plasma.
- Lewis, therefore, is not strictly speaking, a red cell blood group!

Genotypes and phenotypes and their relationship with the Secretor gene

At a basic level, if you do not inherit a Lewis gene (*LE*, or, as it is now named, *FUT3*), whether you inherit a Secretor gene (*SE*, or, as it is now named, *FUT2*) of not, you will be Le(a-b-). if you do inherit a Lewis gene, but you do not inherit a Secretor gene, you will be Le(a+b-). If you inherit a Lewis gene, and you inherit a Secretor gene, you will be Le(a-b+) (see Table 1).

That having been said, the Secretor gene actually defines whether an individual secretes A, B and/or H Substance (Type 1 A, B and/or H substance) in saliva and other body fluids, rather than directly to do with the Lewis types.

It will be noted that there is no Le(a+b+) shown in Table 1, and the reason for this will be explained below.

The genes

The locus for the gene coding for *LE/FUT3*, has been mapped to 19p13.3.

It was soon realised that there was an interaction between the *LE/FUT3* gene and the *SE/FUT2* gene (see Table 1).

The locus for the gene coding for *SE/FUT2* is also found at 19p13.3, but, although they are mapped to the same chromosome, *LE/FUT3* and *SE/FUT2* segregate independently.

The Lewis carrier molecule

As stated earlier, the Lewis antigens are not an integral part of the red cell membrane, but are plasma soluble molecules. They are also carbohydrate-

LE/FUT3 Genotype	*SE/FUT2* Genotype	Red Cell Lewis Type	ABH Secretor Status
le/le	*se/se*	Le(a-b-)	No
le/le	*SE/se*	Le(a-b-)	Yes
le/le	*SE/SE*	Le(a-b-)	Yes
LE/le	*se/se*	Le(a+b-)	No
LE/LE	*se/se*	Le(a+b-)	No
LE/le	*SE/se*	Le(a-b+)	Yes
LE/le	*SE/SE*	Le(a-b+)	Yes
LE/LE	*SE/se*	Le(a-b+)	Yes
LE/LE	*SE/SE*	Le(a-b+)	Yes

Table 1. The interaction between the *LE/FUT3* gene and the *SE/FUT2* gene, and their influence on the Lewis phenotype.

based molecules, and so, like the A, B and H antigens, they are not direct gene products. The gene products are α-1-4-fucosyltransferase (*LE/FUT3*) and α-1-2-fucosyltransferase (*SE/FUT2*). The *SE/FUT2* direct gene product cannot function, unless the *LE/FUT3* direct gene product is present (rather in the same way that the A and B gene products cannot function, unless the *H* gene product is present and functioning.

A schematic of the two carrier molecules can be seen in Figure 1.

There are six antigens recognised by the International Society of Blood Transfusion (ISBT) within the Lewis Blood Group System. These can be seen in Table 2.

Le^a	Le^b	Le^{ab}
Le^{bH}	ALe^b	BLe^b

Table 2. The antigens of the Lewis Blood Group System.

Lewis phenotype frequencies

The normal figures for Lewis types can be seen in Figure 2; however, for various reasons, such as infancy and pregnancy (see below for explanations), such figures should only be taken as true for individuals from the age of approximately two and upwards, and who are not pregnant.

Lewis antigens in newborns and infants

Most newborn babies type as Le(a-b-) for the first month of their life, as the production of Lewis fucosyltransferase is at very low levels. If they are going on to eventually become Le(a-b+), they will, for a time, type as Le(a+b-), as the production of Lewis fucosyltransferase becomes active before Secretor fucosyltransferase. For a very short time, they may type as Le(a+b+), before they become Le(a-b+). By one year of age, 50% of children express their adult phenotype, and by two years of age, the Lewis phenotype of most children will reflect their *SE/FUT2* and *LE/FUT3* alleles.

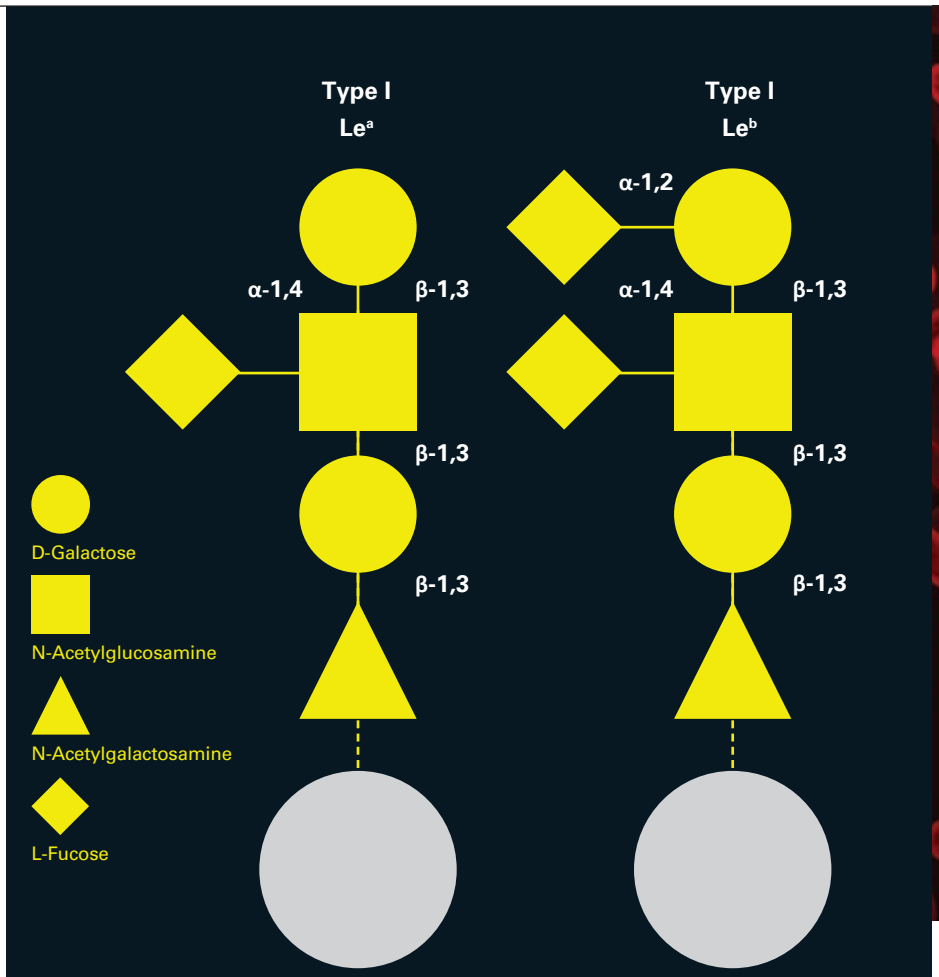


Figure 1. The Le^a and Le^b Antigen Carrier Molecules (Note that these carrier molecules are NOT an integral part of the red cell membrane) (after Race and Sanger).

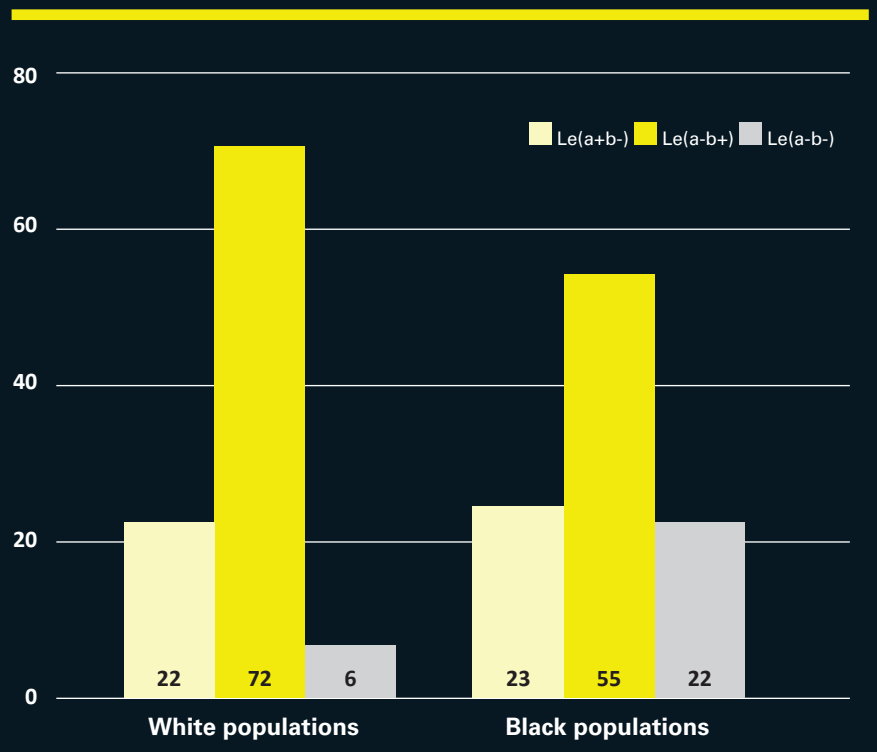
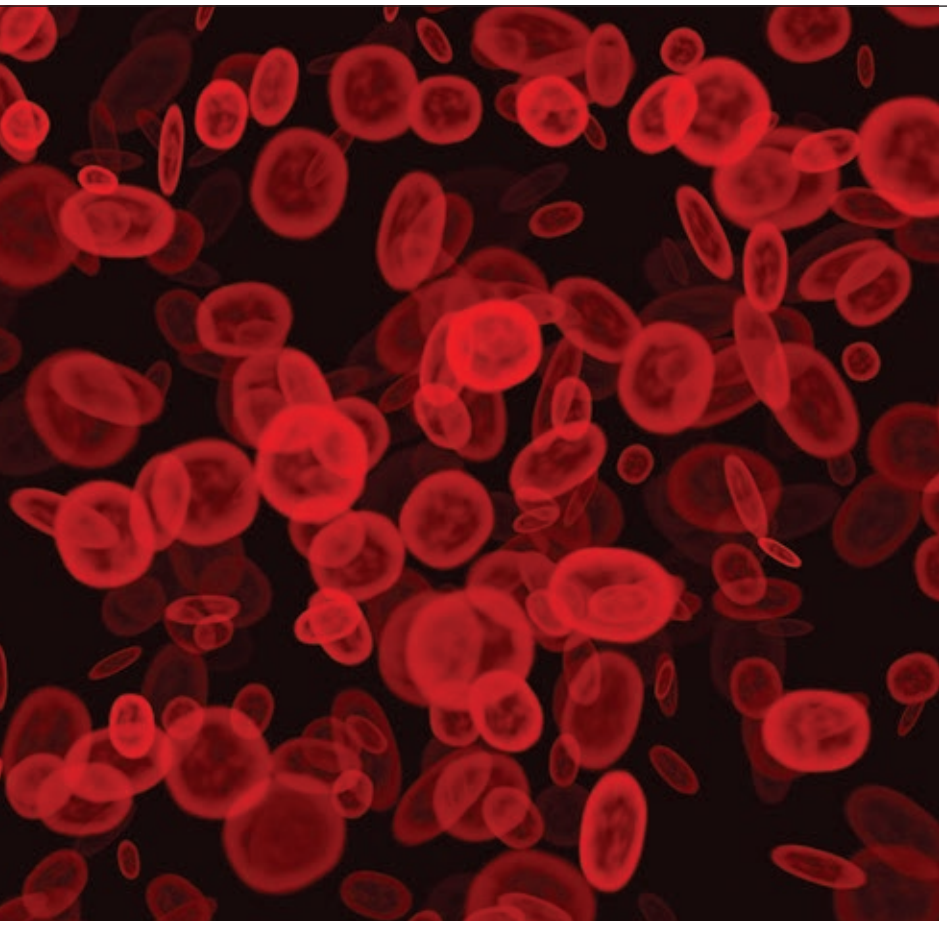


Figure 2. Lewis phenotypes[8].

IMAGES: SCIENCE PHOTO LIBRARY/SHUTTERSTOCK



Lewis Type of the recipient prior to the bone marrow/stem cell transplantation	Lewis Type of the bone marrow/stem cell transplantation	Lewis Type of the recipient after successful bone marrow/stem cell transplantation
Le(a-b-)	Le(a-b-)	Le(a-b-)
Le(a-b-)	Le(a+b-)	Le(a-b-)
Le(a-b-)	Le(a-b+)	Le(a-b-)
Le(a+b-)	Le(a-b-)	Le(a+b-)
Le(a+b-)	Le(a+b-)	Le(a+b-)
Le(a+b-)	Le(a-b+)	Le(a+b-)
Le(a-b+)	Le(a-b-)	Le(a-b+)
Le(a-b+)	Le(a+b-)	Le(a-b+)
Le(a-b+)	Le(a-b+)	Le(a-b+)

Table 3. Lewis Types of recipients and donors of bone marrow/stem cell transplantation, and the resultant recipient Lewis Type following successful transplantation.

Lewis antigens in pregnancy

It has been known for many years that pregnant women may become transiently Le(a-b-) and may even produce Lewis antibodies. It was originally thought that pregnant women produced less Lewis glycolipid, but it is now thought that this is not so. Hammar *et al* put forward the theory that the increased incidence of the Le(a-b-) phenotype during pregnancy may be a result of increased concentration of plasma lipoproteins during pregnancy. In pregnant women, the ratio of lipoprotein to red blood cell mass increases more than four-fold, so that much more Lewis glycolipid is attached to plasma lipoprotein than is available for the red blood cell surface.

The Le(a+b+) phenotype in adults

In truth, in almost every case of the phenotype Le(a-b+), a small amount of Le^a antigen can, in fact, be detected.

The frank Le(a+b+) phenotype in Polynesian adults is, however, quite common (~40%). This is due to a weak or mutated Secretor status.

Lewis phenotypes following transplantation

As has been mentioned above, Lewis antigens are not produced as an integral part of the red cell membrane, but are adsorbed onto the red cell membrane. In 1986 and 1987, Myser *et al* and Needs *et al* independently observed that the Lewis antigens always remain of the recipient type after bone marrow transplantation.

Following successful bone marrow/stem cell transplantation all red cell antigens that are integral to the red cell membrane (*i.e.* are produced in the bone marrow) change from that of the recipient, to that of the donor, although, of course, these are sometimes identical. However, those that are not integral to the red cell membrane (i.e. are produced remote from the bone marrow) remain as the antigen type of the recipient. These include the soluble A, B and H antigens, the Lewis antigens and the antigens within the Chido/Rodgers Blood Group System.

In the case of the Lewis antigens, the final Lewis phenotypes can be seen in Table 3.

Lewis antibodies

IgM anti-Le^a is more frequent than IgG. IgG anti-Le^a can cause a haemolytic transfusion reaction, albeit very rarely and self-limiting, as the Le^a antigen elutes from the transfused red cells and the anti-Le^a is then inhibited by this eluted antigen.

Anti-Le^a has only been reported once as causing mild HDFN.

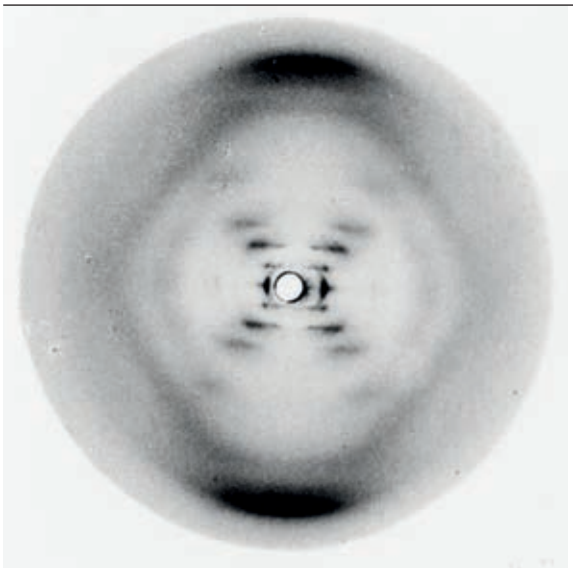
IgM anti-Le^b is more frequent than IgG. IgM and IgG anti-Le^b were thought to be clinically benign, but there has been a recent report of an acute haemolytic transfusion reaction due to anti-Le^b.

There has been one (dubious) report of mild HDN caused by anti-Le^b.

There is some evidence that Lewis antibodies may be involved in renal transplant rejection, but the evidence is slight and the theory controversial. IBMS

Malcolm Needs was the Reference Service Manager at NHSBT-Tooting Centre and is an IBMS Advisory Panel member.

To see the references, view the article online at **thebiomedicalscientist.net**



Left. Photo 51 – an X-ray diffraction image of DNA. **Right.** Rosalind Franklin.

DISCOVERING THE DOUBLE HELIX

A look back in time to the history of the discovery of DNA and its structure – work which would change medicine and science forever.

DNA is as old as history itself, but human understanding of the genetic code that determines the shape, size, colour and behaviour of all living things only began its embryonic formation in 1859 with the publication of Charles Darwin's trailblazing work *On The Origins of Species by Means of Natural Selection*. Though the book offered nothing in the way of a biochemical explanation for its theories, its suggestion that life hadn't magically appeared but had copied itself, adapted and evolved over time – vast time – changed the focus of scientific imagination and enquiry.

Gregor Mendel, a monk and teacher with a sideline in science and research, living in what would be the modern-day Czech Republic, took the next step. Between 1856 and 1863 he conducted thousands of cross-breeding experiments on pea plants. He observed not just the characteristics that passed from one generation to the next but also the ratios of those inherited characteristics. The paper that came out of this intensive observation, *Experiments on Plant Hybridisation*, published in 1866, was so far ahead of its time that it wasn't until 1900 that other scientists had caught up with him and rediscovered his work. Only then could they appreciate the thoroughness of his methodology and understand the implications of what he had found – that

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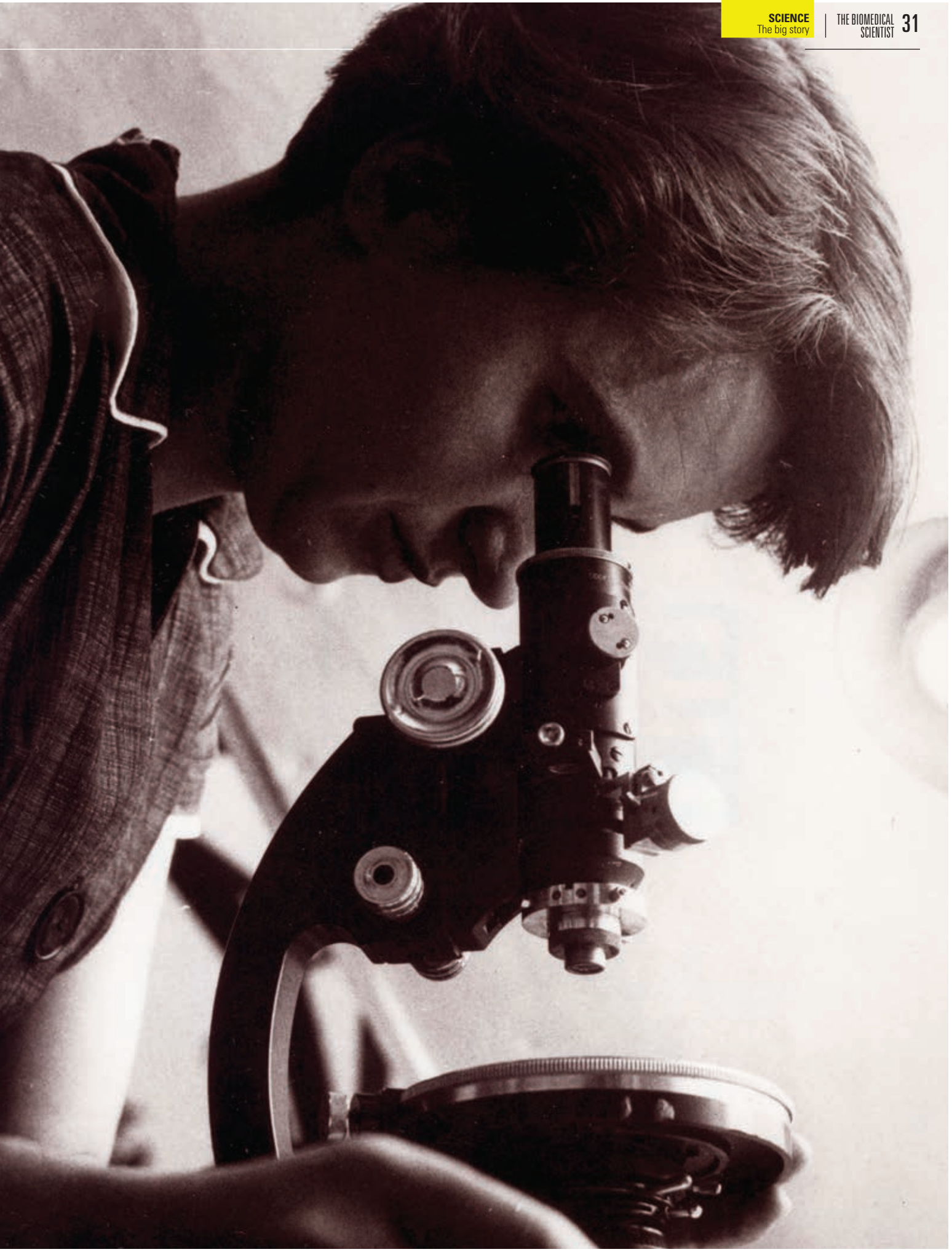


Left. The Nobel winners 1962. Photo shows left to right they are Professor Maurice Wilkins, Dr Max Perutz, Dr Francis Crick, John Steinbeck, Professor James Watson and Dr John C Kendrew.
Right. Francis Crick's original sketch of the structure of DNA made in 1953.

each parent possesses a specific pair of "somethings" and passes one of these "somethings" on to its offspring so that it too now possesses a pair. He had, in effect, mapped out genetic science.

Extraordinary discovery

More was to come, this time from Germany. There, in 1869, the Swiss chemist Friedrich Miescher, asked a local surgery to send him all its used bandages – the pus that filled them being a rich source of the white blood cells he wanted to investigate. He isolated the cells and identified their various proteins, but also he found another substance in the cell nuclei that bore no resemblance to the other proteins and had an unusual chemical makeup. Meischer knew he had found something extraordinary, and though he couldn't say exactly what it was, he suspected it was linked to chemical inheritance. He called his discovery "nuclein", which later become "nucleic acid" and finally morphed into "deoxyribonucleic acid" – DNA. Again, though, it would be several decades before the rest of the scientific community grasped the significance of what he had done.

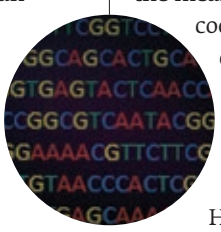
From 1905 onwards, the Lithuanian-born biochemist Phoebus Levene, working at the Rockefeller Institute of Medical Research in New York, was examining nucleic acid in the sort of detail that Miescher could not have dreamt of just 35 years' earlier. Levene found two types of nucleic acid, DNA and RNA (ribonucleic acid), and, more importantly, the components of DNA: adenine (A), guanine (G), thymine (T), cytosine (C) and deoxyribose phosphate. He also detected the phosphate-sugar-base order of the components, which sorted them into units that he named nucleotides. Levene didn't get it all right, though: he described the wrong structure for DNA and believed that its chemical makeup was far too simple to carry any genetic code – a belief that would persist for some time.

At the same time that Levene was working in his laboratory, the theories of evolution and genetic inheritance were being seized upon by the eugenics movement. This made several fundamental misinterpretations of the basic science, then applied them to the goals of social and population control. The movement found expression in sterilisation programmes in several countries, became more overtly political as the underpinning for the US Immigration Act of 1924 and was a driving force behind the theory of racial superiority in Nazi Germany, which grew to horrific proportions with the systematic destruction of the Jews and other "inferior" and "undesirable" people.

Transforming principle

By 1944, with the end of World War Two in sight, the real science was making further progress. Also at the Rockefeller Institute in New York, the Canadian bacteriologist Oswald Avery was busy following up the work from the late 1920s of the British microbiologist Frederick Griffith, who had found that a severe form of pneumonia could, in some way, activate a non-virulent form. Avery and his colleagues, Colin MacLeod and Maclyn McCarthy, went looking for this "transforming principle", and systematically began to isolate the factors that could have caused one type of pneumonia cell to change into another. The belief among the wider scientific community was that a protein had to be responsible, but after eliminating all the possible proteins and carbohydrates the Avery team had shown that nucleic acid, DNA, held the key – their results suggested that it alone was the carrier of hereditary material.

The paper they published in the *Journal of Experimental Medicine* in February 1944 divided opinion. Some biochemists still clung to the belief that the A,G,C,T of DNA was too simple and limited to carry the huge complexity of biological material required. But a few other experts reasoned that since DNA was present in every chromosome it might just as well be the means of transporting genetic coding, even for more complex entities, such as human beings.



A new language

Among the champions of Avery's work was the Austro-Hungarian biochemist Erwin

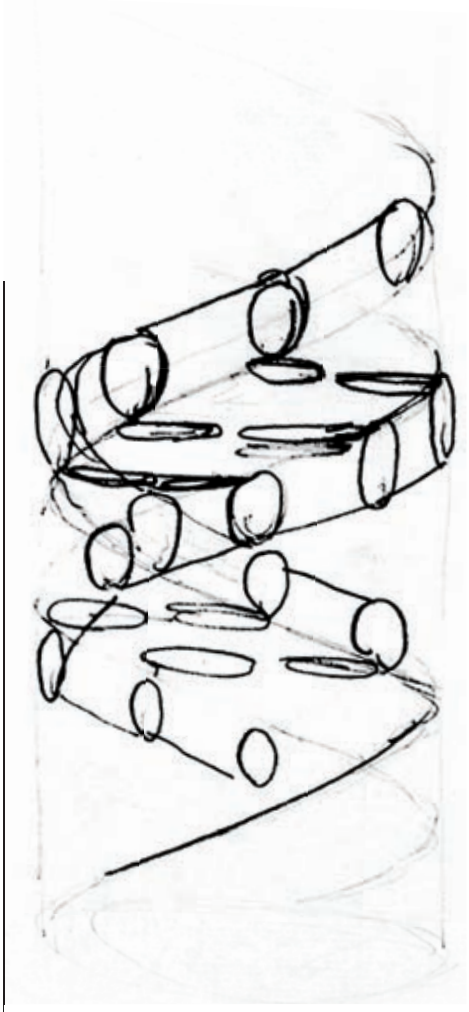
Chargaff, who had fled the Nazis and found a position at Columbia University in New York. "Avery gave us the first text of a new language, or rather he showed us where to look for it," wrote Chargaff. "I resolved where to search for this text." He began to look more closely at the composition of DNA in bacteria and larger organisms.

Also in 1944, the Austrian quantum physicist Erwin Schrödinger, he of the famous cat, and yet another leading thinker who escaped the Nazi regime, published a short book called *What is Life?* In this he suggested that life centred around a complex molecule that stored genetic material and passed it on to future generations. He also proposed that this biological information might resemble the dots and dashes of morse code.

One of the people who read *What is Life?* was James Watson, then a startlingly young student at the University of Chicago. "Schrödinger struck a chord because I too was intrigued by the essence of life," Watson wrote. "The notion that life might be perpetuated by means of an instruction book inscribed in a secret code appealed to me." Schrödinger's book also caught the imagination of the British physicist-turned-chemist James Crick, who had been working in the Admiralty Research Laboratory throughout the war, and whose thoughts now turned to biology.

Focusing efforts

In 1951, at the age of 35, Crick was working on his PhD in the Medical Research Council (MRC) unit at Cambridge University when he found himself sharing lab space with a new arrival from the US – the 23-year-old Watson, who had come to Cambridge in order to master X-ray diffraction, which, he hoped, would help him unlock the secrets of DNA. The pair soon became friends and focused their efforts on DNA. Crick also introduced Watson to Maurice Wilkins, a biochemist from New Zealand who worked at King's College in London, had extensive experience of X-ray diffraction, and even suggested the structure of DNA might be a helix.



One of Wilkins' colleagues at King's was Rosalind Franklin, who had graduated in chemistry from Cambridge in 1938 and gone to Paris after the war to learn X-ray diffraction. She returned to London in 1951 to take up a fellowship in King's MRC unit and set to work on producing diffraction images of DNA, though the head of the unit had failed to inform Wilkins of this. With the help of Raymond Gosling, a PhD assistant, Franklin captured several X-ray images of DNA, including the now-famous Photo 51. The forthright Franklin and the understated Wilkins found it hard to work together, so it fell to Crick and Watson to put the pieces together.

In early 1953 they began constructing a molecular model of DNA, drawing on the work of the team at King's College, and in particular the B version of Photo 51, which showed evidence of the helix structure.

"[Crick] realised right away that it would result in the two strands of the double helix running in opposite directions..."

It's claimed that Wilkins had given Crick and Watson the photo without Franklin's knowledge. Crick and Watson also took what they needed from the findings of Erwin Chargaff on the base-pair ratios, and from the theoretical work of Linus Pauling at the California Institute of Technology, who was also attempting to construct his own model of DNA.

Simple and elegant

Watson writes that on the morning of 28 February 1953 "the key features of the DNA model fell into place. The two chains were held together by strong hydrogen bonds between adenine-thymine and guanine-cytosine base pairs... [Crick] realised right away that it would result in the two strands of the double helix running in opposite directions... It was quite a moment. We felt sure that this was it. Anything that simple, that elegant just had to be right."

Just a few weeks later in April, they published their findings in *Nature*. The structure of DNA had been revealed – the famous double helix – and the path of biochemistry had been set on a new course. The 1962 Nobel Prize in Physiology or Medicine went to Crick, Watson and Wilkins. Franklin's name was absent: she had died in 1958 from ovarian cancer, a disease that has hereditary traits. At that time the structure of the model had not been verified: though it was to follow shortly, Nobel rules prohibited posthumous nominations. BMS

IMAGES: ALAMY/SHUTTERSTOCK

Honorary senior lecturer and consultant haematologist **Dr Farooq A Wandroo** and his colleagues ask, what is the clinical significance of a markedly elevated serum ferritin?

RAISED SERUM FERRITIN

High serum ferritin is a hallmark of genetic haemochromatosis and iron loading anaemias like haemoglobinopathies. Serum ferritin is also an acute phase protein and is raised in a number of other conditions, including inflammatory, autoimmune, malignant and liver disorders. In many such conditions, serum ferritin levels may rise up to several thousand/dl. There is paucity of data on correlation of level of serum ferritin and clinical conditions. In this study we analysed various degrees of high serum ferritin levels and correlated with a range of different clinical conditions. We found serum ferritin levels above 5,000mg/dl are mostly associated with malignancy and Still's disease. Clinicians should therefore be alerted when such high levels of serum ferritin are reported.

What is ferritin?

Ferritin is a soluble 450 kDa protein. It is a storage form of iron readily available and is found in high concentration in marrow macrophages, the spleen and the liver. Ferritin protects cells from iron-mediated free radical formation and toxicity due to reaction between free iron and hydrogen peroxide. Ferritin is composed of 24 monomer subunits that consist of either heavy (H) type (21kDa) or light (L) type (19kDa) polypeptide chains encoded by two different ferritin genes. A total of 24 subunits associate to form a hollow spherical particle that can store up to 4,000 iron atoms as FE^{3+} ions. The L chains are found in liver and splenic tissue whereas ferritin in heart and red blood cells is composed of H subunits. Haemosiderin found in Fe-laden macrophages is an insoluble denatured ferritin from which iron is less readily available.

Measurement of serum ferritin and normal ranges

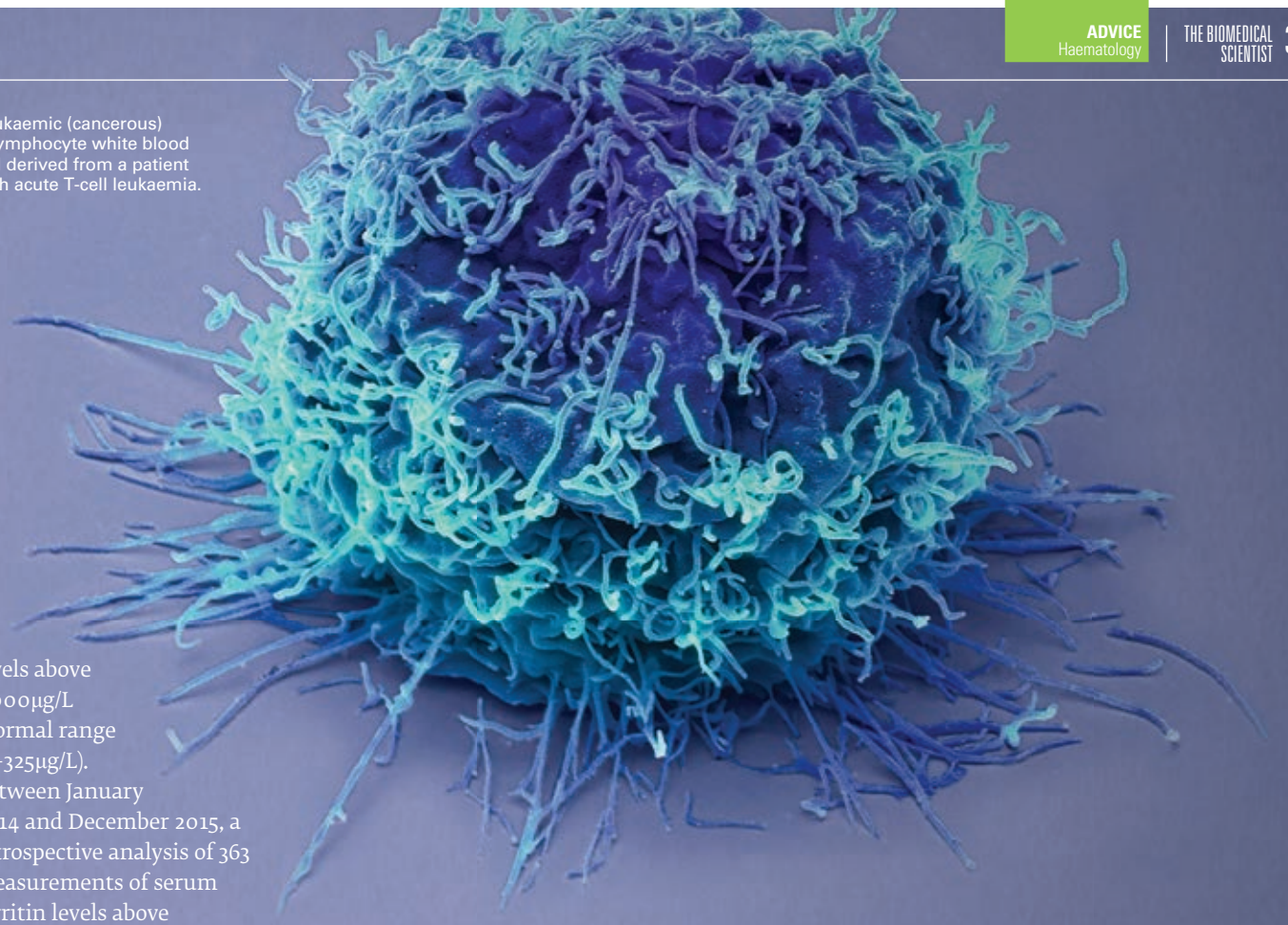
Ferritin is measured using immunoassay, e.g. enzyme linked immunoabsorbant assay (ELISA), immunochemiluminescence assay or immunoturbidimetric assay. The assays are based on using antibodies against liver or splenic ferritin and are calibrated against third international recombinant standard for ferritin (National Institute for Biological Standards and Control code 94/572). Mean serum ferritin varies with age, ethnicity and gender. Mean serum ferritin is higher in blacks and Asians. It is also higher in adult males (60-80µg/L) than adult females (25-30µg/L). With age, serum ferritin levels may rise up to 400µg/L in males and up to 200µg/L in postmenopausal females.

Raised serum ferritin and its significance

Although the most common reason to request a serum ferritin assay is to rule out iron deficiency, many requests are made to diagnose iron overload and genetic haemochromatosis. The common causes of raised ferritin, however, are inflammatory disorders, malignancy, liver disease and alcohol consumption. The levels of serum ferritin in these disorders are variable (1,500-10,000µg/L). The levels can go up to 50,000µg/L in haematological malignancy, haemophagocytosis renal failure and liver disease.

Current study

The aim of this study was to find if any particular level of raised serum ferritin is associated with specific clinical conditions. The researchers were mainly interested in looking at serum ferritin



Leukaemic (cancerous) T-lymphocyte white blood cell derived from a patient with acute T-cell leukaemia.

IMAGE: SCIENCE PHOTO LIBRARY

levels above 5,000µg/L (normal range 25-325µg/L). Between January 2014 and December 2015, a retrospective analysis of 363 measurements of serum ferritin levels above 5,000µg/L was carried out in the laboratory at Sandwell and West Birmingham Hospitals NHS Trust. This corresponded to 99 different patients over a two-year period. Clinical case notes and electronic records were then searched for 85 of the 99 patients and correlated with serum ferritin results. The most common cause of raised serum ferritin level above 5,000µg/L was transfusion-dependent anaemias (41%), then liver disease (17%), unexplained (15%), malignancy (13%), sepsis (08%), haemophagocytosis (3%), rheumatological conditions (2%) and haemochromatosis (1%) cases. Haematological malignancy and haemophagocytic syndrome were the only two conditions seen to be associated with median serum ferritin levels above 10,000ng/mL with some cases having levels up to 40,000ng/mL. C-reactive protein (CRP) tended to be higher in conditions with higher serum ferritin levels, but white cell count and serum ALT level did not show any correlation. Serum albumin, however, tended to be lower in all clinical conditions, with markedly raised serum ferritin suggesting some hepatic synthetic defect. This is an important observation and helped the researchers to guide clinicians in investigating patients for such underlying disorders.

The findings are consistent with a number of previous observations. In 2007, Uppal *et al* described serum ferritin levels in a series of patients with adult onset Still's disease (characterised by fever, rash and arthritis), the majority of whom had ferritin levels five times above normal and some reaching as high as 50,000µg/L. In haemophagocytic lymphohistiocytosis (characterised by pancytopenia, hypertriglyceridemia, hyperferritinemia and multiorgan failure) serum ferritin levels are frequently above 10,000µg/L. In a study on 800 adults in three large US hospitals, Schram *et al* (2015) showed that markedly raised serum ferritin levels (above 10,000 µg/L, small proportion had levels above 50,000µg/L) was associated with a variety of disorders such as renal failure (65%), liver disease (54%), infection (46%), haematological malignancy (32%), rheumatological conditions (18%) and haemophagocytic lymphohistiocytosis (17%).

The message for clinicians

Raised serum ferritin levels are associated with multiple aetiologies, such as iron loading conditions such as primary (genetic) and secondary haemochromatosis due to thalassemic syndromes, but also due to non-iron loading conditions such as inflammatory, renal and liver disorders as well as malignancies. Serum transferrin saturation helps to differentiate between iron loading and non-iron loading conditions (transferrin saturations are high in the former disorders and normal in the latter).

Both this study and the published literature suggest that in cases of raised serum ferritin with normal transferrin saturations we should consider inflammatory disorders, renal and liver disease and malignancy. In situations with markedly raised serum ferritin levels (above 10,000µg/L) clinicians should specifically consider causes such as haematological malignancy, Still's disease, and haemophagocytic lymphohistiocytosis. The authors also direct readers to a recent review in the *British Journal of Haematology* by Cullis *et al* (2018) on investigations and management of a raised serum ferritin. BMS

Dr Farooq A Wandroo works in the Department of Haematology at the Sandwell & West Birmingham Hospitals NHS Trust, as do co-authors **Francesca Lenforte** and **Sukhjinder Marwah**. **Ifrah Farooq** is from the Medical School, University College London.

T LEVELS: TECHNICAL EDUCATION FOR THE FUTURE

Pathology Services Manager **Sue Alexander** introduces a new qualification and outlines its development.

A little over a year ago, I answered an advertisement for scientists with an interest in education and training to join a panel working with the Department for Education (DfE) on the development of a new national qualification.

I was successful and joined a panel of around 10 scientists from different backgrounds plus a few science education providers. We are supported by a wonderful link person and an education advisor and have a great panel chair. We meet monthly to work first on the outline ideas for the qualifications and more recently a much deeper development of the whole programme.

The group has gelled very well and there is a true spirit of collaboration, appreciation of what everyone brings and robust discussions. We are very pleased that we are one of the only groups working on T levels that has met all its targets for time and meeting the requirements of the department. It's exciting to be working on a programme to reformat national technical education.

What are T levels?

They are a new technical, A level standard qualification aiming "to prepare students for entry into skilled employment (including higher-level apprenticeships), either immediately or after higher levels of technical education (L4+)," says the DfE. "T Levels and apprenticeships are two options within the same technical education system, and both are based on the same occupational standards, developed by employers as part of Institute for Apprenticeships." These quotes from the official DfE slides show where T levels sit. They are basically a vocational alternative to the academic A level, which in many cases is used as preparation for university. Both qualifications, however, will have equivalence to allow entry to university via either route if desired. The T level also takes two years, but rather than being fully classroom-based the programmes will be delivered over two years by a further education (FE) provider (80% in college and 20% in a relevant work setting). The courses will have a workplace element as part of the overall structure of the course as opposed to apprenticeships which have an 80% work-based/20% college element.

Technical education

T Levels are part of a comprehensive reform of technical education, which currently has a bewildering 15 pathways, alongside apprenticeships and the National Retraining Scheme. They are planned to be part of a long-term solution to ensure that employers get the skilled workers they need for the future. Rather than adding new qualifications to the system, the aim is to simplify qualifications.

T levels are designed with reference to the world's best technical education systems, with much longer hours than other qualifications, a meaningful industrial placement, and the inclusion of English, maths and digital studies. As employers, we are fully involved in the development of T Levels setting out the knowledge, skills and behaviours required for each occupational area.

CONSULT AND ENGAGE

Phase 1: Increasing audience insight, developing our branding strategy, delivering direct content to parents, young people, employers and FE providers, 2018-2019.

Phase 2: Supporting launch and roll-out in the early adopter areas through advertising/social media channels, ramping up each year, 2019- 2021.

Phase 3: Supporting launch and roll-out in the early adopter areas through advertising/social media channels, ramping up each year, 2021 onwards.

The study period is around 1,800 hours over the two-year course. The behaviours are of real importance to us as a group as that is a significant part of preparing someone for the workplace. The placement will take between 45 and 60 days to give a real flavour of the workplace and what it is like to work. There will also be a "substantial" project requiring to be written up and presented to demonstrate communication skills.

Once the outline content has been developed, it goes to the Institute for Apprenticeships for final approval. The next step is to procure for awarding organisations to turn the content into a qualification, which can be assessed. FE providers will then finalise the curriculum.

The outline content for the first three T Levels, which will be delivered in September 2020, has been finalised and included in the Invitation to Tender to find an awarding organisation, published on 3 September this year. Overall, there are 25 T level panels in place, the full set required, with 16 working now and the last nine recently announced.

There is a consultation, engagement and communication strategy in place to raise awareness across all relevant areas of the educational world (see box, left).

Funds

The DfE has allocated nearly £60m to education providers through the Capacity and Delivery Fund to help them establish the infrastructure and resources needed to deliver industry placements. Working alongside ESFA, more arrangements are being put in place to ensure more intensive support for those providers who need it. There is also an investment of £5m into the National Apprenticeship Service to expand their current remit to raise awareness and promote industry placements through their employer networks.

There will be "how to" guidance for both providers and employers, based on good practice from the pilots. There has been an industry placement pilot scheme testing different models and approaches to delivering T Level placements in the academic year 2017/18; 21 providers piloted these, which involved over 2,000 students. From these comes the message that "one size doesn't fit all", and models need to vary between route, pathway and employer type. The qualifications will be across a very wide range of subjects – from metrology technicians, laboratory technicians to beauty subjects – hence the need for a diverse delivery model.

This is just the beginning, so look forward to hearing more about the programme at the upcoming IBMS Congress and in the media. IBMS

Sue Alexander is the Principal Biomedical Scientist and Pathology Services Manager at The Royal Marsden NHS Foundation Trust.

HOW TO... PROMOTE BIOMEDICAL SCIENCE

Dan Nimmo, IBMS Communications Manager, reflects on the successes of the past year, highlights some of the plans for 2019 and discusses how members play the biggest part in promoting biomedical science.

One of the key themes of the IBMS's current strategy is to raise the profile of biomedical science. We're pleased with the progress that has been made, but recognise there is much more work for us to do. With your help we're aiming for 2019 to be our busiest and most successful year yet.

Over the past 12 months we have been working with you to promote your work and research, public engagement activities and events, and award nominations and success stories, all the while highlighting the vital role you play in healthcare. You often make this easy for us, winning awards and honours that are featured on TV and radio, and in local and national news – so thanks for all you already do.

We've also reached a wider audience through our social media channels, with followers and engagement increasing month on month. Our largest impact was made through our second annual Biomedical Science Day, with posts using the hashtags #BiomedicalScienceDay and #AtTheHeartOfHealthcare receiving more than 5 million impressions and our short animated video gaining over 200,000 views.

In 2019 we will be releasing a series of animated sample journey videos with accompanying leaflets and posters for the public explaining what happens to their blood, urine and tissue samples; creating engaging and fun activities and resources for children in primary and secondary schools focused on biomedical science and its role in healthcare; and running our 3rd Biomedical Science Day celebrations with more resources that will enable more members to get involved.

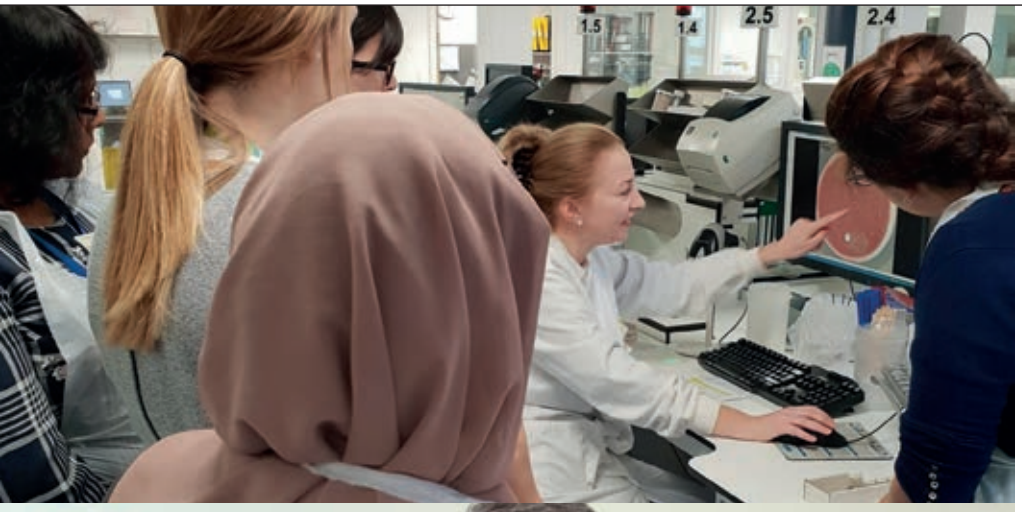
We're sponsoring Biomedical Scientist of the Year at the Advancing Healthcare Awards and the early-career research scientists' poster competition for STEM for Britain, as well as introducing Champion of Biomedical Science awards to our region and branches network (alongside our current awards, bursaries and prizes). Also, we'll continue to reach out to other healthcare organisations and charities to help promote their awareness events and to highlight where biomedical science is involved in the issues at hand.

This year, in order to continue to increase public awareness of the profession, we're asking you to help and get involved. There are lots of ways of supporting us: engaging with our campaigns on social media, taking part in public engagement, keeping us informed of news stories and events, or contacting the media to generate interest in biomedical science.

Share and engage online

Our social media accounts – Twitter, Facebook, LinkedIn, Instagram and YouTube – continue to grow. If you are not following us already, please give us a follow and help us to promote our posts by commenting, liking and sharing. Twice a day, we create positive and engaging content, highlight relevant news stories and IBMS comment, and promote the profession and our members' news.

We also hold fun monthly competitions for people to get involved in and, on the first Wednesday of every month, we run



"Our largest impact was made through Biomedical Science Day, with posts receiving more than 5 million impressions"

#IBMSChat on Twitter to encourage and guide other members, trainees and students with any questions they have about the profession or our services. We are very grateful to all our members who take part in the conversation on Twitter or share fun pictures through the competitions.

Share your news and events

Every day, the IBMS communications team is looking for the newest and most relevant biomedical science content to promote to our members, while also generating stories and press releases to gain media and public attention for the profession.

The part our members play in creating our news stories is vital. If you have a story to tell, are involved in an important piece of work or research, have taken part in a public engagement event, won an award or seen a news story in the media that relates to biomedical science and you have an opinion or comment to make, we want to hear from you. Email us at communications@ibms.org and we'll get back to you to create a news story or press release. In most cases, we'll ask you to fill in our short news pro forma, asking for a few pieces of information, a photo and quotes, and then we do the rest. Before publication you will be sent the write-up for your sign-off and agreement.

Work with us

We also work with journalists from local and national publications to create news stories. These tend to be based on healthcare awareness events but can also be reactive articles aimed at setting the record straight, or telling the story of how biomedical science is involved in healthcare. In these instances, we rely on our members' expertise and knowledge for comment. Members are chosen by their specialism and area of work and we only contact those who have given us an indication they are happy to speak to us.

When we ask members to provide comment or speak to a journalist, we ask that they speak as an IBMS representative and not as an employee of their trust or hospital. Your place of employment will not be mentioned unless you ask for it to be included. Once agreed, we pass on your details to a journalist to contact you at a convenient time. News changes fast so we have to react as quickly as possible to ensure our message is heard. If you are unable to help with a comment, let us know as soon as you can so that we can find another member who can.

Promote the profession

We are always seeking opportunities to promote the profession and have various methods for checking the news, nationally and locally, but we sometimes rely on members to bring stories and issues to our attention. It also helps us when members contact the media themselves when they see the opportunity. Remember that news outlets want "stories" not "events" – we can help you think of a way to turn your press release into a story if you need us to: communications@ibms.org IBMS

MY IBMS NEWS

IBMS COUNCIL ELECTIONS

YOUR CHANCE TO SHAPE THE FUTURE OF THE IBMS

The IBMS prides itself on being a professional body that is run by its members for its members. The IBMS Council is elected by Institute members to make key decisions, provide leadership for the profession and effective and transparent governance, as well as be a compelling advocate on their behalf.

The Institute is looking for IBMS corporate members to stand for election to Council; members who will use their professional knowledge, leadership skills and experience to set the strategic direction of the IBMS, shaping the professional body's future and ensuring it continues to meet its members' needs.

Becoming an IBMS Council member offers an excellent opportunity to make a significant contribution to the future direction of the Institute and the profession and to build your experience, broaden your skills and networks.

Two National and five Regional (Irish Region, Scotland, South West, West Midlands, Yorkshire) Council members are to be elected in 2019.

→ You can find out more about becoming an IBMS Council member, and access the online nomination form on the IBMS website at ibms.org/councilelections

INTERNATIONAL QUALITY AWARDS

IBMS members win Team of the Year

The laboratory team at Hull and East Yorkshire Hospitals NHS Trust was awarded Quality Team of the Year at the 2018 International Quality Awards.

Three biomedical scientists make up part of this outstanding team: IBMS members Amy Duckles, Kay Anderson and Ernesto Jr Quider.

The International Quality Awards is a global competition that celebrates excellence in various sectors promoting quality systems across the globe.

Judged via a rigorous evidence-based process, the awards acknowledge the contribution of quality systems in enhancing the reputation of organisations around the world.

The judging panel stated: "The pathology team won for the rigorous quality structures in place across their laboratories. The team provides a high level of clinical and scientific services by working within a culture of transparency and a shared drive for continuous improvement."

IBMS COUNCIL

PRESIDENT ELECT

Allan Wilson has been voted by IBMS Council members as the new IBMS President Elect.

He will take office from 1 January 2019, providing support for Allison Geddis in her final year as President.

Allan is the lead biomedical scientist for cellular pathology in NHS Lanarkshire.

BIOMEDICAL SCIENTIST OF THE YEAR

AHA AWARDS DEADLINE

There are just a few days to go until nominations close for the Advancing Healthcare Awards.

The IBMS is sponsoring the Biomedical Scientist of the Year award and the deadline for submissions is 14 January.

To apply for this award, nominees must hold HCPC registration and be a practising biomedical scientist based in the UK. Successful candidates will be contacted in January and a celebration lunch and awards ceremony will be held Friday 12 April.

→ ahpandhsawards.co.uk

PRESIDENT'S PRIZES
Continuing the coverage of winners from around the country

PRESIDENT'S PRIZE WINNERS

These prizes are awarded to students graduating from IBMS-accredited BSc (Hons) programmes who have achieved academic distinction.

A UNIVERSITY'S FIRST COHORT
YORK ST JOHN UNIVERSITY

November 2018 saw the first graduation from the newly-established biomedical science programme at York St John University. This first cohort of students joined the university in 2015 and completed the three-year version of the programme, with fellow students taking the four-year (with placement) route to complete the IBMS training portfolio and allow them to register with the HCPC after graduation in 2019.

The biomedical science degree is the first biology-based science programme at York St John University and the academic and technical team have created the laboratory space, designed the programme and organised various placement routes through the course to broaden the portfolio of the university and enhance the employability of the students.

The first cohort have achieved excellent results, from 12 students they were awarded seven first class, four 2.1s and one 2.2 honours degrees.

The biomedical science programme also received outstanding National Student Survey (NSS) results with 14 of the 27 questions asked, receiving a 100% satisfaction score and no question about the programme receiving a score of less than 88% satisfaction.

Several students have gone on to secure postgraduate study in MSc or Physician Associate courses or found employment in NHS and industry laboratories locally. The highest achieving student was Sophie Dods, who graduated with first class honours and was awarded the President's Prize for York St John University. She is pictured with Deborah Cammish, Head Biomedical Scientist, Microbiology, York Hospital NHS Foundation Trust, who presented the prize in York Minster before the graduation ceremony. Sophie's identical twin sister Chloe also graduated with first class honours.

MANCHESTER METROPOLITAN UNIVERSITY

Azziza Ziad Zaabalawi received the IBMS President's Prize following her graduation with a first class BSc (Hons) Biomedical Science degree from Manchester Metropolitan University. The highlight of her studies was her final year project in the area of hypertension, entitled "Investigating the influence of Resveratrol on vasodilator function after tension elevation in murine aortic vessel". This has given Azziza a passion for cardiovascular research and she intends to

PRESIDENT'S PRIZES

Continuing the coverage of winners from around the country

pursue a PhD at Manchester Metropolitan University, continuing her training within this very interesting and beneficial area of research. Azziza received the prize from IBMS North West Council Member David Eccleston.

UNIVERSITY OF KENT

Keith Sai Kit Leung was awarded the IBMS President's Prize at the University of Kent. The accredited degree helped him to gain a supplementary medical professional qualification in his home country, Hong Kong, as a medical laboratory technologist. While enrolled at the University of Kent, Keith completed a number of summer placements which enabled him to conduct biomedical research in various specialities such as obstetrics and gynaecology, pathology and cardiology. All these research experiences has inspired him to become a clinician-scientist in the future. Currently, Keith is a first-year medical student at Aston Medical School, and hopes to get accepted into the academic foundation programme.

UNIVERSITY OF THE WEST OF ENGLAND

Biomedical science is a second career for Maja Orna, the winner of the IBMS President's Prize at the University of the West of England. After practising as a midwife for five years, she knew it wasn't for her and arranged a day visit in a microbiology laboratory at Southmead Hospital, Bristol. Maja immediately felt at home and decided there and then on the big career change. She applied for the University of the West of England BSc (Hons) Healthcare Science course. Maja had the opportunity to undertake her placement in the very same lab at Southmead Hospital that had inspired her.

Her hard work and newly-found passion for microbiology resulted in a first-class degree and two prizes (IBMS President's Prize and the Microbiology Society Prize in her second year). Maja's commitment and enthusiasm throughout her placement was rewarded when she successfully secured a biomedical scientist post six months before graduating and, quite remarkably, in the very same laboratory she fell in love with microbiology. She is pictured with Michael Palmer, from the IBMS Southwest Region.

SHEFFIELD HALLAM UNIVERSITY

Katie Hudson was awarded the IBMS President's Prize by Margaret Hunt, Chair of the IBMS Sheffield Branch at the Sheffield Hallam University awards ceremony. Katie graduated with a BSc (Hons) Biomedical Science degree which included a placement year working with the Sheffield Myeloma Research Team at the University of Sheffield. Her project during her placement was the "Development of an in vivo plateau phase model of multiple myeloma", this work was carried through to her final year project where she looked at the molecular changes after bone anabolic and chemotherapy treatment in a mouse model of myeloma bone disease. Katie started a PhD at Sheffield Hallam Univeristy in October 2018. Her research is elucidating the intrinsic role of immune biomarkers in human cancers. Following her PhD, Katie would like to pursue a career in academia. Katie is pictured with Professor Susan Laird, Head of Department of Biosciences and Chemistry and Margaret Hunt, Chair of the Sheffield Branch.

UNIVERSITY OF WESTMINSTER

Monica Desir was awarded the IBMS President's Prize at a University of Westminster ceremony earlier in the year. Monica was honoured that her hard work was recognised and following graduation, she aims to continue her education with postgraduate study in microbiology and immunology. Monica said that she "still aspires to become a biomedical scientist, as they play a vital role in healthcare." Sue Alexander from the London Region awarded the prize on behalf of the President.

EVENTS AND TRAINING COURSES

A wide range of training courses, CPD and local events and activities is listed below. Members are advised to contact organisers for further information. A full list is available on the IBMS website.

DATE	TITLE	VENUE CONTACT
January		
15 Jan	**Antimicrobial Chemotherapy Conference 2019**	London I ecarruthers@bsac.org.uk
15-17 Jan	**BMS/cytoscreener update course in gynaecological cytology**	Harrow I LNWH-tr.lrctcbooking@nhs.net
21-25 Jan	**Follow-up course in gynaecological cytology**	Harrow I LNWH-tr.lrctcbooking@nhs.net
February		
4 Feb-1 Mar	**Introductory course in gynaecological cytology**	Harrow I LNWH-tr.lrctcbooking@nhs.net
13 Feb	**UK NEQAS Cellular Pathology Technique tissue preparation techniques workshop**	Gateshead I chantell.hodgson@nhs.net
14 Feb	**UK NEQAS Cellular Pathology Technique tissue morphology and recognition workshop**	Gateshead I chantell.hodgson@nhs.net
March		
5 Mar	**POCT governance and quality event**	Reading I info@thornhillhealthcareevents.co.uk
6-7 Mar	**Beginners immunohistochemistry course**	Sheffield I l.baxter@sheffield.ac.uk
12 Mar	**UK NEQAS Cellular Pathology Technique Mohs workshop**	Gateshead I chantell.hodgson@nhs.net
13 Mar	**UK NEQAS Cellular Pathology Technique BMT workshop**	Gateshead I chantell.hodgson@nhs.net
14 Mar	**UK NEQAS Cellular Pathology Technique renal workshop**	Gateshead I chantell.hodgson@nhs.net
19-21 Mar	**BMS/cytoscreener update course in gynaecological cytology**	Harrow I LNWH-tr.lrctcbooking@nhs.net
21-22 Mar	**2019 Spring Conference: Global views, local problems: Innovative solutions to AMR and infection challenges**	Birmingham I ecarruthers@bsac.org.uk
April		
8-12 Apr	**Pre-exam course in gynaecological cytology**	Harrow I LNWH-tr.lrctcbooking@nhs.net
8-12 Apr	**BMS/cytoscreener update course in gynaecological cytology**	Harrow I LNWH-tr.lrctcbooking@nhs.net
10 Apr	**UK NEQAS Cellular Pathology Technique immunocytochemistry staining beginners workshop**	Newcastle-upon-Tyne I chantell.hodgson@nhs.net
11 Apr	**UK NEQAS Cellular Pathology Technique immunocytochemistry intermediate/trouble shooting workshop**	Newcastle-upon-Tyne I chantell.hodgson@nhs.net
13 Apr	**Biomed online learning courses 2019**	Online I c.e.ronan@gre.ac.uk
17 Apr	**Medical laboratory assistant - introductory course**	Harrow I LNWH-tr.lrctcbooking@nhs.net
May		
8 May	**UK NEQAS Cellular Pathology Technique non-gynae cytology beginners/refresher workshop**	Gateshead I chantell.hodgson@nhs.net
9 May	**UK NEQAS Cellular Pathology Technique non-gynae cytology intermediate workshop**	Gateshead I chantell.hodgson@nhs.net

JOURNAL-BASED LEARNING EXERCISES

IBMS CPD

Each article's contents should be read, researched and understood, and you should then come to a decision on each question. The pass mark is 17 out of 20 questions answered correctly. JBL exercises may be completed at any time until the published deadline date. Please select your choice of correct answers and complete the exercises online at: **www.ibms.org/cpd/jbl**

DEADLINE WEDNESDAY 3 APRIL 2019

	Biomarkers of acute kidney injury: the pathway from discovery to clinical adoption. Kashani K, Cheungpasitporn W, Ronco C. *Clin Chem Lab Med* 2017; **55** (8): 1074–89. Assessment No: 010319		**Drucker's Top Tips to Successful Leadership** (www.managementmattersnetwork.com/strategic-leadership/columns/druckers-top-tips-to-successful-leadership), AND **Management by Objectives** (www.toolshero.com/management/management-by-objectives-drucker). Assessment No: 010919
01	There are no biomarkers that are completely specific for acute kidney injury (AKI).	01	Leadership involves a manipulative element.
02	Kidney injury molecule 1 (KIM-1) has been approved by the US Food and Drug Administration as an AKI biomarker for pre-clinical drug development.	02	Successful leaders achieve via the help and support of others.
03	[TIMP-2]x[IGFBP7] may be elevated in diabetic patients.	03	Having great deals in place for staff ensures support for your leadership.
04	Neutrophil gelatinase-associated lipocalin (NGAL), KIM-1 and interleukin (IL)-18 are elevated in patients with chronic kidney disease (CKD) as well as those with AKI.	04	You must be in a senior position to become a leader.
05	NGAL is only upregulated after ischaemic AKI.	05	Leadership helps people perform to their top potential.
06	Serum creatinine is a delayed and insensitive biomarker of changes in kidney function.	06	Inspiring people's minds overcomes tough conditions and provides strong leadership wins.
07	KIM-1 may be suitable to distinguish patients with acute tubular necrosis.	07	Leadership is the same, no matter what field of work.
08	IL-18 is a mediator of AKI.	08	Leadership is absolutely combined with management.
09	Liver-type fatty acid-binding protein (L-FABP) can be used in conjunction with NGAL to improve the detection of AKI.	09	Deciding to become a leader is a crucial, significant step towards leadership.
10	Urine and plasma levels of microRNA miR-21 can predict AKI progression.	10	Leadership can make the difference between success and failure in an operation.
11	L-FABP expression occurs after increases in serum creatinine.	11	Management by objectives seeks to balance personal and organisational objectives.
12	Timely identification of AKI can improve AKI outcomes.	12	There is no need to reward the achievement of objectives.
13	[TIMP-2]x[IGFBP7] is a good biomarker in patients at low risk of AKI.	13	Objectives will be set for employees, not with them.
14	A raised calprotectin will only be found in patients with AKI.	14	Drucker favoured the use of SMART goals.
15	"Acute kidney stress" is synonymous with AKI.	15	Without clear performance indicators, staff cannot be managed well against objectives.
16	NGAL can be detected as early as one hour after tubular injury.	16	Management by objectives is suitable for executives, directors and senior staff only.
17	NGAL production is age- and gender-related.	17	Coaching and pathways are necessary to support employees.
18	Serum creatinine can differentiate between structural and functional causes of AKI.	18	Management by objectives is intended to be motivational.
19	NGAL is only expressed in the kidney.	19	Objectives must be clearly quantitative only.
20	NGAL is an early marker of structural renal tubular damage.	20	There must be an identified organisational vision and aims to base management by objectives on.

REFLECTIVE LEARNING

01	Outline the current strategy for detecting AKI in your hospital.	01	Consider your own leadership impact and whether you agree with Peter Drucker's summation of the key points. If not, why not?
02	Which (if any) of the biomarkers reviewed in this paper would you recommend that your laboratory offers for routine use?	02	Is management by objectives suitable for medical laboratory staff of all grades, or indeed any grades at all?

HERE TO HELP

REFLECTING ON SUCCESS

As we leave the old year and enter the new **Jocelyn Pryce**, IBMS Deputy Executive Head of Education, looks back on some of the Education Team successes of 2018.

We hosted a number of update and training days for verifiers and examiners both at Coldbath Square and nationally. Over 160 people attended the days here at HQ, every session was fully booked soon after the dates were released and we even added an extra day to ensure that we were able to reach as many people as we could. We already have more than 40 people on the waiting list for next year's events and we will be releasing the dates for these very soon.

As a result of these events, we have recruited 68 new verifiers and 52 new examiners and have updated experienced verifiers and examiners so that they are able to run "approved" IBMS training events in their local areas. This brings our total number of verifiers to 662 and our examiners to 502. As only half are active, recruitment this year was crucial to provide additional support for those who regularly volunteer and should result in a faster response to our calls for volunteers for verifications and examinations.

Feedback from the new-format sessions held at Coldbath Square has been positive, with an overall satisfaction score of 88%.

In addition to the above sessions, there were several CPD Officer Update days and two HSD candidate preparation days. CPD Officers discussed the evolution of their roles and looked at ways in which they can support their colleagues undertaking CPD. The HSD events covered portfolio production, exam techniques, expectations when studying for the HSD, and subject-specific sessions on past exam questions. Again, the feedback was very positive and each event was highly successful.

The number of registration portfolios issued increased by 13% between 2017 and 2018 to reach almost 900 and, as a result of a process review, the issuing turnaround time was reduced from three weeks in 2017 to a same-day service in 2018. Almost one thousand certificates of competence were issued in 2018, a rise of 9% on 2017.

The number of specialist portfolios issued has risen by 10% in 2018 (740+) from 2017 and, as above, the portfolio issuing turnaround reduced from four and a half weeks to a same day service.

The processing and screening of all applications for CPD events is also now a same-day service, allowing a faster acknowledgment of external events and sessions for members.

We continuously review internal processes to ensure that service users and members receive a timely and efficient service and although we recognise that we don't always get it right first time, we want to assure you that we are committed to improving. There has been a great deal of very positive feedback on the reduction in turnaround times and we continue to engage with our users and members to look at ways to further improve the services we offer. We'd like to take this opportunity to wish you all a happy and healthy 2019.

HEALTH SERVICES LABORATORIES

BIOMEDICAL SCIENTIST OPEN DAY - 1ST FEBRUARY 2019

HSL are delighted to open their doors to newly-qualified and experienced Biomedical Scientists for an open day event at our state of the art laboratories in Central London.

There will be two sessions, one morning and one afternoon, which will comprise of a tour of our world class facilities across all disciplines, including Europe's largest automated Blood Sciences and Infection Sciences laboratories, as well as the chance to learn about HSL's training and development opportunities. Heads of department will also be on hand to answer your questions. Applicants must be HCPC registered and hold an IBMS accredited degree. To attend this event, you must register via the email address below.

HSL is a partnership with two of the leading teaching hospitals in the United Kingdom - the University College London Hospital and the Royal Free Hospital. Research, innovation and staff progression is at the heart of everything we do - visit us at the Halo Building to see this for yourself.

To register your interest in attending or for further information, email:
OpenDay@hslpathology.com

HCA Laboratories: Making huge strides in pathology

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At HCA UK, we're excited to share with you the transformation of our laboratory service. Not only have we invested £3 million in laboratory equipment and laboratory space, but we also have new leadership and a brand new vision.

We're looking for HCPC Registered Biomedical Scientists and experienced Medical Laboratory Assistants to keep our service at the cutting-edge. A range of shift patterns will be available, and you will be expected to participate in the night shift rota to provide a comprehensive blood sciences services to our users.

Our rewards – We offer a competitive salary, a night shift premium and access to flexible benefits.

To find out more, please contact

Zoe Blausten on 020 7034 2512

HCAHealthcare UK
Laboratories

MY LAB

PAEDIATRIC MICROBIOLOGY

Deputy Manager of Microbiology at Great Ormond Street Hospital, **Francis Yongblah**, gives a guided tour of his lab.

Great Ormond Street Hospital (GOSH) is a tertiary specialist paediatric hospital to which patients are referred from all over the world, with significant and very complicated clinical conditions. As a result, in-depth laboratory investigations take place to help diagnose different conditions, disease and infection.

The microbiology laboratory receives approximately 350 to 500 samples a day from within the trust and externally.

As a specialist paediatric hospital, GOSH carries out many specialised services, which include specialist clinics, solid organ and bone marrow transplants and specialist surgery. Most of the work carried out in microbiology is the screening of patients for carriage of significant bacteria, such as methicillin-resistant *Staphylococcus aureus*, carbapenem-resistant Enterobacteriaceae (CRE), extended-spectrum beta-lactamases, gentamicin-resistant Enterobacteriaceae, using chromogenic and selective media.

As well as screening, we look for pathogens and opportunistic organisms, which can be clinically significant. Examples include new detection methods for *Candida auris* and VRE monitoring from enteric specimens.

The diagnostic work carried out is very different to that of a routine district general hospital and we are lucky to have specialist diagnostics techniques, such as 16S PCR and 18S PCR. Many of the diagnostic techniques that are carried out in-house have been validated, as they are appropriate to our patient population.

The microbiology team is extremely patient-focused, despite the great pressures that face the NHS. This is due to the support and the close working relationship with the clinical team and infection control. Working on the same floor means that there is always clear communication and that we are able to work together to benefit the patient.

On a daily basis the consultant microbiologists come into the laboratory to discuss patient cases with laboratory staff and this has a significant impact on raising staff awareness about individual patients and the important role that diagnostic microbiology plays in patient management and treatment. Because the trust looks after a unique group of patients, laboratory staff are familiar with those who are long-term within the hospital and this allows laboratory staff to build a relationship with them. In the past, patients and families have given thanks by sending cards and presents. For the laboratory staff, this gives an amazing feeling, as it is nice to get recognition of the work that we do and for people to realise we go above and beyond.

This year brings new challenges, including implementing a new electronic patient record system, which affects the whole trust, as well as laboratory medicine. This will mean that the laboratory will go completely paperless and will have to adjust to a new system of working. With a constant increase in antimicrobial resistance, we are working hard to research methods to improve detection and are expanding the use of MALDI ToF and using it as part of an algorithm for CRE detection. Finally, we are implementing a new Sepsityper extraction method to improve time to detection and identification for positive blood cultures. BMS

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