THE BIOMEDICAL SCIENTIST

THEBIOMEDICALSCIENTIST.NET

OCTOBER 2020

THE BIG QUESTION

COVID & INFLUENZA

What impact will COVID-19 have on the influenza season?: *p.14*

MEDICAL EPONYMS

ALOYSIUS ALZHEIMER

A look back over the attempts to understand Alzheimer's disease: *p.26*

PANDEMICS

HONG KONG FLU

First-hand reflections on the forgotten sixties pandemic: *p.38*

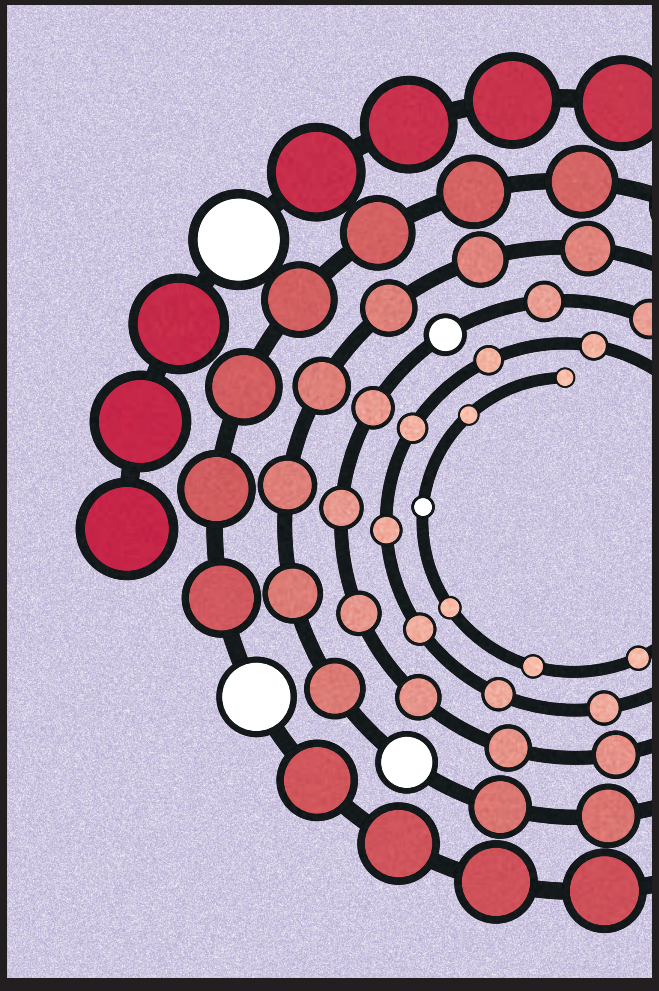
BOILING POINT

Managing workplace pressures in clinical laboratories

IBMS Institute of Biomedical Science

HEALTHY DATA MEANS FASTER DEVELOPMENT AND BETTER DECISIONS.

InterSystems®
Creative data technology



InterSystems makes your data healthy so it's accessible, useable, and ready for action.

HealthyData.com

CONTENTS

IBMS.ORG

OCTOBER 2020

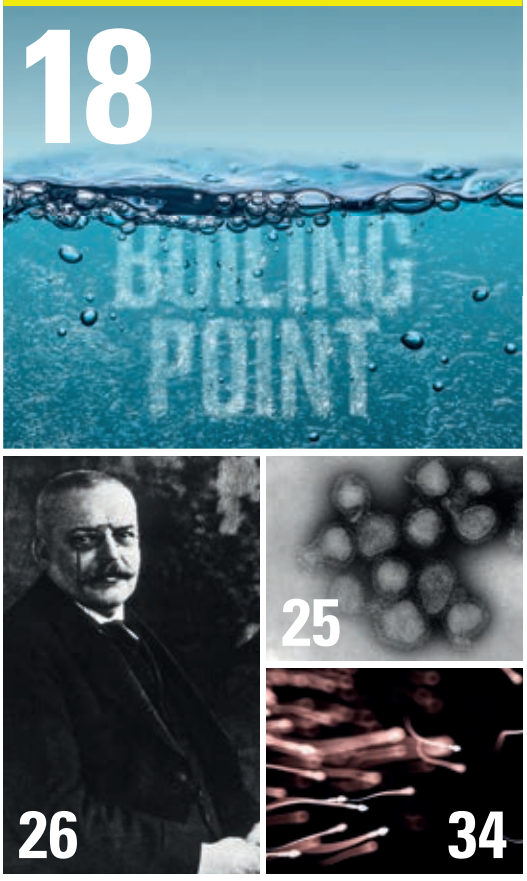
EDITORIAL

NEWS

OPINION

SCIENCE

COVER FEATURE



ADVICE

MY IBMS

MY LAB

COVER IMAGES: SHUTTERSTOCK

EDITOR
Rob Dabrowski

SENIOR DESIGNER
Gary Hill

PICTURE EDITOR
Akin Falope

PUBLISHING DIRECTOR
Aaron Nicholls

PRODUCTION
Rachel Young

DISPLAY ADVERTISING
+44 (0)20 7880 7556
biomedical@redactive.co.uk

redactive

PUBLISHED BY
Redactive Publishing Ltd
Level 5, 78 Chamber Street, London E1 8BL
+44 (0)20 7880 6200 redactive.co.uk

Recycle your magazine's plastic wrap – check your local LDPE facilities to find out how.

4 LDPE

RECRUITMENT ADVERTISING
+44 (0)20 7880 7665
biomedicaljobs@redactive.co.uk

ISSN 1352-7673

PRINTED BY
Warners Midlands plc
Bourne, Lincolnshire PE10 9PH

SUBSCRIPTIONS
Subscriptions are available by calling 01580 883844

Innovations in COVID-19 testing

VitaPCR

Rapid COVID-19 PCR for Point of Care

Rapid 20 minute Real Time PCR

eCL8000

Rapid COVID-19 IgG/IgM Antibody Tests

Bench Top Laboratory analyser

Wide assay menu, including IL-6, Procalcitonin

KH Medical Radi Detection Kit

100% Sensitivity and Specificity found in study by FIND on behalf of the WHO

24 Test Magnetic Bead Extraction and PCR Plate setup Platform

24 Test Magnetic Bead Extraction and PCR Amplification Platform

Community Antibody Testing Healgen/ Orient Gene Lateral Flow Antibody Cassettes

Second generation cassettes

Demonstrated 100% specificity and 100% sensitivity in the study completed by the WHO Virus Reference Laboratory

Menarini Diagnostics
Wharfedale Road, Winnersh, Wokingham, Berkshire, RG41 5RA.
Telephone: 0118 944 4100 | Fax: 0118 944 4111
Email: enquiries@menarinidiag.co.uk

A.MENARINI diagnostics

SHALL WE ZOOM?

Sarah May, Deputy Chief Executive of the IBMS, on the era of virtual meetings and bookshelf snobbery.

At some point, in the dim and distant past, a Zoom was a brand of stripy ice lolly; fashionable in its time, visually pleasing but highly synthetic. Today a Zoom is something totally different, but I think the same description probably applies equally well.

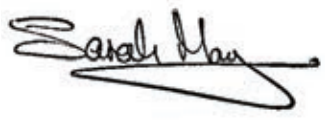
In the past six months my working life, along with that of millions of others, has changed drastically and at its heart are Zoom meetings. At first I wrestled with where to sit and what feature to have in my background; would my wallpaper be a source of hilarity? Would I appear to have a light fitting sprouting from my head? Then I started to embrace the concept and wasn't happy unless there was a Zoom meeting somewhere in the very near future, but now I feel like a child who has consumed one too many Zooms. Just a teensy bit tired of them.

The problem is it's all too easy to say "shall we have a Zoom?" And hey presto – there's yet another virtual meeting in the diary. I'm so busy with Zooms I'm now falling behind on answering my emails – I would never have received this much correspondence if it had to be committed to paper and put in an envelope.

Before I'm deluged with accusations of being a Luddite, I must stress that I love the ease with which we can communicate and "meet" as a group without the hassle and expense of travel. But like emails, which are an amazing tool of ease and convenience, virtual meeting technology can also create its own problems and become a voracious consumer of the time we thought we had liberated.

Virtual meetings are changing how we work at the Institute; there are undoubted savings to be made in both time and money by cutting down on face-to-face meetings. Part of our good corporate governance is looking at ways to make us more efficient and effective for our members, while enabling our Council, advisors, examiners and representatives to combine their voluntary professional work with their paid employment. Our future support from our many volunteers in their various capacities depends on the judicious use of technology whenever possible and wherever appropriate.

To finish on a lighter note, I am sure I am not alone in my fascination for the growing culture of bookshelf snobbery; my attention is repeatedly drawn during television interviews to the contents of the bookshelf behind the interviewee. Well, I'm off to prepare for my next Zoom meeting and I'm debating over whether to position myself strategically with a copy of *Muir's Textbook of Pathology* or see who spots my dog-eared copy of *Lady Chatterley's Lover*.



Sarah May
Deputy Chief Executive

IBMS

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

INSTITUTE OF BIOMEDICAL SCIENCE
12 Coldbath Square
London, EC1R 5HL
United Kingdom
+44 (0)20 7713 0214
+44 (0)20 7837 9658
Email: mail@ibms.org
Web: www.ibms.org

PRESIDENT
Allan Wilson CSci FIBMS

CHIEF EXECUTIVE
Jill Rodney

DEPUTY CHIEF EXECUTIVE
Sarah May CSci FIBMS

EXECUTIVE HEAD OF EDUCATION
Alan Wainwright CSci FIBMS

EXECUTIVE HEAD OF MARKETING AND MEMBERSHIP
Lynda Rigby

HEAD OF COMMUNICATIONS
Dan Nimmo

EDUCATION AND TRAINING
education@ibms.org

EXAMINATIONS
examinations@ibms.org

MEMBERSHIP
mc@ibms.org

CHARTERED SCIENTIST
chartered@ibms.org

FOLLOW THE INSTITUTE

Join us on **facebook.com/biomedicalscience**

Follow us on Twitter **@IBMScience**

Find us on **LinkedIn**

FUJIFILM
Value from Innovation

What's your strategy for combating this year's winter season?

The new **IMMUNO AG2** is a rapid diagnostic system for influenza, RSV and adenovirus that can help you fight back.

NEW

Densitometry analyzer

DRI-CHEM IMMUNO AG2

A Complete NPT Solution

- Combining Dry Chemistry and Haematology

DRI-CHEM NX700

Boule

DRI-CHEM NX10N

Fecal Occult Blood Analyzer
QUICK RUN (II)

FUJI DRI-CHEM
NX500
Automated Clinical Chemistry Analyzer

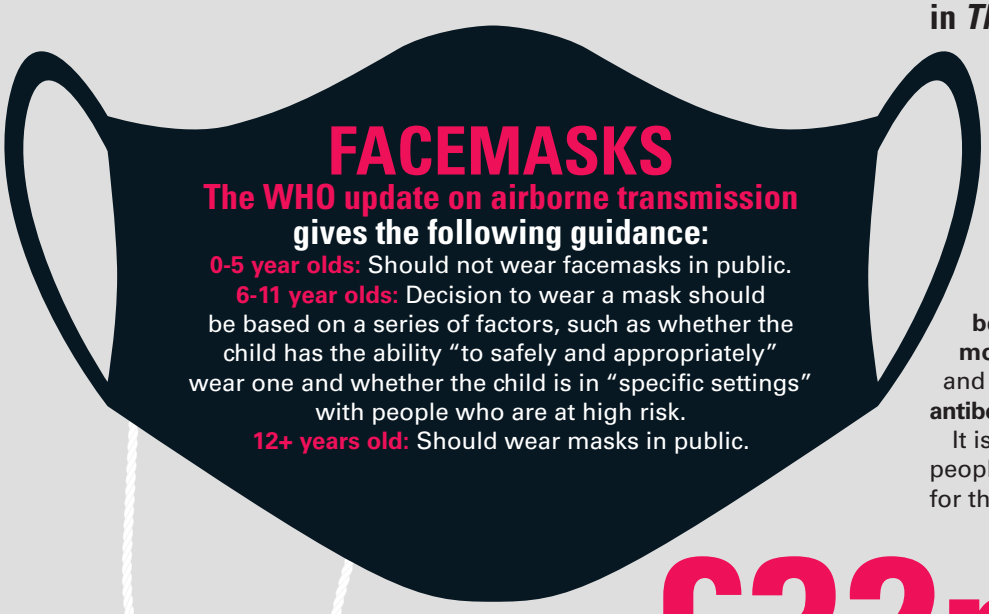
ivd_uk@fujifilm.com • www.fujifilmivd.com • 01234 326780

SCIENCE NEWS IN NUMBERS

ANTIBODIES IN THREE WEEKS

Two trials of the vaccine named Sputnik-V have been reported in *The Lancet*. Each involved 38 healthy volunteers given a dose of the vaccine and then a booster vaccine.

The participants, **aged between 18 and 60**, were **monitored for 42 days** and all of them **developed antibodies within three weeks**. It is reported that 3000 people have been recruited for the next phase of trials.



FACEMASKS

The WHO update on airborne transmission gives the following guidance:

0-5 year olds: Should not wear facemasks in public.

6-11 year olds: Decision to wear a mask should be based on a series of factors, such as whether the child has the ability "to safely and appropriately" wear one and whether the child is in "specific settings" with people who are at high risk.

12+ years old: Should wear masks in public.

£32m

A total of £32m in investment has been pledged as part of plans to increase overall UK R&D spending for futuristic healthcare projects to £22bn a year by 2024-25.

Science Minister Amanda Solloway said **six new projects would be backed**, each aimed at using technology to transform care and treatment in the NHS by 2050.

DISPOSABLE GOWNS

5 million

The Department of Health and Social Care said, since the pandemic started, the government has ordered:

- **Five million disposable gowns**
- **from seven UK manufacturers.**

It added that it was on course to meet its target of **buying 20% of PPE from UK manufacturers** by the end of the year.

4,204,613

India now has the second largest number of confirmed COVID-19 cases in the world.

In early September, it recorded **4,204,613 cases – overtaking Brazil** after recording more than **90,000 new cases in 24 hours**.

In early September, India had the largest daily rises in confirmed cases with more than **75,000 new infections confirmed per day**.

The only country with more cases is **the US**.

SCIENCE NEWS

COVID-19

Patient zero discovered?

A person on a poorly ventilated Chinese bus infected nearly two dozen other passengers with coronavirus and may be patient zero, it is claimed.

The new research probes the threat of airborne infection by taking a close look at passengers who made a 50-minute trip to a Buddhist event in the eastern Chinese city of Ningbo aboard two buses in January.

The scientists believe a passenger on the bus was likely patient zero because the person had been in contact with people from Wuhan.

The scientists managed to map out where the other passengers sat, and test them for the virus, with 23 of 68 passengers subsequently confirmed as infected.

What is notable is that the sickness infected people in the front and back of the bus, outside the perimeter of 1–2 metres that authorities and experts say infectious droplets can travel.

On top of that, the sick passenger was not yet showing symptoms of the disease, such as a cough, when the group made their trip.

The paper states: "The investigations suggest that, in closed environments with air recirculation, SARS-CoV-2 is a highly transmissible pathogen."

→ **bit.ly/2GH6gvG**

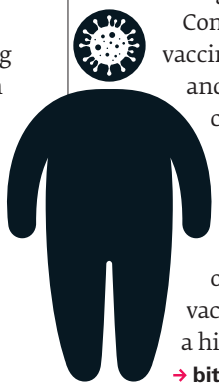
COVID-19

VACCINE MAY NOT BE AS EFFECTIVE FOR OBESE PEOPLE

New research voices concerns that vaccines for COVID-19 will be less effective for individuals with obesity.

The systematic review says obesity impairs the development of immunological memory.

Influenza vaccination in adults with and without obesity results in equivalent influenza-specific antibody titres at 30 days post-vaccination, but antibody titres wane significantly more in adults with obesity.



Compared with influenza-vaccinated lean adults, vaccinated adults with obesity have impaired CD4 and CD8 T cell production of key inflammatory cytokines IFN-γ and granzyme B.

Obese adults also have two times the odds of influenza, despite a robust antibody response.

The authors write: "T cell responses have been shown to be impaired in individuals with obesity. This suggests that a future COVID-19 vaccine may be less effective in an population with a high prevalence of individuals with obesity."

→ **bit.ly/35jK19g**

GENETICS

UNCOVERING ORDER IN CANCER'S CHROMOSOMAL CHAOS

Researchers at the Francis Crick Institute and the UCL Cancer Institute have identified how different cancers go through some of the same genetic mutations at the same point in their evolution.

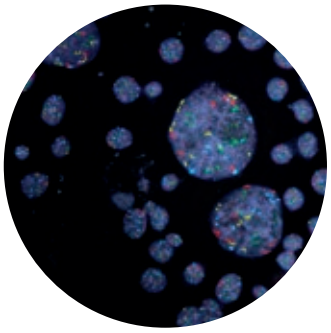
Their findings could bring us a step closer to an "evolutionary rule book" to help predict and block cancer's next move.

The genetic make-up of a tumour changes over time. This is the result of mistakes made when cancerous cells replicate their DNA to create a copy needed for the cell to divide. Researchers have previously shown that patients whose tumours have more diverse genetic mutations are less likely to survive, and now they're working to understand why these mutations occur and if there's a pattern.

The team found that changes in the chromosomes of cancer cells happen frequently and throughout the development of a tumour, and changes that help it survive and grow are more likely to take hold.

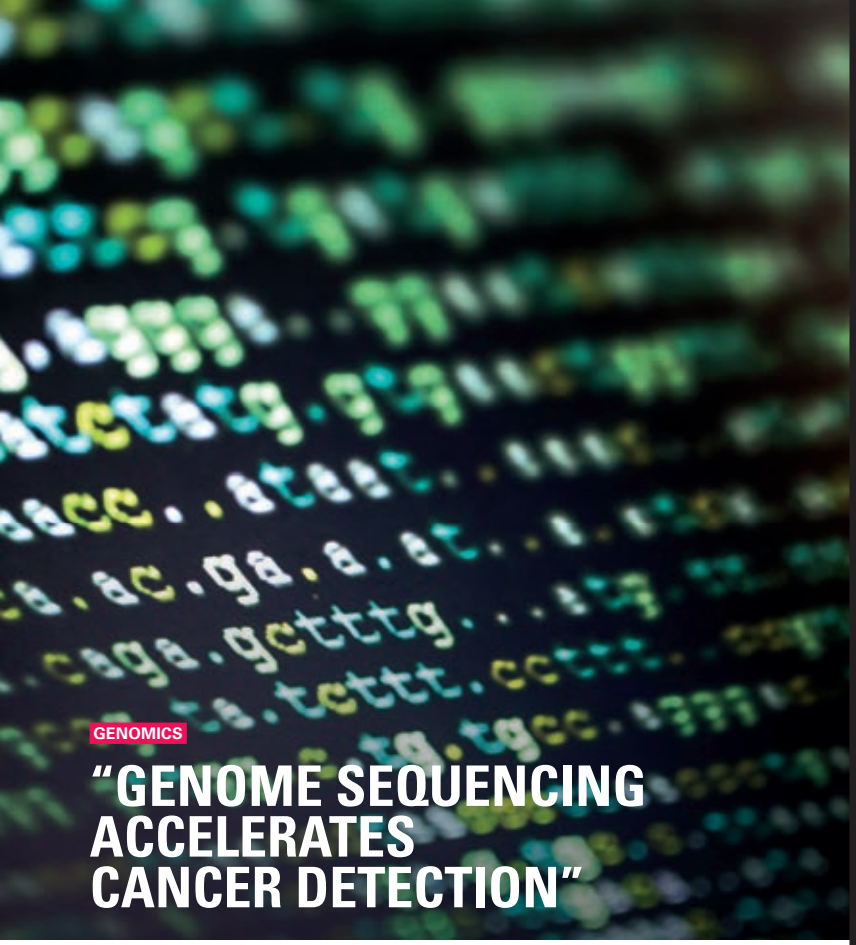
They developed a technique that analyses multiple samples from a single tumour to identify chromosomal changes in 1421 samples taken from 394 patients and across 22 types of tumours.

When looking at the nature and timing of these chromosomal changes, they found that often similar chromosomal changes had taken place in different subclones within a tumour from the same patient. These subclones are different populations or groups of cells within the same tumour. This evidence of subclones evolving in parallel was observed in samples taken from 37% of patients (146 patients).



→ **go.nature.com/3jWwyrZ**

IMAGES: GETTY/SCIENCE PHOTO LIBRARY/ISTOCK/SHUTTERSTOCK



GENOMICS

"GENOME SEQUENCING ACCELERATES CANCER DETECTION"

A statistical model has been developed that uses genomic data to accurately predict whether a patient with Barrett's oesophagus has a high or low risk of developing cancer.

Researchers at the University of Cambridge, EMBL's European Bioinformatics Institute (EMBL-EBI), and collaborators sequenced genomes from biopsies routinely collected from patients with Barrett's oesophagus. These patients are monitored for early signs of oesophageal cancer.

The researchers used the data to look for differences between patients who were ultimately diagnosed with cancer and those who were not.

The data were used to develop a statistical model measuring each patient's individual risk.

Other recent cancer studies have shown that genomic mutations leading to cancer may occur many years before a patient is diagnosed with the disease. Being able to identify these mutations could provide a new route to early diagnosis and treatment.

Using genomic data from 88 patients with Barrett's oesophagus, the researchers identified half of the patients who were diagnosed with oesophageal cancer as "high risk" more than eight years before diagnosis.

The numbers went up to 70% two years before diagnosis.

Equally important, the model also accurately predicted patients who were at a very low risk of developing cancer.

→ **go.nature.com/35fdz87**

70%

OF PATIENTS IN THE STUDY WHO WERE DIAGNOSED WITH **OESOPHAGEAL CANCER** WERE IDENTIFIED AS **"HIGH RISK"** TWO YEARS BEFORE DIAGNOSIS THROUGH THE USE OF **GENOMIC DATA**.

WHAT'S HOT AND WHAT'S NOT

HOT

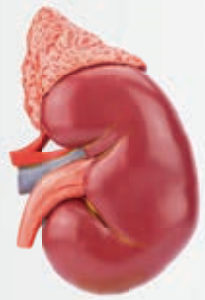
ASTRONAUTS

A review highlights that treatments targeting the gut microbiome could protect space travellers against negative health effects of space travel.

HOT

VITAMIN D

New data suggest the free, precursor form of vitamin D circulating in the bloodstream is a more accurate predictor of future health than the often-measured total vitamin D.



HOT

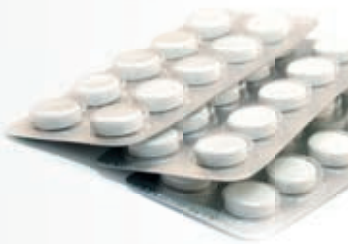
KIDNEY TRANSPLANTS

In a new paper, researchers describe ways to achieve optimal patient advocacy for kidney recipients and donors during the COVID-19 pandemic and beyond.

NOT

ANTICHOLINERGIC MEDICATIONS

This class of medications, which is used for a broad range of conditions, might also accelerate cognitive decline in older adults, according to a new study.



NOT

SCRATCHING

Stroking an itch, rather than scratching, can relieve it by activating an anti-itch pathway in the spinal cord, according to research in mice.

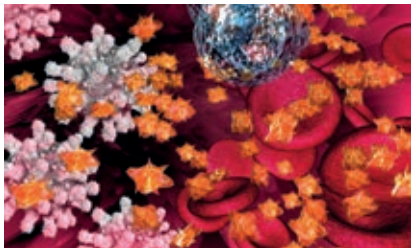
NOT

LAB-GROWN MEAT

The results of an online survey of 227 randomly selected Generation Zs based in Australia show 72% were not ready to accept cultured meat.

IMMUNOLOGY

COVID-19 NOT CHARACTERISED BY A CYTOKINE STORM



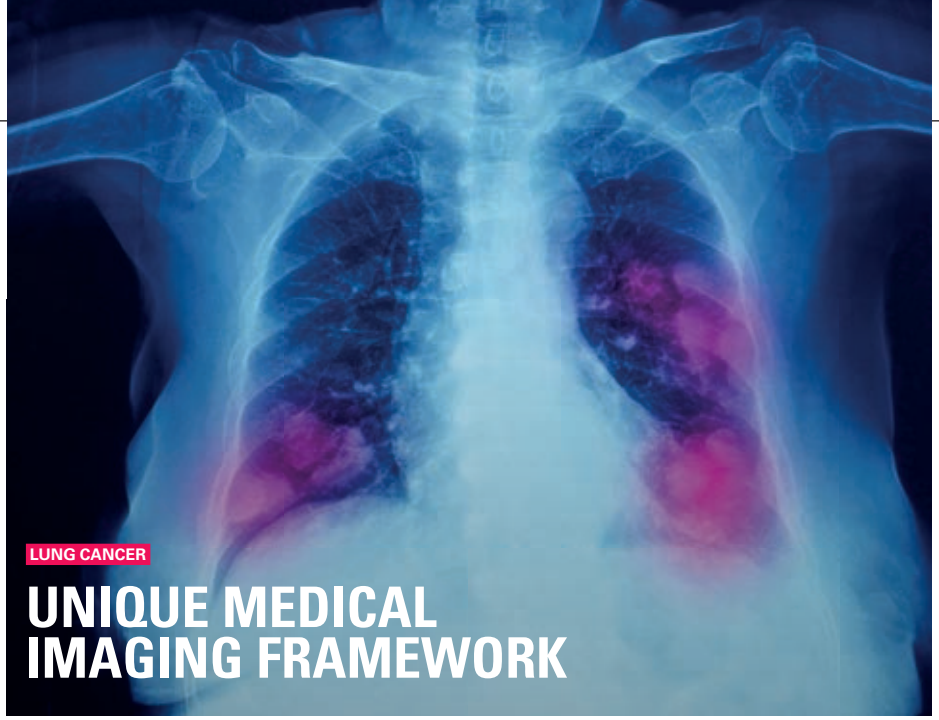
Inflammatory proteins known as cytokines play a crucial role in the immune response. If this response is too strong – a phenomenon known as "cytokine storm" – it can cause harm to the patient.

It had been thought that a cytokine storm contributes to disease severity in patients with COVID-19.

Following the measurement of several important cytokines in patients with COVID-19 and various other severe diseases, researchers said that COVID-19 is not characterised by a cytokine storm. This may have consequences for the treatment of these patients, the researchers write in *JAMA*.

Researcher Matthijs Kox said: "The level of cytokines was significantly less elevated in COVID-19 patients than in patients with septic shock and severe acute respiratory infection."

→ **bit.ly/35eZOGj**



LUNG CANCER

UNIQUE MEDICAL IMAGING FRAMEWORK

Researchers are developing a unique medical image processing framework aimed at helping oncologists treat lung cancer tumours more effectively.

In most cases, treatment decisions are made based on the patient's clinical history and visual information from medical scans such as computed tomography (CT) and positron emission tomography (PET).

A CT scan gives information on tissue density, while a PET scan uses radioactive tracers to help doctors identify areas of high metabolic activity in the body.

These visual representations of the cancer only offer partial information, and the only way to confirm these findings for sure is by comparing the scans to the actual cancerous tissue.

A four-year study has resulted in the development of a medical image processing framework to match up these different sources of information for clinicians.

The retrospective study used resected tissue from nine lung cancer patients who had been treated using radical surgery.

The framework will shed light on how particular information on the scan is related to the pathology of the tumour and its surroundings, which could result in an improvement of treatment effectiveness in the future, the scientists claim.

Clinical trials are now set to follow, which will use another type of PET scan to give more precise information of the metabolic fingerprint of the tumour.

→ **bit.ly/2Rc6wod**

UNDER THE MICROSCOPE

This month: Ibuprofen

Why are we looking at ibuprofen?

There have been rumours over recent months that taking ibuprofen while suffering with COVID-19 can lead to an increased risk of death.

I'm assuming that's not true.

No, it's not. The World Health Organization and the European Medicines Agency, among others, dismissed the information as untrue, but it carried on gaining traction.

Where did these false claims come from?

In March, in the early days of the coronavirus pandemic in Europe, a tweet from the French Health Minister, Olivier Verán, advised patients with COVID-19 not to take ibuprofen. Even though the statement was not backed by any scientifically valid evidence, it subsequently spread to a number of countries.

Why did people believe it?

A team from the Universitat Oberya de Catalunya have been looking at this question. They traced the story's trail back to a WhatsApp voice message in Germany and, following the digital footprint on the microblogging network, they also analysed how the story spread from its country of origin to users in the Netherlands, France and, finally, Spain and Italy.

Did people believe it straight away?

Not at first. The voice message was forwarded to different users but, as it was not possible to identify who originally recorded the message, it lost credibility and the general tone of comments was to debunk it or make jokes about it, the researchers state.

Then what happened?

In France, where the message was circulated by the health minister, the misinformation had a big impact and comments refuting the claim were virtually non-existent. Other reliable sources, such as the media, then reproduced the Minister's tweet without fact-checking, helping to take the information to greater segments of the population.

IMAGES: ISTOCK/SHUTTERSTOCK/SCIENCE PHOTO LIBRARY

TECH NEWS

CANCER RESEARCH UK

ARGINASE 2

Researchers at the Cancer Research UK-AstraZeneca Antibody Alliance Laboratory in Cambridge, UK have pioneered the development of an innovative affinity maturation technique to generate an inhibitory, high-affinity antibody against Arginase 2 (ARG2) – an enzyme implicated in major human diseases including cancer.

ARG2 targets and destroys L-arginine, an amino acid critical for immune cells to fight diseases such as cancer, as well as infections.

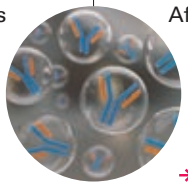
cancerresearchuk.org

AVACTA GROUP

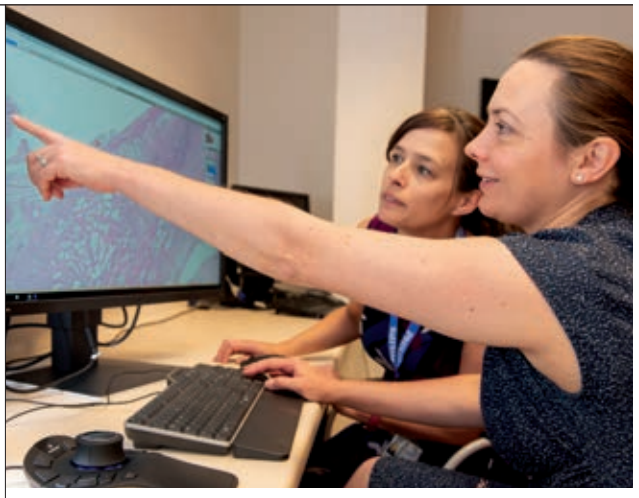
SARS-COV-2 TEST

Avacta Group is launching an ELISA laboratory test for the SARS-CoV-2 spike protein to support global research efforts into the coronavirus.

Enzyme linked immunosorbent assays ("ELISAs") are research tools used to detect and quantify a target of interest in a wide range of samples. Using the same Affimer reagents that are incorporated into its rapid coronavirus saliva test, Avacta has developed an ELISA laboratory test to detect SARS-CoV-2.



→ **avacta.com**



PHILIPS

DIGITAL PATHOLOGY

Philips has supported Oxford University Hospitals (OUH) NHS Foundation Trust to become one of the earliest UK adopters of a fully digitised cellular pathology (histopathology) department.

OUH is one of the first NHS trusts in the country to achieve the status of digitising all surgical histology and referral slides within the cellular pathology department.

This step-change is expected to unlock greater collaboration between OUH and its wider network of trusts and pathologists.

→ **philips.co.uk**

INNOVATIONS IN CELLULAR PATHOLOGY

A.MENARINI diagnostics

ARKIVE

COMPLETE ONSITE ARCHIVING & RETRIEVAL MANAGEMENT

ARKIVE BC FOR BLOCKS

ARKIVE SL FOR SLIDES

SAFE . TRACEABLE . TIME SAVING . MODULAR.

- Complete and unique solutions to manage your histology samples onsite
- Fast and automated sorting, storage and retrieval
- Full traceability of histological blocks and slides
- Improved security and optimal storage conditions for sample preservation
- Increased productivity with lean working and scheduled retrievals
- LIMS integration for requests
- Modular, tailored and space efficient solutions

www.totaltissuediagnostics.com

Telephone: 0118 944 4100
Email: enquiries@menarinidiag.co.uk

TOTAL TISSUE™ DIAGNOSTICS
From surgical specimen to diagnosis

Menarini Diagnostics launches ARKIVE BC™ for the complete management of histological blocks

Menarini Diagnostics, one of the UK's leading suppliers of diagnostic equipment, is expanding its comprehensive cellular pathology portfolio with ARKIVE BC solution for automated archiving and retrieval of histological blocks.

ARKIVE BC™ for blocks streamlines and automates the archiving and retrieval process, optimises traceability, ensures the safety of important patient tissue blocks, and reduces the time and effort needed to sort and store these. Patient samples will always be viable for future use. Automating this process means staff time is freed up, laboratory productivity can be improved and resources can be focused on what matters most – reliable diagnostics and better patient care.

The automated storage of blocks on the ARKIVE BC units starts with the operator authorisation by ID badge or pin code and the loading of storage racks into the unit. Inside the unit a robotic arm moves the blocks to a barcoded location and tracks where each barcoded block is placed. All information is transferred to the LIMS making the retrieval as quick and easy as storage. You can even schedule retrievals to make the lab leaner.

Beside full traceability, this unique solution will provide you with full safety for your histological block; with temperature and humidity monitoring, controlled and restricted user access and dedicated racks for physical protection from contact and cross-contamination. The ARKIVE BC is a modular solution that fits every lab's needs. One unit can store up to 36,400 blocks and it is easy to add additional units in the future if required.

ARKIVE BC is a Safe, Traceable and Modular solution with Time-Saving benefits for the lab!

For more details about the ARKIVE BC block storage solution or any of Menarini's cellular pathology range please get in touch:

Email: enquiries@menarinidiag.co.uk

Telephone: 0118 944 4100

www.totaltissuediagnostics.com

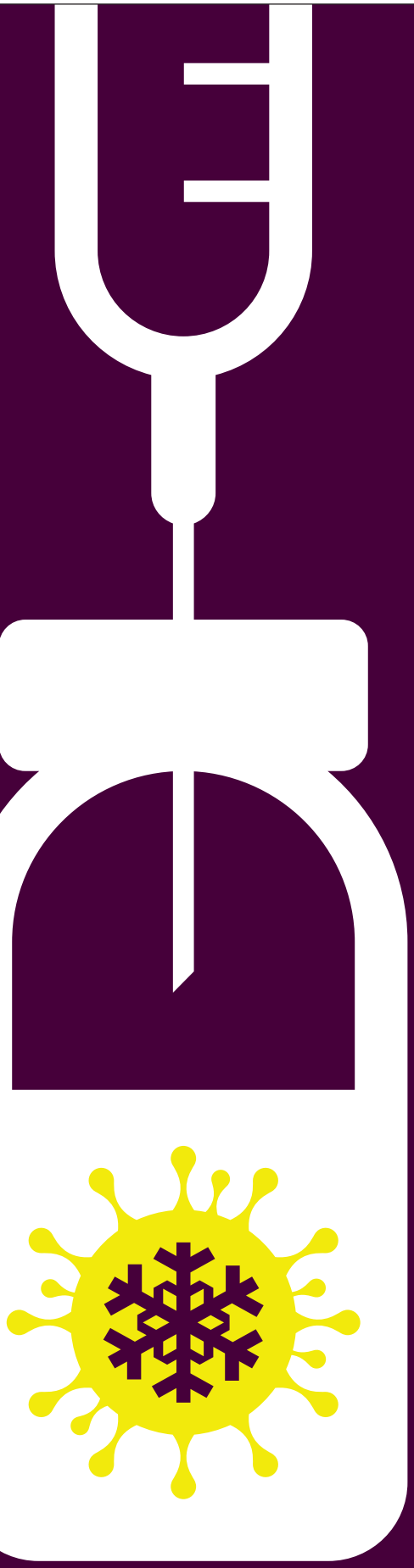
www.menarinidiag.co.uk

A.MENARINI diagnostics

THE BIG QUESTION

THIS MONTH WE ASK

"What impact will COVID-19 have on this year's influenza season?"



Alistair Gammie

ValuMetrix Global Senior Director
Ortho Clinical Diagnostics

The evidence we are seeing from WHO surveillance, albeit in the low seasons, suggests that global incidence is lower than expected for this time of year. The WHO labs tested more than 198,000 specimens in the first half of August, with 46 positives – 15 (32.6%) of which were influenza A, the remaining 31 (67.4%) were influenza B. The two flu A that were subtyped were H1N1.

This must be taken in context with COVID-19 and the effect it has had on the daily routines of these centres, i.e. access to molecular equipment and sufficient staffing, as well as the behavioural change in patients with respiratory illness and local testing strategies.

Hand washing and social distancing measures will also have influenced the potential spread of the flu virus, as well as many other respiratory viruses. The UK Respiratory Data Mart reported in weeks 34-35 that rhinovirus had a slight rise in positivity, but adenovirus, RSV, human metapneumovirus and parainfluenza all remained low.

The concern is the growing number of people who are indulging in high-risk behaviours has the potential to not only create a second wave of coronavirus, but to also create the incubator for influenza.

Does the health service and the general population have the resilience to tackle both COVID-19 and the flu? I personally hope that we maintain discipline, beat COVID and learn lessons about reducing overall respiratory disease burden – coughs and sneezes spread diseases.

Mark Cioni

Senior Lecturer in Biomedical Science
Nottingham Trent University

The answer to this is "potentially significant" and I suppose what we would all like to know is "how significant". The PHE influenza report (3/9/2020) states that no samples tested positive for influenza.

This is a better position than this time last year and, at the waning of summer, influenza testing workload seems low. Even so, labs are experiencing testing capacity issues with respiratory samples. From a laboratory perspective, they may have no or limited capacity for influenza testing with any gap in capacity ultimately being absorbed by reference facilities. Looking at the wider picture, last year, influenza vaccine take-up rates for at-risk groups (two- to three-year olds and the elderly) was running at around 43% and the vaccine was reported to be 42.7% effective. The take-up of the vaccine may be higher this year, especially as the vaccine programme has been extended, with more people wanting to prevent the potential issues of coinfection with COVID-19.

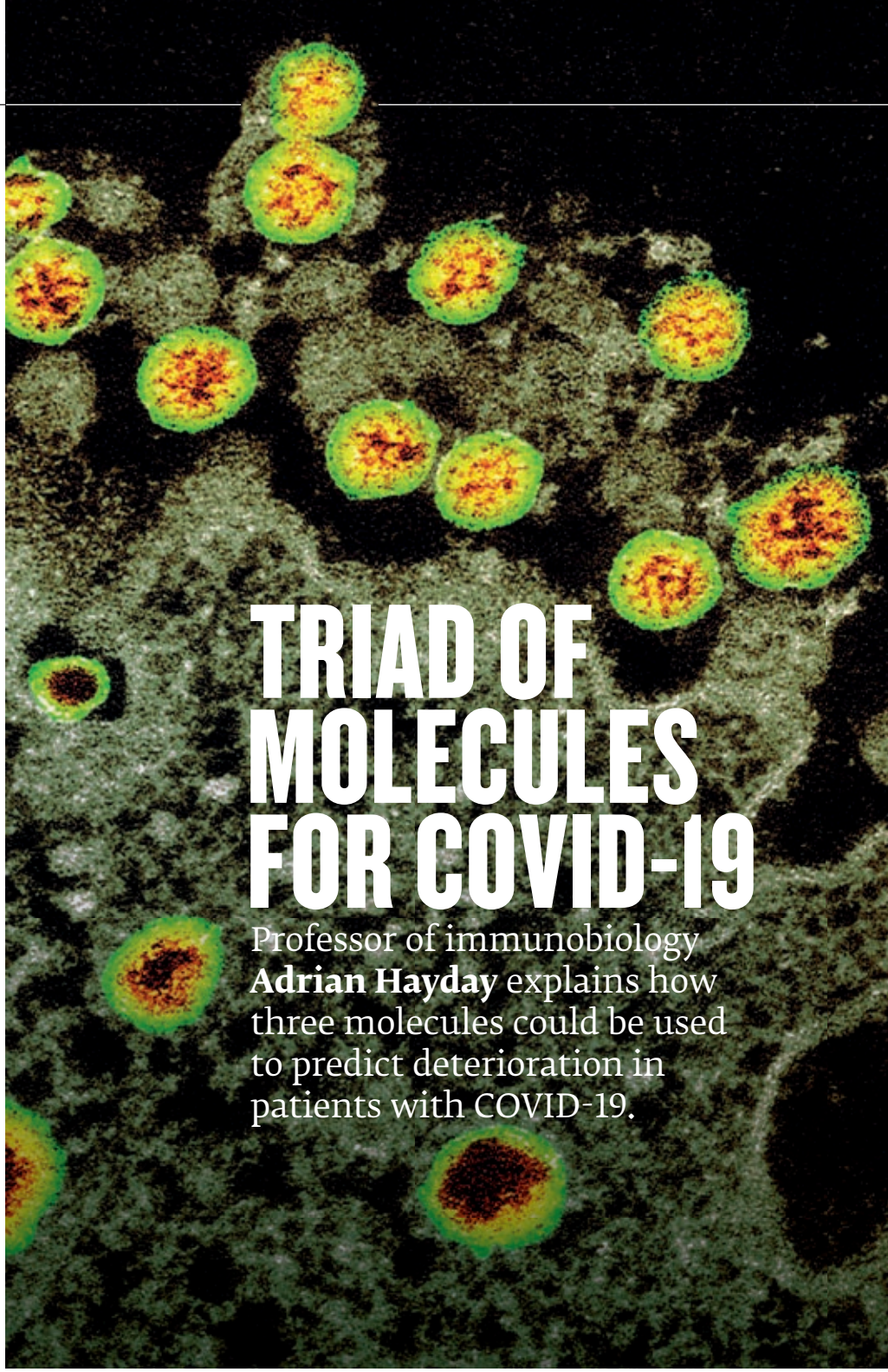
However, questions exist as to when these extra vaccines will be provided and who is going to deliver them. There are already reports of small family-owned GPs cancelling flu vaccination clinics as members are symptomatic for COVID, unable to get a test and are isolating. It can be envisaged that vaccine delivery and efficiency may be low, demand for both COVID and influenza testing could significantly increase, and healthcare professional staff may be shielding or isolating – the impacts on the wider health system could be momentous.

Martin Khechara

Associate Professor for Engagement in STEM
University of Wolverhampton

Well, what a strange time we are in! We went into lockdown and most of us, myself included, thought "everything will be fine soon". Now we find ourselves six months later with the spectre of potential further restrictions around the country looming on the horizon.

As we move into the darker months, we are also moving into the time of year where the respiratory viruses rule. Ultraviolet light is down and humidity is up; viruses will survive for longer periods and spread more easily as we hide indoors from the British winter. This unfortunately includes SARS–CoV-2, but just as worrying is the good old influenza virus. The Centres for Disease Control (Atlanta, US) reports that influenza was associated with more than 35.5 million illnesses, more than 16.5 million medical visits, 490,600 hospitalisations, and 34,200 deaths during the 2018–19 influenza season in the US alone. Globally, up to 650,000 deaths are associated with respiratory diseases associated with seasonal influenza annually. With the prospect of this to come as we move into winter, and the fact that many common cold-like illnesses are caused by coronaviruses, biomedical science faces a very busy time as the burden of testing increases to give people the reassurance they need to carry on with life and return to work. Of course we will all be working together to get it done and keep our patients safe.



TRIAD OF MOLECULES FOR COVID-19

Professor of immunobiology **Adrian Hayday** explains how three molecules could be used to predict deterioration in patients with COVID-19.

Back in March the fight against COVID-19 set in motion a vast mobilisation of biological research resources around the world, and barely six months later this unprecedented effort has yielded a multitude of discoveries and insights, not least the results of the work published in *Nature Medicine* by a team drawn from the Francis Crick Institute, King's College London, and Guy's and St Thomas' NHS Foundation Trust.

Looking at blood samples from 63 patients treated for COVID-19 in London, they found a common immune signature, which could help doctors predict how ill individuals might become and how long they might need to stay in hospital. This immune signature contains high levels of three molecules in particular: IP-10, interleukin-10 and interleukin-6, which the researchers have collectively dubbed the "triad".

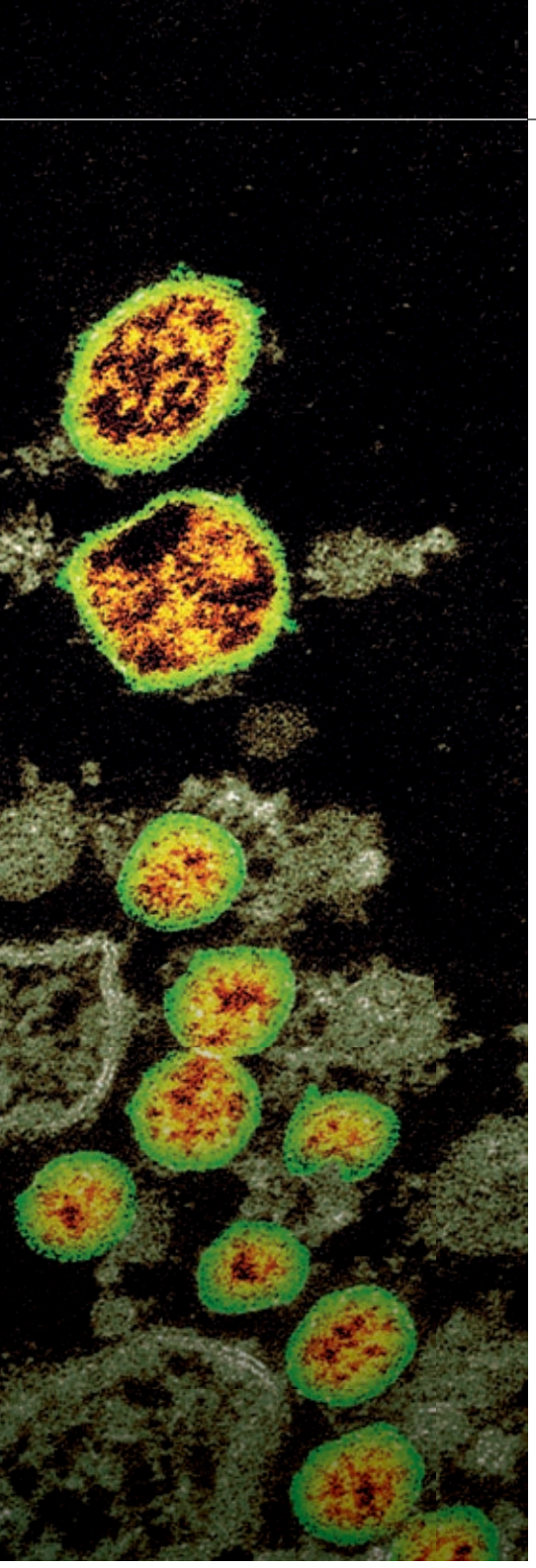
Immune system

Project leader Adrian Hayday, head of the immunosurveillance laboratory at the Francis Crick Institute and professor of immunobiology at King's College London, says the team didn't set out with any great expectations. "We are not virologists or vaccine developers, but we are pretty good at trying to track what the immune system is doing in patients who are suffering from the worst consequences of this infection. We figured that as long as we don't get in the way of other groups, we're not competing for samples or other more proximal needs, then finding out what the immune system is doing could be useful in trying to understand why certain individuals gets sick and others do not."

Even more pressing was the need to discover why the condition of certain individuals deteriorated from severe to catastrophic so unpredictably. "There were wards full of people with the same disease at St Thomas', which is unprecedented in modern history. And among all those individuals, about 20% would go downhill. But there was just no way of telling with any certainty on day one who was going to get worse and who was going to get better. Of course there are a lot of clinical markers that are measured – CRP, ferritin, albumin – but we wanted to look at the immune response and see if there was something that could distinguish what was going on with these patients."

Molecules

Analysing the blood samples of patients versus healthy individuals who had or had not themselves been infected – "a nice set of controls," he says – Hayday and his team detected something related to the "cytokine storm" – the flood of proteins that signal a potentially fatal overreaction by the body's immune system. The molecules associated with this process in inflammatory conditions normally include TNF, interleukin-6 and



IMAGES: SCIENCE PHOTO LIBRARY

interleukin-1. But what they encountered was more a breeze than a storm. "That is to say we didn't see huge amounts of TNF or interleukin-1, but we did see some other molecules expressed at high levels. Three in particular caught our attention. Interleukin-6 was there, but we also saw interleukin-10 and another one called IP-10, formally a chemokine rather than a cytokine, though they're similar."

The IP-10 molecule is particularly interesting, adds Hayday. "When you look back at the literature for the MERS and first SARS epidemics, everybody reported very high levels of IP-10. So I wonder whether this IP-10 molecule isn't fundamental to the biology of coronavirus infection and pathology? It's speculation, but it's a fascinating speculation."

Robust predictors

Besides noticing that most of the patients had high levels of the "triad" molecules, they also observed that the higher the levels of the molecules, the more severe the disease appeared to be. More than that, they found that the levels were particularly high on the actual day patients were hospitalised. This raises the question of whether these molecules not only correlate with the severity of COVID-19, but actually anticipate that severity in a way that might guide doctors as to which patients are likely to deteriorate. "Of course it's not perfect," says Hayday. "Nonetheless, if you do the maths, if you look at the statistics, those molecules are the most robust predictor of who's going to get worse rather than better. Even to the point that IP-10 levels can pretty much predict how long you're going to be in hospital. If we get to a situation again where there is pressure on hospital beds and resources, it could make a big difference."

But how easily might this be translated into a workable test at the bedside? "These conversations are beginning. I'm not an engineer, but there are some really good engineers out there. I think they will be able to make a fairly routine test for these molecules, a triad-test as it were. Some of the markers that are used in clinical chemistry have been fantastic but they are decades old. With the level of sophistication and understanding we now have, we really ought to be providing doctors with tests that can give a better assessment of a patient's condition."

Spin-off benefits

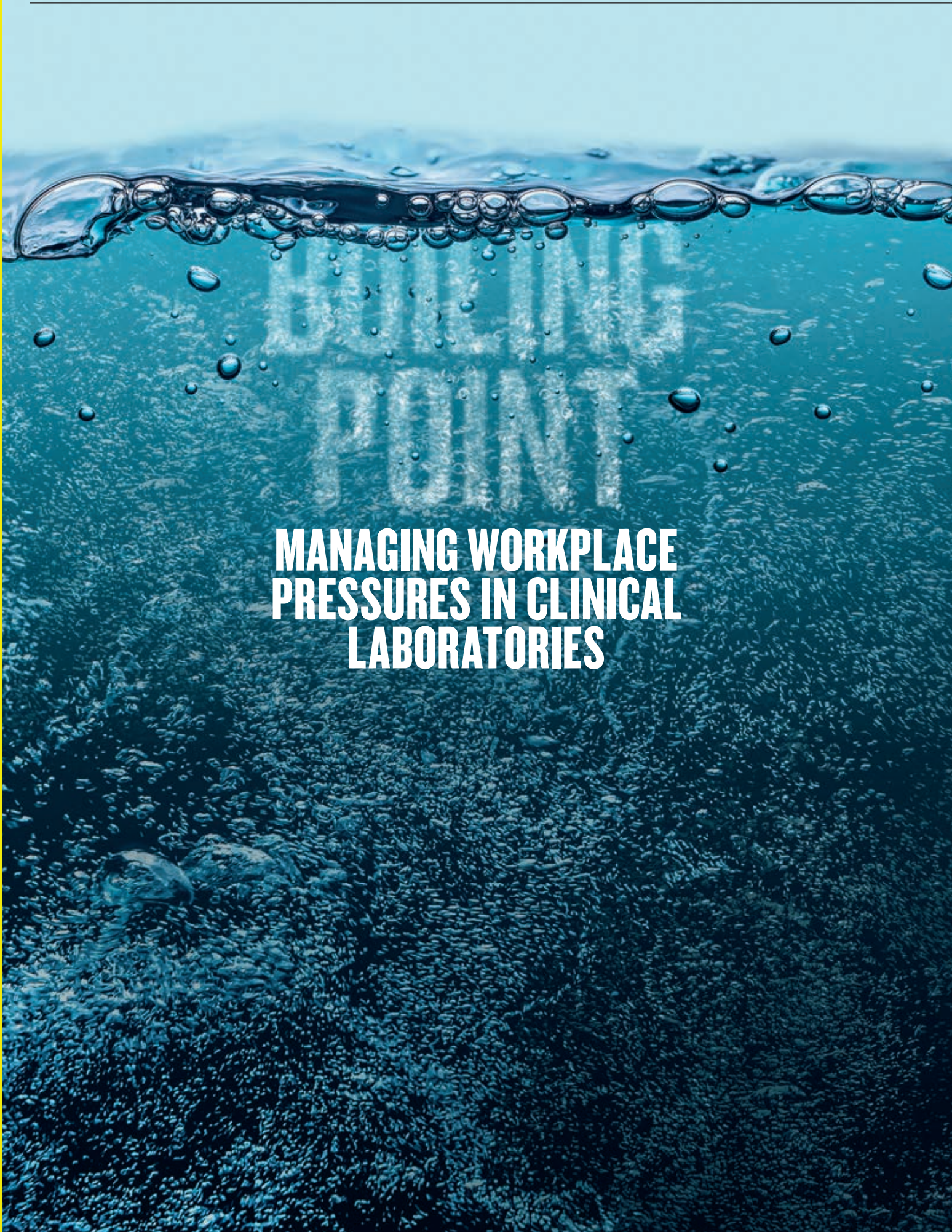
And what does he make of the whirlwind of research that is swirling around COVID-19? "I've been running a lab for 34 years and I have never seen the speed with which basic research findings are being picked up for clinical bed-proximal translation as we're seeing now. That has to change the way we do science. Once the pandemic is over we can't suddenly go back to how it was. We have to learn."

Part of this learning, he argues, is to reconsider the priorities that inform research funding. "There's never enough money. So funding committees tend to be risk averse. But groups such as ours have just stopped what they were doing and undertook the most adventurous, risky projects, and they have worked. If we were risk averse and conservative, we could never have responded to COVID-19. At all levels, we need to embrace this new era."

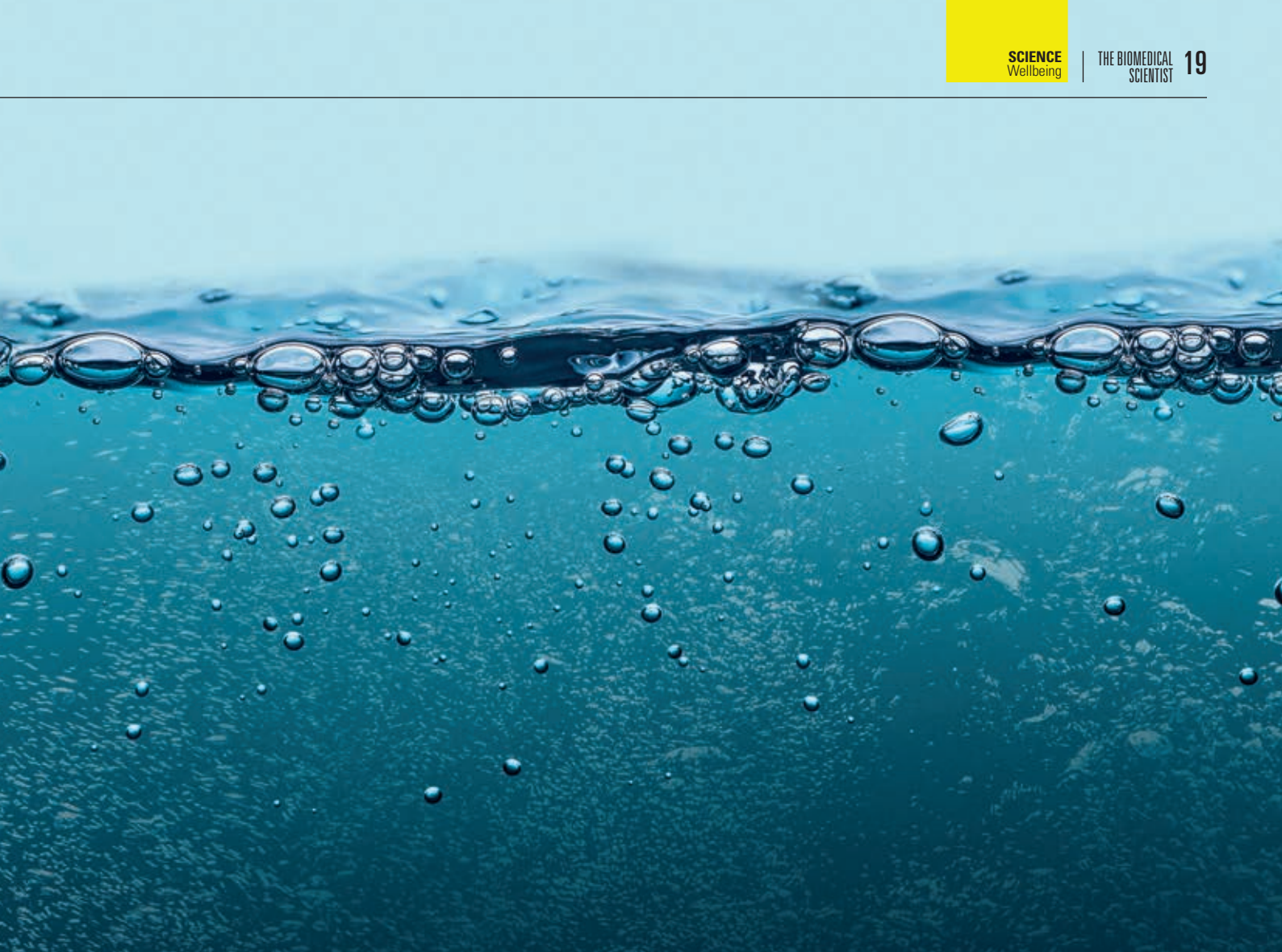
There is also huge potential for spin-off benefits in other clinical areas. "We've had an unprecedented opportunity to watch a live immune system response. We've learned huge amounts, and that's going to be hugely informative about the immune response to cancer, for example. The basic fundamental research lessons that we can pick up here are innumerable," he concludes. BMS

ADRIAN HAYDAY

- ✔ **1979** – PhD, Imperial College London
- ✔ **1982** – Postdoctoral, MIT
- ✔ **1985** – Faculty, Yale University
- ✔ **1998** – King's College London School of Medicine
- ✔ **2009** – Established lab at the London Research Institute, Cancer Research UK
- ✔ **2015** – Group leader, the Francis Crick Institute.



MANAGING WORKPLACE PRESSURES IN CLINICAL LABORATORIES



Senior Specialist Biomedical Scientist **Azuma Kalu** looks at pressure in the workplace and presents two case studies.

Biomedical Scientists have been under increasing pressure over recent months. The already overstretched and underfunded NHS, combined with the added stress and workload caused by COVID-19, means many labs are reaching boiling point. Since the start of the pandemic, the IBMS has been asking members to share their experiences through a regular wellbeing survey. The most common way members describe their work environment throughout has been "unpredictable". "Emotionally challenging" and "intense" have also been prominent. The survey indicates an increase in members describing their work as "overwhelming", coupled with a rapid decline in the numbers saying it is "quiet".

In the mid-September survey, when compared with the survey a couple of weeks earlier, there was an increase in the proportion of members describing their work as "relentless" (33%, up from 27%), "frantic" (22%, up from 16%) and "stretching" (28%, up from 24%). While the feeling that members saw their work as worthwhile increased (65%, up from 57%), as did better mental wellbeing (25%, up from 19%), the mounting pressure on workload continued to rise.

Aside from workload pressure, which is a constant (if recently exacerbated) feature of clinical laboratories, three other more infrequent events that cause stress and concern for the workforce are preparations for inspections, the logistics of laboratory relocation and the work involved in changing from one laboratory informatics system to another.

Heightening the scale

On Biomedical Science Day this year, I received a phone call from a colleague and friend. For about thirty minutes he talked about the pressure at work and the stress he was going through. A number of changes had been made in his laboratory to accommodate the analysis of more

than one thousand COVID-19 samples per day. I could feel the stress in his voice. A lot of what he said got me thinking and asking questions about the support structure in place for scientists who work in clinical laboratories.

COVID-19 has exposed the cracks and fault lines in the way individuals and laboratories manage pressures, which have always been there, but have been heightened by the pandemic.

There are common factors that most people who work in clinical laboratories are familiar with – stress from daily commute, pressure from managers and other staff about meeting expectations, overwork due to staff shortages or increase in workload. These can lead to burnout and result in days or weeks of absence and recovery. All these have their tolls on the physical and mental wellbeing of all grades of staff – be it the medical laboratory assistants who receive and book in the samples and test requests, through to the senior or consultant scientists who authorise the results.

Pressure is fundamentally perception-driven. What individuals at different stages and grades of practice perceive as pressure varies and even for the same individual, as they progress from a trainee scientist to more senior grades.

Pressure is the trigger that leads to stress. In so much as pressure is the catalyst, the enablers are failure to plan, prioritise, organise and carry out tasks in rational order, efficiently and in good time.

Pressure is associated with any undertaking, tasks, chore or activity where there are targets, goals and expectations.

"COVID-19 has exposed the fault lines in the way individuals and labs manage pressures"

To accomplish any given goal, humans utilise both physical and mental faculties, so stress becomes manifest when the body is feeling under pressure and this is evident in different ways.

Following are two case studies that have been anonymised to protect the individuals featured.

CASE STUDY ONE

LABORATORY-ACQUIRED PRESSURE

Mark, a very senior scientist with more than twenty years' experience as a principal scientist, took on a new role as lead scientist in a highly specialised laboratory soon after the laboratory had its first United Kingdom Accreditation Service (UKAS) inspection. Being a specialised laboratory, the centre serves as a referral laboratory for many tests and assays, some of which are still based on manual methods that have not evolved with time.

Mark's predecessor, an accomplished scientist, delayed his retirement to see through the UKAS inspection. Prior to his appointment as the new lead scientist, Mark was given a detailed briefing of the enormous task awaiting him by the retiring lead scientist. The laboratory's preparation for their first UKAS inspection was marred by issues such as staff absences/sickness and lack of in-depth understanding of the requirements of the inspection and, as expected, there were a considerable number of non-conformances and recommendations made by the assessors. Mark was confident, from his many years of experience as a principal scientist in another specialised laboratory, that he was going to get the non-conformances resolved in a timely manner.

On his first day as lead scientist, Mark arrived at 7am and started work. By 9am other staff arrived and were delighted to see him. At 5pm, the staff were closing for the day, but Mark was still at his desk and he continued to work until 7pm. To help him cover more ground, working on Saturdays and Sundays became the norm. Mark had no experience of UKAS inspections from his previous places of employment and most of the action plans he prepared during his weeks of long hours did not have much effect because the laboratory's post-inspection response could not address most of the issues raised by the UKAS assessors. After many weeks of long hours of work and with a significant number of the non-conformances still not addressed, the pressure began to take its toll on Mark. He began to feel unwell and made an appointment with his GP, who was so shocked to see an emaciated man, who was close to losing most of his hair, that

IMAGES: SHUTTERSTOCK

she quickly signed him off for three months. Three months became six, and six became twelve and, to date, Mark has not been able to return to work.

After the first three months of Mark's sickness absence, the laboratory brought in a temporary lead scientist who, among other things, was tasked with conducting a review of work practices among the rank and file of the laboratory. Based on the recommendation of the review report and in agreement with Mark, who on medical advice could not return to full practice, the laboratory went on to employ another lead scientist as well as a quality and governance officer.

Mark was at the peak of his career and yet he succumbed to the vagaries of stress arising from workload pressure. He was very determined to help the laboratory clear all the non-conformances, but he was not amenable to delegating duties. He wanted to do it all alone.

CASE STUDY TWO

NON-LABORATORY-ACQUIRED PRESSURE

Sandra's career was going well until 7 February 2019. On that day she received a phone call that changed her already high-pressured life. She had just finished her day shift in the laboratory and was on her way home when the news reached her that her mum Linda, had been taken to the accident and emergency unit of their local hospital. Linda was Sandra's rock. On her way to work every day, Sandra would drop her daughter at her mum's flat and then on her return, pick her up.

The thought of her being in the hospital bed with cables and tubes attached to her body and the need for her to even consider that she may no longer be available to help her look after her daughter was just too much for her to take. The next day, Sandra called her manager and was given some time off work.

Three weeks passed and Sandra resumed work in the laboratory, albeit for reduced hours. Within days, the pressure of home life began to tear her apart. She now had to do the school runs, which was not easy, given that she lived in East London and had to do half an hour bus journey to drop her daughter at school before travelling on the underground to central London for work. She did it for a week and was exhausted. The thought of finding a nearby school for the daughter did cross her mind, but she did not want her daughter to lose her friends.

In the laboratory, Sandra became moody and withdrawn and it was not long before her work became affected. Her colleagues began to notice mistakes in her work, and then there were reports of bouts of forgetfulness and instances of looking very tired at work. On the twentieth day after she returned to work, her manager invited her to his office to discuss some concerns that have been raised by her colleagues about her work. On leaving the manager's office, Sandra suffered a meltdown and had to go home. She was signed off work by her doctor. Two months into her sickness absence, Sandra tendered her resignation.

Support is available

The importance of taking good care of one's mental and physical wellbeing cannot be overemphasised. Given that the greatest asset of any organisation is the people that make up the structure at different levels, providing support to the workers is the first step towards reducing pressure in the laboratory.

The culture in workplaces should encourage staff to be open and willing to acknowledge they are in difficulty or may need assistance when the pressure of work begins to be burdensome.

As individuals, it is imperative to have a good understanding and awareness of one's strengths and weaknesses. Having knowledge of these, as well as the acknowledgement that in order to safeguard our health and wellbeing we should seek help from more informed professionals, is needed more than ever in our high-pressure society.

It is good for one's general wellbeing to understand oneself and to know when to stop as pressure begins to become unbearable. At this point, one just needs to take a deep breath, reassess the situation and priorities and ask for help or guidance, if required, from other

"He was not amenable to delegating duties. He wanted to do it all alone"

colleagues or a manager. Accepting that one needs help in a difficult circumstance is not a show of weakness, rather it should be seen as a genuine acknowledgement of strength in the individual's judgement and their alertness to prioritising their health and wellbeing. Something else that would be beneficial is learning to share our stories and worries. We all have our individual personal circumstances, but we belong to a community of families, friends and colleagues and it always helps to remember that we are not alone in whatever situation we find ourselves.

Raising issues

Staff with concerns about their wellbeing should not feel scared to raise such issues with their managers. That readiness to share one's burden is born out of the trust that such information is volunteered in confidence and therefore serves to facilitate support for the staff. Being able to listen and show understanding of the concerns of the staff is a fundamental aspect of good management. It is vital that the manager shows empathy and willingness to address the worries as well as readiness to escalate and seek further support when necessary.

It is important for managers to ensure that staff are appropriately trained and well-resourced in the jobs they do. Being realistic about the work that staff are allowed to take on is a good step in the right direction. Some work may take a longer time to complete and, in some cases, things will crop up unexpectedly, leading to further delays. So there should be an understanding that on some days things will not go as planned and on such days, ensuring that the pressure does not morph into unbearable stress for the staff ought to be considered.

For people who are on the edge with regards to personal pressure, additional work pressure can easily exacerbate their conditions.

Organisations should provide relevant training and support to managers on how to handle personal and sensitive information. This should enable the managers to seek suitable support for their staff, thereby ensuring that the workers are fully supported and know that their welfare is important to the organisation. Pointing the staff in the right direction is important. It could be a referral to the occupational health team, an appointment with a GP or the chaplaincy, or booking with a counselling organisation.

A manager with knowledge of when and how to access support for staff is good for an organisation as it promotes staff retention. Laboratories that are part of a hospital benefit from the occupational health team and other facilities on site or in the organisation. However, in standalone laboratories without onsite support facilities, greater emphasis should be placed on equipping the managers with suitable training. The IBMS has also created a range of wellbeing webinars and resources for members, with more set to be released soon, and members can also access legal assistance and counselling (see box).

Good managers create a conducive environment in the laboratories for the staff to thrive and work as a team. Such managers are the first ports of call to assist staff to cope with pressure and, in cases where additional support is needed, enable them to access relevant support towards their general health and wellbeing. However, the primary responsibility of ensuring that the pressures of life and work do not result in catastrophic stressful outcomes lies with the staff and the key is to use the relevant channels of communication available in the workplace and community to achieve this. IBMS

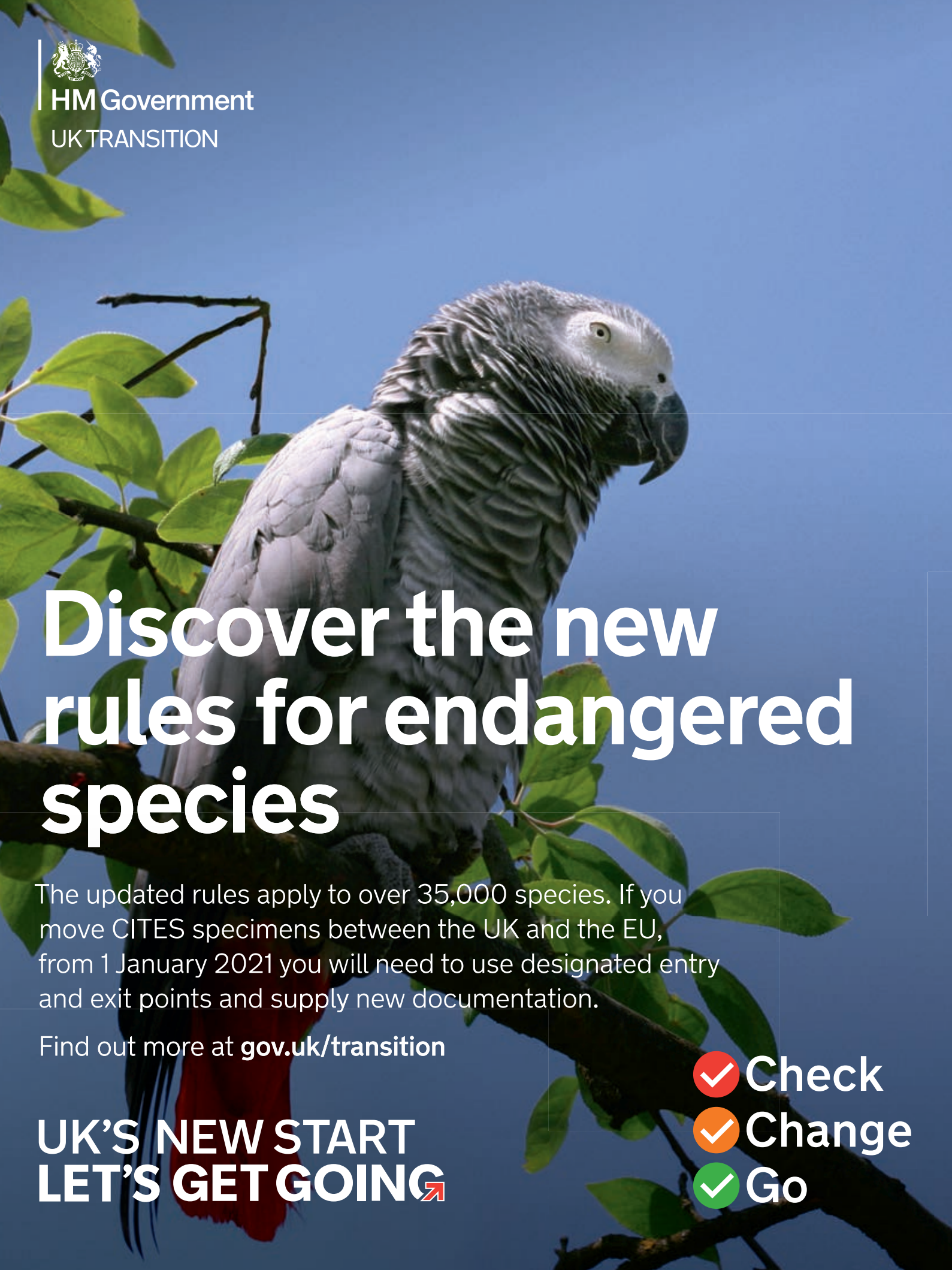
WELLBEING WEBINARS AND SUPPORT

The IBMS has been providing members with a series of wellbeing webinars that have been produced for NHS staff (but are open to everyone) working during the pandemic. The webinars are free to sign up for and previous webinars can still be accessed. So far these include webinars entitled Low Mood, Coping with Burnout and Anxiety and BAME Wellbeing with David Truswell. To access these, visit **ibms.org/resources/news/wellbeing-resources-for-members**

IBMS members can also access free resources if affected by any issues in the workplace or at home. Using their website login to access MyIBMS, members can access a legal assistance helpline and find professional advice and a counselling service through IBMS Additions (Wellbeing Support Services).

Azuma Kalu is a Senior Specialist Biomedical Scientist at Great Ormond Street Hospital


HM Government
UK TRANSITION
Is your business ready for the UK's new start?
The UK has left the EU. Check to see the changes your business may need to make.
Find out more at gov.uk/transition
UK'S NEW START
LET'S GET GOING
Check
Change
Go


HM Government
UK TRANSITION
Discover the new rules for endangered species
The updated rules apply to over 35,000 species. If you move CITES specimens between the UK and the EU, from 1 January 2021 you will need to use designated entry and exit points and supply new documentation.
Find out more at gov.uk/transition
UK'S NEW START
LET'S GET GOING
Check
Change
Go

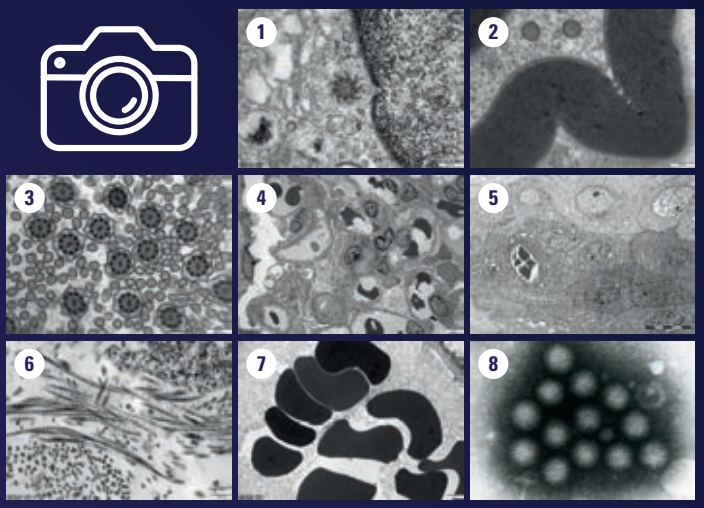
THE GREAT BIG BIOMEDICAL LOCKDOWN QUIZ

PART 3

The third instalment of our biomedical science quiz. This time, we have a picture round and eight questions relating to ultrastructure, compiled by **Catherine Griffiths**, an Electron Microscopist from the Biomedical Imaging Unit at University Hospital Southampton.

ROUND 1: PICTURE ROUND

1. What is the tubular structure in the centre of the image? (Nucleus to the right)
2. Which insulating layer shown here allows efficient transmission of electrical impulses?
3. These cilia and microvilli in cross section can be found on which type of cell?
4. What is the name for this cluster of capillaries?
5. A symptom of multiple myeloma, this image shows crystalline paraprotein deposit in which tissue type?
6. What is the banded fibrous structure shown here?
7. What sort of cells are these homogeneous electron-dense structures?
8. Which technique allows us to see viruses by TEM, such as this rotavirus cluster, by staining the background?



IMAGES: BIOMEDICAL IMAGING UNIT, UNIVERSITY HOSPITAL SOUTHAMPTON

ROUND 2: ULTRASTRUCTURE QUESTIONS

1. Why are heavy metals used instead of coloured dyes to stain electron microscopy samples?
2. For transmission electron microscopy, thin sections are prepared using ultramicrotomy. How thick is the ideal thin section for TEM? (A standard histology section is 4 µm thick).
3. What is the difference between magnification and resolution?
4. Why is EM still required/helpful when immunohistochemistry shows the diagnosis, for example when a renal biopsy has positive immunostaining?
5. Amyloid can build up and deposit in various organs, and can be seen by using a congo red stain. What is the approximate diameter of an individual amyloid fibril when viewed on TEM?
6. Which primary and secondary fixatives are (generally agreed to be) most effective for preserving biological samples for EM?
7. Which group of heritable connective tissue disorders, which notably affect joint and skin elasticity, can be diagnosed by using TEM to identify abnormalities in the collagen fibrils?
8. Ultrastructural defects in which motile organelle can cause *situs inversus* (arrangement of major organs in the abdomen/chest is reversed/mirrored) *in utero*?

A To see the answers, visit **thebiomedicalscientist.com**

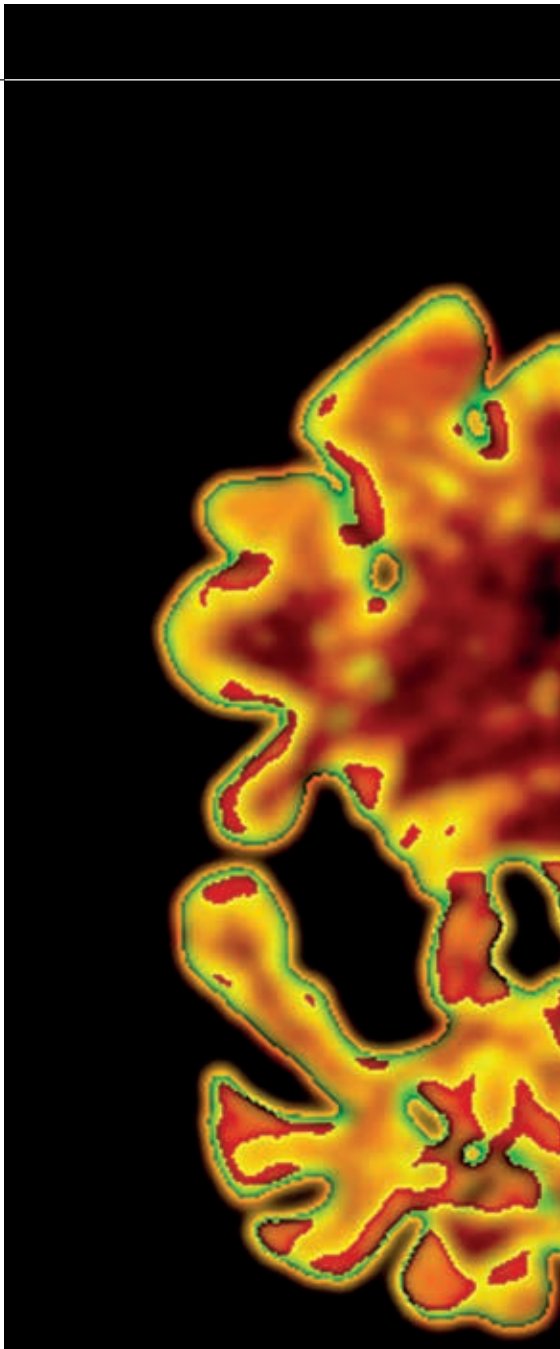
MEDICAL EPONYMS: PART 2

ALOYSIUS ALZHEIMER

This is the second of selected short biographies of persons whose names are directly used for diseases, conditions, syndromes or tests familiar to those working in clinical pathology laboratories.

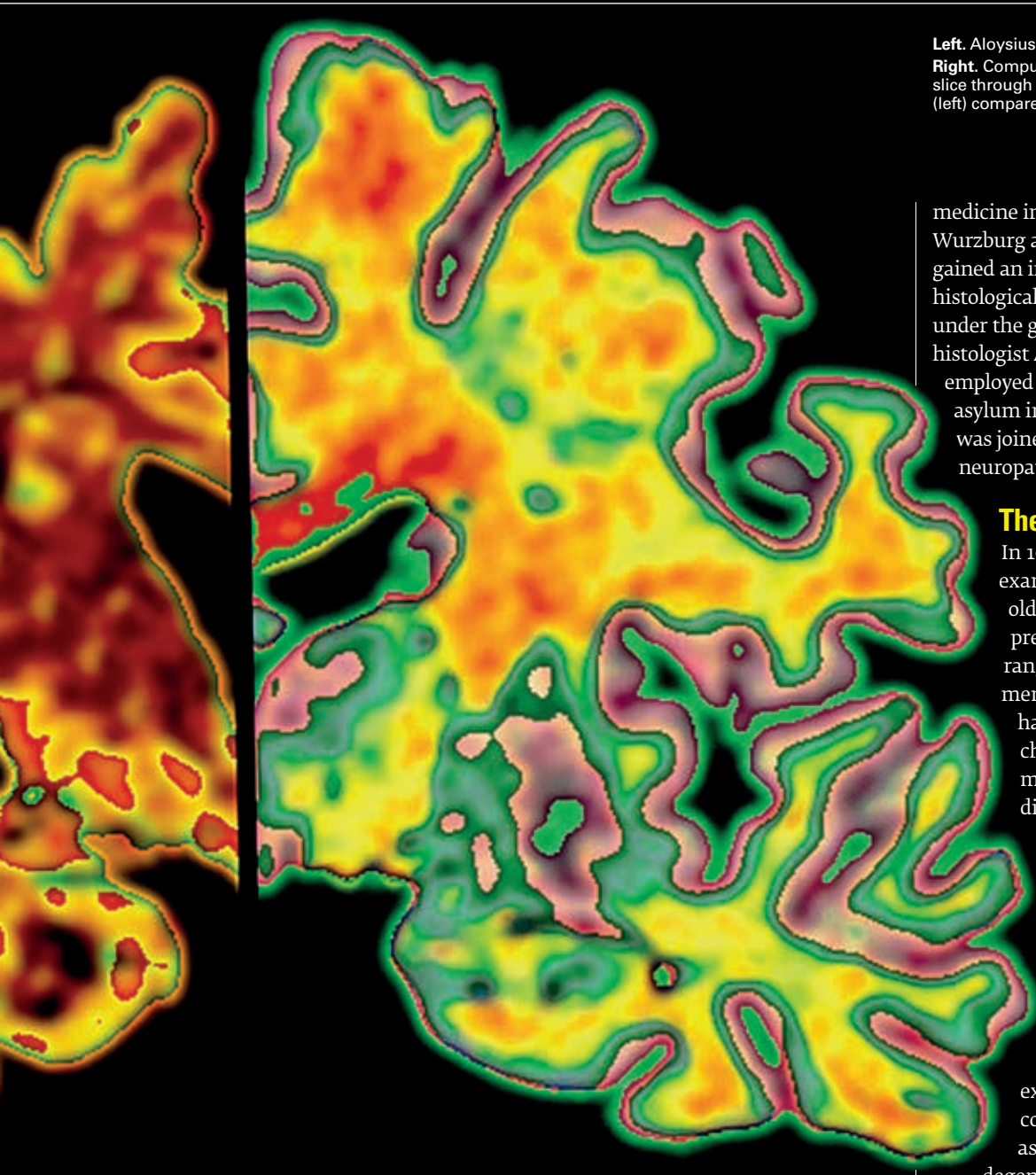
In the 3rd century BC, the Greek physician Herophilus differentiated the cerebrum and cerebellum, identified a number of cranial nerves and realised motor and sensory nerves were different. The great Flemish anatomist Andreas Vesalius published *De Humani Corporus Fabrica* in 1543, which contained the most complete description of the anatomy of the brain. Over a century later, Thomas Willis, an English physician, pioneered research on the brain and nervous system through his publications, notably *Pathologiae cerebri*, which described the pathology and neurophysiology of the brain. He is regarded as the founder of clinical neuroscience.

During the late 19th century, advances in neuroanatomy were achieved by the German neurologist Korbinian Brodmann to map the cytoarchitecture of the cerebral cortex. This promoted the wider use of histopathological techniques on brain tissue using microscopy with improved tissue processing and staining procedures. Foremost stains for nervous tissue were developed by Camillo Golgi in 1873 and Santiago Ramon y Cajal in 1889. Golgi found that when treating brain tissue sections with silver chromate a relatively small number of neurons were darkly stained. Later Cajal resolved in detail the structure of individual neurons and his work supported the neuron doctrine – that neurons are the basic structural and functional units of the nervous system.



The concept of dementia

This can be traced to ancient Egypt, Greece and Rome, where it was regarded as an inevitable consequence of growing old with mental and cognitive decline and regression of mental abilities. From the 16th century with advances in anatomical pathology, cerebral atrophy was often observed. People with mental illness or



Left. Aloysius Alzheimer and coworkers.
Right. Computer graphic of a vertical (coronal) slice through the brain of an Alzheimer's patient (left) compared with a normal brain (right).

IMAGES: ALAMY/SCIENCE PHOTO LIBRARY/ISTOCK

intellect deficit were confined to asylums or institutes. However, French physician Phillipe Pinel (1745-1826) pioneered the more humane care and treatment of those judged mentally ill in asylums and in 1797 he coined the term "dementia" of those showing symptoms such as short-term memory loss and wild, often aggressive behaviour.

In 1822, the English physician James Prichard published a treatise on insanity and introduced the term senile dementia.

In the 1890s, Swiss neurologist Otto Binswangler and Aloysius Alzheimer described the role of atherosclerosis and stroke in brain atrophy and senile dementia.

The scene was set

Knowledge of the general anatomy of the brain and the development of silver stains in the preceding years were crucial to the landmark discovery of Alzheimer's disease (AD). Alzheimer was meticulous in his microscopy work, and most of all he had the fortuitous opportunity to extensively interview the index patient with compassion and the foresight to realise her type of dementia was a new finding.

Aloysius Alzheimer (1864-1915)

The German physician, psychiatrist and neurologist was born in Marktbreit, a small Bavarian city in Germany, studied medicine in Berlin, Tubingen and Wurzburg and qualified in 1887. Alzheimer gained an interest and competence in histological techniques while at Wurzburg under the guidance of the renowned Swiss histologist Albert von Kolliker. He was first employed at a state institute mental asylum in Frankfurt-am-Main and was joined there by the German neuropathologist Franz Nissl in 1889.

The index patient

In 1901, Alzheimer was asked to examine and interview a 51-year-old female, Auguste Deter, presenting with an intriguing range of symptoms, notably memory loss, paranoia, delusions, hallucinations, psychological changes and marked left-sided muscular weakness. She also displayed abnormalities in comprehension, speech, reading and writing and Alzheimer had never seen such a range of symptoms combined before. During the interview, frustrated by her inability to respond, Auguste remarked: "I have, so to say, lost myself" – a poignant expression of this devastating condition. Auguste was assessed as an unusual form of presenile degeneration with dementia. Despite moving on, Alzheimer maintained an interest in her progress.

In 1902, Alzheimer moved to the University of Heidelberg after an invitation by the distinguished German psychiatrist Emil Kraepelin, who has been hailed as the founder of modern scientific psychiatry. He worked again with Nissl and shared a common research interest in the pathology of the cerebral cortex and Nissl developed a histological stain for alcohol-fixed sections of neural tissue using basic dyes to stain and highlight certain structural features of neurons. In 1903, Alzheimer followed Kraepelin to the University of Munich where he specialised in teaching microscopy and interpretation

Stool testing

LIAISON® Calprotectin

The new standard in Calprotectin quantitation

FOR MORE INFORMATION CONTACT:

DiaSorin Ltd

T: +44 (0) 1322 317949
E: info@diasorin.ltd.uk
W: www.diasorin.com

DiaSorin

The Diagnostic Specialist

FOR OUTSIDE THE US AND CANADA ONLY

Left. Auguste Deter – the first person to be diagnosed with Alzheimer's disease.

of results in a large anatomical laboratory that soon gained an international reputation under his leadership.

Death of Auguste Deter

Auguste's condition was deteriorating, with more aggressive behaviour, unintelligible speech leading to aphasia, apathy and became withdrawn in her final year until her death in 1906 from septicaemia. Alzheimer requested her case records and brain be sent to Munich for anatomical and histopathological examinations in an attempt to explain her unusual condition. At autopsy the brain was reduced in size and microscopic examination of sections with Max Bielschowsky's silver stain were examined by Alzheimer, and two physicians Gaetano Perusini and Franscesco Bonfiglio. The brain was atrophied with a massive loss of cells, the sections showed unusual, thick and strongly staining neurofibrillary clumps or "tangles" (NFTs). In addition, there were deposits in the form of "plaques" of an unidentified substance throughout the cerebral cortex.

In 1906 Alzheimer presented her case and histology at a South West German meeting of psychiatrists and was disappointed by the lack of interest. Nevertheless, his presentation was published in 1907. During the following year, three more of his patients had similar symptoms to Auguste Deter and the same "hallmark" changes on autopsy. These were reported by Perusini in 1909 with sketches of the NFTs.

The influential Emil Kraepelin published his *Textbook of Psychiatry* in 1910 and credited Alzheimer for the condition that he had described. In 1911, Alzheimer published the clinical and histopathological results of Auguste Deter and included his second patient Johann F who displayed the same features, except for an absence of NFTs in brain sections. This may be classified as a less common

Frustrated by her inability to respond, Auguste said "I have, so to say, lost myself"

"plaque-only" form of AD. In 1911 Alzheimer assisted Arnold Pick by performing histology studies to identify the "Pick bodies" – ovoid, smooth-edged neuronal inclusions using silver staining.

In 1912 Alzheimer was appointed professor of psychiatry at the University of Breslau in Poland. However, following a serious infection his health deteriorated and he died just aged 51 in December 1915.

Legacy of Aloysius Alzheimer

Alzheimer reported the first case of this devastating disease over 100 years ago, describing the early onset of dementia, severe symptoms and the progressive pattern of dementia. Strange as it seems, his findings were largely disregarded for at least five decades, and cerebral vascular disease and stroke were held responsible for cognitive decline in later life.

AD revisited

There was a long-running debate that dementia was a natural part of ageing and this was more scientifically investigated by a research team, led by Martin Roth at Newcastle upon Tyne University, commencing with their landmark studies reported in 1966. Quantitative methods were developed to score the severity of dementia, such as Gary Blessed's dementia test, and the score compared with counts of the number of senile plaques and a significant correlation was found between plaques and quantitative measures of intellectual and personality deterioration.

In 1976, leading US neurologist Robert Katzman argued that no distinction should be made between AD and senile dementia and projected that there were over a million cases of AD in the US that year, which could lead to around 750,000 deaths.

Senile plaques and NFTs

The chemical composition and structure of these cardinal features of AD were unknown to Alzheimer, but with renewed interest in AD and the added power of electron microscopy and biochemical analysis, advances were made. In 1963 London-based researcher Michael Kidd used electron microscopy to describe the paired helical filaments of NFTs and in the same year US neuropathologist Robert Terry found that tangles were paired microtubules organised as a double helix. In the following year the same two researchers independently studied the senile plaques in more detail and Terry found the nucleus of senile plaques mainly consisted of amyloid protein. In 1984 physician George Glenner and biochemist Caine Wong at the University of California sequenced the amino acids of the amyloid-β protein (Aβ) as a 40-42 peptide. A year later Australian neuropathologist Colin Masters and German molecular biologist Conrad Beyreuther isolated Aβ in cerebral plaques, which led to the characterisation of amyloid precursor protein – a transmembrane polypeptide of 771 amino acids found in almost all tissues, and located its encoding gene on chromosome 21.

In 1986 Terry and protein biochemists Khalid Iqbal and Inge Grundke-Iqbal isolated tau protein associated with the microtubules of NFT.

AUTOMATE YOUR MICROBIOLOGY WORKFLOW AND SERVE PATIENTS FASTER

Introducing the DxM 6100 Autoplak Advanced system

Advance efficiency in the laboratory by automating plate streaking, broth inoculation and slide preparation with the DxM 6100 Autoplak Advanced system.

- **Inoculate and standardize streaking of up to 125 plates per hour through set protocols and robotics**
- **Automate decapping and recapping of multiple specimen containers**
- **Simplify processing of challenging specimens, such as stool and sputum**
- **Decrease turnaround time by minimizing the need for subculturing**

Learn more at beckmancoulter.com/dxmautoplak-ppc

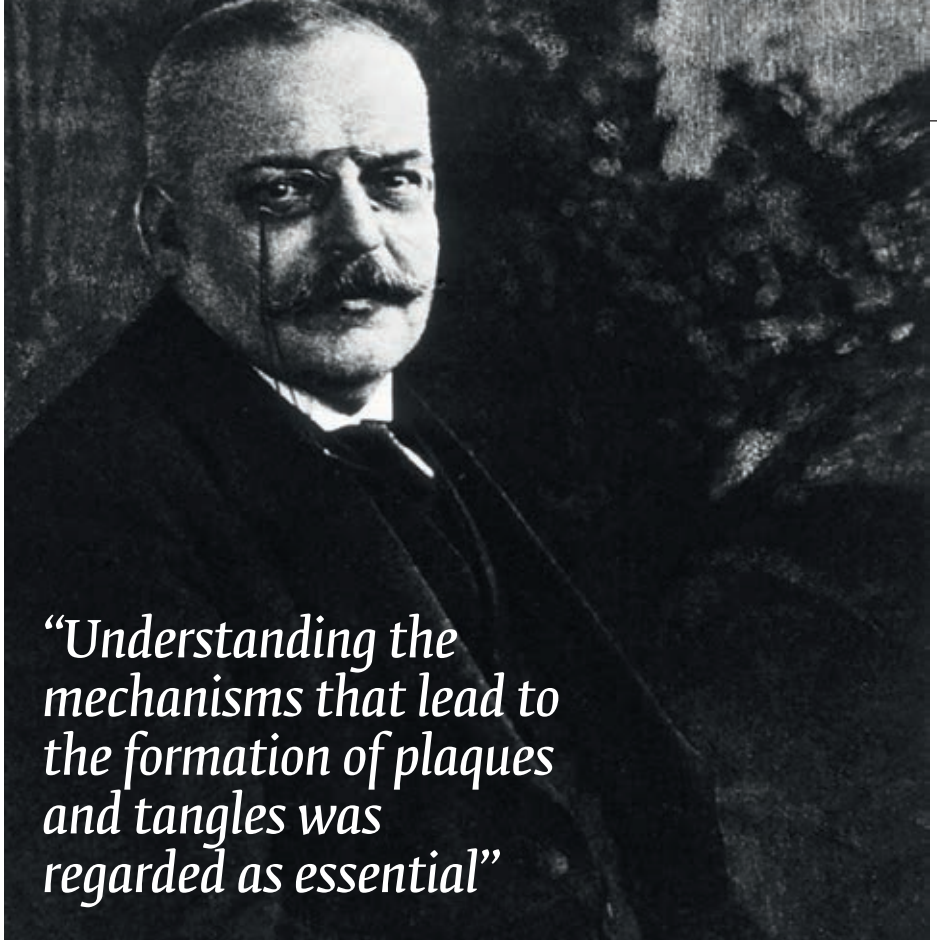
Not available in all countries.

Autoplak and Autoplak Advanced are property of SENER Ingenieria y Sistemas, S.A.

AD-137391

BECKMAN COULTER

Move healthcare forward.



Left. Aloysius Alzheimer (1864-1915) – the German psychiatrist after whom Alzheimer's disease is named.

"Understanding the mechanisms that lead to the formation of plaques and tangles was regarded as essential"

Cause of dementia in AD

Understanding the mechanisms that lead to the formation of plaques and tangles was regarded as essential to the design of therapeutic options. In 1992 British neuroscientists John Hardy and Gerald Higgins proposed the amyloid cascade hypothesis in that aggregation of Aβ interferes in neuronal signalling to cause dementia and, despite some controversy, this is the current dominant view on the cause of AD. The aggregates begin in the cerebral cortex and toxic dimers and oligomers are formed, which develop into diffuse and fibrillar insoluble plaques. Their increasing presence may cause oxidative injury and damage to synapses, which leads to hyperphosphorylation of tau protein and tangle formation. The cascade of events, which may take over a decade, ultimately results in severe and widespread neuronal dysfunction and dementia.

In 2004 the mitochondrial cascade hypothesis was postulated that reduced cell energy promotes tau phosphorylation in sporadic and autosomal dominant AD. Oxidative stress may be involved in the pathogenesis of AD. Neuron components may be oxidised due to mitochondrial dysfunction, inflammation or presence of excess Aβ peptide leading to Aβ deposition and hyperphosphorylation of tau and loss of synapses and neurons.

The existence of a genetic risk factor for AD, notably the apolipoprotein E ε4 genotype, which reduces the efficiency of repair mechanisms and clearance of plaques and tangles, has been recognised.

The diagnosis of AD

In 1984, the US National Institutes of Health produced criteria for the diagnosis of AD. However, this only addressed the final stage of dementia and focused on memory loss. This was revised in 2011 due to a greater understanding of AD and the availability of biomarkers. There is an acceptance that there is a spectrum of AD progression with three stages. Firstly, an early preclinical stage without symptoms but with amyloid deposition in the entorhinal cortex and hippocampus. This is followed by mild cognitive impairment (MCI) with symptoms which include memory loss, confusion and thinking ability difficulties with continued brain changes, but MCI may persist and not develop into AD. The increasing range of symptoms tends to match the increase of plaques and tangles and the cortical areas affected. In the final stage there is a failure to recognise family or loved ones, loss of effective communication and total dependence on care and ultimately death from other causes, frequently aspiration pneumonia. The life expectancy following diagnosis varies but may be three to nine years.

CSF and plasma biomarkers

With developments in the treatment of AD during the 1990s, research attention turned to early biomarkers to predict whether MCI will progress to AD with dementia. Enzyme-linked immunosorbent assays were developed for CSF Aβ and total tau and numerous studies were performed to evaluate their diagnostic performance. Subsequently assays were available for peptide fractions of CSF Aβ, tau and phosphorylated tau. CSF Aβ is typically decreased in AD and tau increased. There is some evidence that these assays improve discrimination with other dementias. However, a 2018 Cochrane review cites insufficient evidence for their use in routine settings, as these are invasive and expensive assays, which may lead to overdiagnosis and thus overtreatment. A plasma Aβ assay has been developed at Washington University School of Medicine, using immunoprecipitation, liquid chromatography mass spectrophotometry to measure Aβ42 & Aβ40 with a ratio which correlated well with amyloid PET scans.

A study in 2019 by research teams at King's College, London and the University of Gothenburg have identified new biomarkers of AD pathology in cognitively unimpaired individuals independently replicated(confirmed) by non-targeted mass spectrometry

MRI, PET & FDG-PET imaging

Although expensive and time-consuming, neuroimaging can make a significant contribution to the diagnosis and prognosis of AD and a number of imaging modalities using MRI and PET are available to study cerebral metabolism and characteristic brain changes in AD.

Structural MRI has the advantage of allowing 3D assessments, notably of the size of the hippocampus. Molecular methods with fluorodeoxyglucose -PET (FDG-PET) or single photon CT can provide more diagnostic specificity. Medial temporal lobe atrophy is regarded as a predictor of cognition in MCI. Pittsburgh compound B PET scans match histological distribution of Aβ in ageing and AD. Neuroimaging can also be used to detect MCI and exclude other causes of dementia, such as multiple infarcts, subdural haematoma or brain tumours.

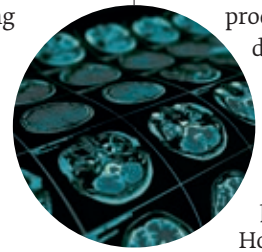
CT and MRI scans are primarily used to assess cerebral and hippocampal atrophy, enlarged cortical sulci and ventricles. However, there is low specificity.

Functional MRI can be used to measure cerebral perfusion and detect focal areas of hypoperfusion, which may occur in AD. PET imaging can be used for non-invasive quantitation of cerebral blood flow, metabolism and receptor binding and is used for diagnosis, to monitor disease progression and the response to treatment. FDG-PET can be used to detect temporoparietal glucose hypometabolism, characteristic of AD, and correlates with severity due to neuronal cell loss and decreased synaptic activity.

Large studies, such as those in Australia, the long-term AIBL and DIAN cohort studies, used a combination of imaging and CSF biomarkers whilst another large study IDEA in the US only used amyloid PET scanning to differentiate AD from other dementias. The AIBL also considered risk factors for AD and identified obesity, cardiovascular disease, hypertension, insulin resistance, type 2 diabetes and stressed the importance of lifestyle including diet, exercise, sleep and stimulating activities.

Treatment-inhibitors

In 1976, British neuroscientist David Bowen, using autopsy



"It is predicted that the number of people with dementia will double every 20 years"

tissue and cerebral biopsies, showed that the enzyme responsible for the synthesis of acetylcholine was deficient in AD tissue. It was later shown that cholinergic neurons were low in the cerebral cortex and substantia innominata and were replaced by plaques and NFTs. Consequently, to maintain adequate reserves of acetylcholine, drugs were used to inhibit the catabolic enzyme acetylcholinesterase (AChE). In 1986, US neuroscientist William Summers reported that the synthetic drug tacrine inhibits AChE and appeared to improve patients with AD, and tacrine was FDA approved in 1993. However, with a growing list of serious side effects and fatality it was withdrawn and replaced by safer and more effective second-generation oral AChE inhibitors such as donepezil (1996) and galantamine (1998) In 2002, oral memantine was introduced – a voltage-dependent, N-methyl-D-aspartate receptor antagonist to block tonic levels of glutamate. All three drugs are approved by NICE but may only result in modest improvements in patient management, cognitive processes and behaviour, and even this outcome may be short-lived, typically 12 months.

Aβ immunotherapy

Based on the amyloid cascade hypothesis, treatment research has focused on the production, clearance and deposition of Aβ and immunological procedures using specific monoclonal antibodies are undergoing clinical trials with some promising early results. However, recent studies have suggested that Aβ accumulation may be secondary and a compensatory event only and not pathological. In an alternative approach, the inhibition of β-secretase, involved in the initial production and deposition of Aβ, has been investigated but finding a safe and effective inhibitor has proved most challenging.

Tau protein immunotherapy

Tau protein has also been targeted for therapy for AD by attempting to clear tau involved in propagation to attempt to slow the spread of tau pathology and possibly cognitive decline. During the last decade some positive results of immunotherapy have been demonstrated in animal models. Both passive and active immunotherapy clinical trials have been performed but are under revision due to adverse reactions.

Discussion and conclusion

Well over a century after Alzheimer described AD there is a much better understanding of the mechanisms involved in the pathology of AD and the central role of Aβ .

There have been significant advances in brain imaging and CSF biomarker methods have been developed and with the increasing size of the ageing population it makes early detection and effective treatment of the highest priority. The neurological trauma to the patient and the stress and distress to their families is incalculable.

Alzheimer's disease is responsible for around 78% of degenerative dementias and it is estimated there are 47 million people living with dementia worldwide including 850,000 in the UK with respected support from the Alzheimer Society and Alzheimer Research UK. It is predicted that the number of people with dementia will double every 20 years. IBMS

Stephen Clarke is a retired IBMS Fellow.

To read this article with full references, visit **thebiomedicalscientist.net**

PHOENIXSOFT

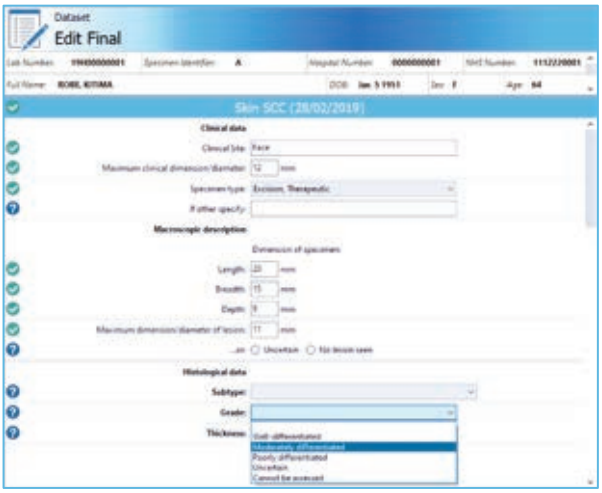
COSD COMPANION

The solution for COSD data collection

Compliance with COSD Pathology v4 (COSD v9) is required from 1st October 2020

Developed with the assistance of NHS Trust histology consultants, COSD Companion has been in successful operation since January 2017, meeting evolving regulatory requirements by facilitating rapid, intuitive and accurate reporting of all cancer datasets.

- Data captured using COSD-specific datasets or Royal College of Pathologists proformas
- Extracted data is compliant with the latest COSD format
- COSD extract verified by the National Cancer Registration and Analysis Service (NCRAS)
- COSD entry provides a formatted, user-defined clinical report
- Installation and setup, providing full compliance, in one day (subject to available hardware and infrastructure)



A practical and intuitive workflow…

PPI — Workflow starts with positive patient identification using demographics from your LIMS.

Select Dataset — Dataset selection follows; available datasets can be filtered by category to ease selection.

Dataset Entry — Relevant questions are answered by selecting from predefined options or entering text where necessary. Partially completed datasets can be saved for later completion.

Clinical Report — When complete, the dataset information is ready for extraction, and a clinical report document is made available for import into your LIMS.

COSD Extract → **NCRAS** — Data extraction, in the COSD Pathology v4 (COSD v9) format, is produced on demand for submission to the NCRAS.

COMPLIANT

- ✓ 25 COSD datasets supported
- ✓ 51 Royal College Pathology reporting proformas supported
- ✓ 2 Public Health England reporting proformas supported
- ✓ Positive patient identification
- ✓ Final and Supplementary reports supported
- ✓ Customisable patient clinical report templates
- ✓ On demand extraction data for submission to the NCRAS
- ✓ Full compliance with COSD Pathology v4 (COSD v9) format
- ✓ Automated import of COSD Datasets
- ✓ Rapid installation and deployment with minimal configuration
- ✓ Intuitive and modern user interface
- ✓ Additional datasets and proformas developed upon request
- ✓ Access to all data for statistical analysis
- ✓ Options for LIMS connection

Please contact us, quoting IBMS1, for further information, pricing or to arrange a demonstration

web: www.phoenixsoft.co.uk
email: contact@phoenixsoft.co.uk

RETROGRADE EJACULATION

A PROPOSED METHOD TO ALLOW ISO 15189 ACCREDITATION

David Sanders and colleagues discuss laboratory assessment of samples for retrograde ejaculation and outline how accreditation could work.

Retrograde ejaculation occurs when semen enters the bladder instead of emerging from the penis during orgasm. There are several causes of retrograde ejaculation, including:

- Surgery to the bladder neck, prostate or retroperitoneal lymph node
- Some medication for the treatment of high blood pressure, depression or enlarged prostate gland may have side effects including an increased likelihood of retrograde ejaculation
- Nerve damage due to a spinal cord injury or medical conditions affecting the nervous system
- Congenital defects, such as utricular cysts.

Diagnosis is based on the absence of sperm in the antegrade ejaculate and the presence of sperm in post-masturbatory urine. Retrograde ejaculation may be suspected whenever the semen volume is significantly reduced, not present or intermittent.

Whilst retrograde ejaculation is relatively rare, it is important to distinguish it from the absence of ejaculate (aspermia) rather than just the absence of sperm (azoospermia). The treatment options for these are potentially different.

Compared with semen analysis for fertility assessments and post-vasectomy clearance, requests for examination of urine samples for spermatozoa as part of the investigation of retrograde ejaculation are very low. It is the small numbers of samples received by the diagnostic laboratory that deters laboratories adding the examination of urine for spermatozoa to their scope of accreditation.

The correct diagnosis of patients with retrograde ejaculation is important, potentially preventing a patient from having to undergo unnecessary surgical sperm retrieval. Therefore, any diagnostic test performed on these patients should be performed accurately and under the same levels of control as any other diagnostic test.

Assessments and examinations

Laboratories that are ISO 15189 accredited for fertility assessments and post-vasectomy analysis of semen samples should already be able to evidence their ability to detect and count low numbers of sperm and to assess sperm motility. Whilst these assessments are performed on seminal fluid, transferring these techniques to urine is not difficult as the media in which the sperm are present is the only change. In addition, the laboratory will have to consider both how they are going to control these assessments, given the infrequency with which they are received, and how they address uncertainty.

Determination of retrograde ejaculation is performed in the diagnostic laboratory by the examination of post-orgasmic urine samples.

As sperm denatures in urine, examination should be carried out within 30 minutes (no later than 60 minutes).

There is no need to alkalise the patient's urine as the laboratory is determining whether there are sperm in the urine and the medication of patients can bring another set of complications. This is not to say that alkalinisation is incorrect, but will need to be considered carefully if this is a requirement of the referrer.

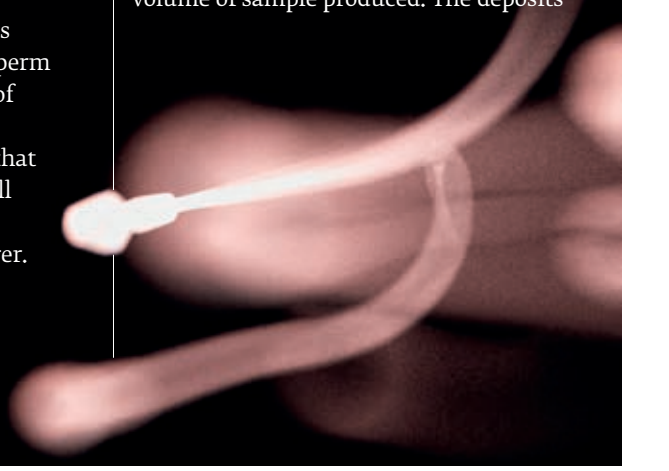
Processing samples

Laboratories processing samples with a view to retrieving sperm should consider an appropriate buffer. The patient should be asked to empty their bladder and then shown to the sample production room. They are given two labelled sample containers; one in case they produce an ejaculate and the second to collect a urine sample. Each one should be clearly marked with the fluid to be collected. The patient is instructed to masturbate until they achieve a sensation of orgasm, collecting any fluid they produce into one of the containers. They are then to urinate into the second sample container, collecting all fluid produced. It is important that the collection container used for the ejaculate is accepted into use by means of a sperm toxicity testing procedure.

Any ejaculate produced is examined following normal WHO 2010 protocols for fertility analysis.

Urine should be examined for macroscopic semen threads within the urine that can be aspirated and examined as a wet prep using phase contrast illumination. If the urine is clear the authors recommend using phase contrast illumination and a minimum of 25ul for an initial scan. Historical practice suggested 10ul volumes be used, but there are no published data regarding the lower level of detection using this small volume.

If no sperm are seen on the direct microscopy, centrifuge the whole sample, using conical tubes, at 500g for 10 minutes. This may require several centrifuge tubes depending on the volume of sample produced. The deposits



IMAGES: SCIENCE PHOTO LIBRARY

from all the tubes should be resuspended and combined before centrifuging again at 500g for 10 minutes. The deposit is resuspended in a small volume (<0.5ml) of the supernatant and examined using phase contrast illumination at x200 or x400 magnification.

The laboratory should determine how it will assess and report the detection/absence of sperm in conjunction with the clinical lead and users of the service.

Accreditation

Because of the methodology used and the infrequency of testing, many laboratories see this as a barrier to accreditation. To achieve accreditation, the testing laboratory needs to be able to validate the methodology they use, be able to provide an estimation of uncertainty for the test and be able to demonstrate that there are robust controls in place for the test.

The use of large volume, disposable chambers may provide a solution to some of the challenges. When assessing post-vasectomy semen samples these slides have been shown to be at least as sensitive as the centrifugation methods. Examination of post-orgasm urine samples is in principle similar. However, Poiseuille flow of specimen into these chambers causes migration of any suspended cells in a direction transverse to the flow, which results in their preferential accumulation in the Segre–Silberberg (SS) planes. This SS effect depends on the velocity gradient in the laminar flow and varies between semen and urine. For this reason laboratories must establish the lower levels of detection that are achieved in urine.

It is not practical given the small number of urine samples potentially received by a laboratory to validate the method by parallel testing of patient samples. Validation can be performed using samples prepared in house. This can be done using urine or another fluid, such as a commercial sperm diluting/wash fluid. A known volume of diluent can be seeded with a volume of seminal fluid. The seminal fluid should be well liquefied and be shown to have a reproducible concentration. From this, it is possible to determine the number of sperm present in the volume of diluent. The sample can then be processed by both centrifugation and large volume chamber methods to determine correlation. It is possible that the centrifugation method will demonstrate a higher level of sensitivity over the large volume chambers when examining large volumes of urine. However if the patient is producing their sample on an empty bladder the volume of urine to examine is normally less than 100ml.

Controlling processes

To determine the uncertainty associated with this method, or the lower limit of detection, seeded samples containing reducing concentrations of sperm can be produced. When staff examine these samples, there will be a calculated level of sperm below which they are not able to detect. This forms the minimum detection limit for the process.

The laboratory must have a robust IQC process, in line with ISO 15189 requirements. In view of the low numbers of potential analyses, samples should be examined by all analytical staff. This can work well if enough samples are received and staff are available when the samples arrive. In order to control these processes, we need to be more creative. Digital imaging allows for an unlimited number of staff to look at the same sample over an extended period of time. The laboratory should ensure that the quality of recording can provide unambiguous results. The laboratory may consider replicating a "sample" as they would for the validation process in order to ensure staff can prepare the sample and analyse as per protocol. There must be criteria in place for what may be acceptable for comparison of results between staff involved and justification of the approach, documented appropriately with evidence.

The video clips can be stored and viewed at any point. This means a relatively small library of video images can provide quality control over a considerable period. There is also no reason why they cannot be shared as a form of inter-laboratory comparison (ILC). However, laboratories should ensure they meet the requirements as laid out in EA-4/21. To further increase the robustness of the control processes, a seeded sample can be processed by laboratory staff to assess for systematic errors. It is incumbent on laboratories to ensure medical illustration/policies and trust procedures are adhered to, in addition to EA-4/21.

Conclusion

Whilst samples for determining retrograde ejaculation pose their own set of challenges, there are no reasons why a laboratory that is already ISO 15189 accredited for diagnostic semen analysis and post-vasectomy testing should not, with a little work, be able to add assessment of urine samples for sperm to their schedule of accreditation. BMS

David Sanders, freelance andrologist at DS Consulting, **Stuart Long**, Andrology Department, University Hospitals Birmingham NHS Foundation Trust, Heartlands Hospital, Birmingham, **Lauren Powis**, Wales Fertility Institute, University Hospital of Wales Cardiff, **Paul Hancock**, Association of Biomedical Andrologists.

To see this article with references, visit **thebiomedicalscientist.net**

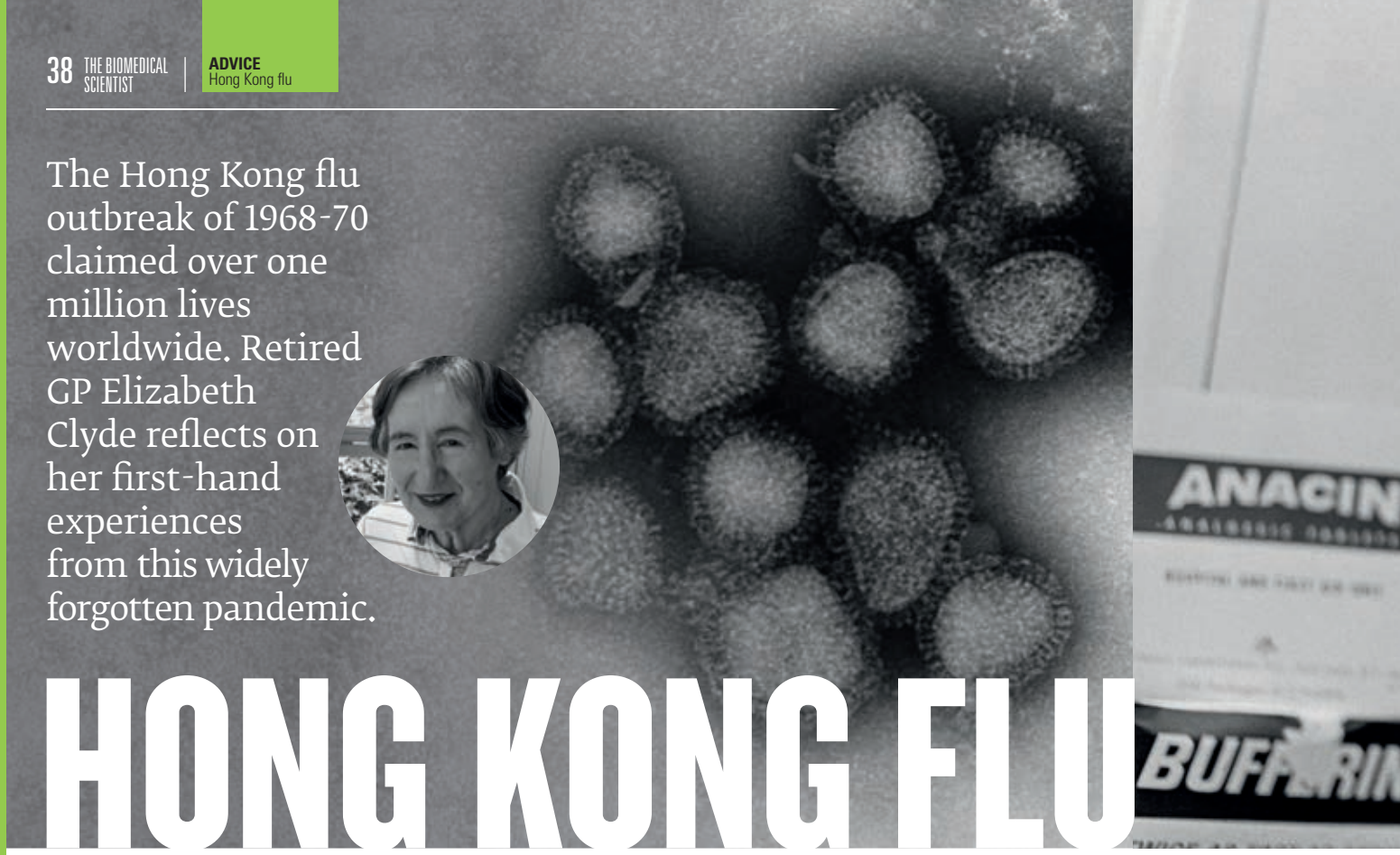
HOLOGIC®

PROUD
to play a part

This global pandemic has been a defining moment for diagnostics. We've delivered over 10 million tests to date and will continue to work with you and governments until the fight against COVID-19 is over.

To find out more visit: **hologic.com/COVID-19**

Creating Defining Moments Together



The Hong Kong flu outbreak of 1968-70 claimed over one million lives worldwide. Retired GP Elizabeth Clyde reflects on her first-hand experiences from this widely forgotten pandemic.

HONG KONG FLU

REMEMBERING THE FORGOTTEN PANDEMIC

In July 1968, a new strain of the influenza virus was identified in the then British colony of Hong Kong. Referred to by some as the "Mao Flu", due to a suspicion the virus originated in mainland China, Hong Kong flu rapidly spread across the globe, with more than 30,000 deaths in the UK, half of which were people aged under 65. The disease was considered to be mild compared to other flu outbreaks, such as the Spanish Flu, which is estimated to have killed around 50 million worldwide. With several major historical events occurring at a similar time – including the Moon landings, Vietnam war and Stonewall riots – Hong Kong flu is often overlooked and dubbed by historians "the forgotten pandemic".

A lack of measure

Nathaniel Moir, a postdoctoral fellow at Harvard University, said in the *New York Post*: "It was like the pandemic hadn't even happened if you look for it in history books. I am still shocked at how differently people addressed – or maybe even ignored – it in 1968 compared to 2020."

HONG KONG FLU FACTS

- ✔ Symptoms included: chills, fever, muscular aches, fatigue, cough, sore throat, runny nose, headache and vomiting and diarrhoea for some.
- ✔ Symptoms would last approximately 4-6 days, though could persist for two weeks.
- ✔ The first peak occurred in the winter school holidays and a vaccine was developed early, but not widely available until later.
- ✔ The pandemic occurred in two major waves – winter 1968-69 and 1969-70.
- ✔ The second wave of Hong Kong Flu in Europe and Asia had far higher mortality. This was not the case for the US.
- ✔ H3N2 still circulates today, among the usual seasonal winter flu strains.

There was no formal lockdown and no social distancing measures, as we see today. The advice from one Hong Kong official was to "stay at home and take aspirin, tea, lemon drinks, whisky or brandy, according to taste".

In the UK, the medical council alerted the public to the threat, saying it was likely to "spread through the country like wildfire".

The daughter of Phillip Snashall, a retired professor of medicine had the first case of Hong Kong Flu in Europe. He told the *British Medical Journal*: "How things change. The stock market did not plummet, we were not besieged by the press, men in breathing apparatus did not invade my daughter's playgroup."

Society had experienced the Spanish and Asian flu, the Second World War and diseases such as tuberculosis and measles were commonplace. There was also less pressure for governments to act in a world without social media, 24/7 news and the internet.

"That generation approached viruses with calm, rationality and intelligence", said Jeffrey Tucker, from the American Institute for Economic

Research. "But as with now, no one knew for certain how deadly it would turn out to be. Regardless, people went on with their lives".

Nathaniel Moir added: "There were few precautions taken during the H3N2 pandemic other than washing hands and staying home when sick."

Highly contagious

Due to advances in technology and healthcare, the virus was quickly identified by virologists as the H3N2 strain of the influenza A virus, thought to have jumped to humans from pigs. However, it descended from the earlier H2N2 Asian flu strain.

Hong Kong Flu was highly contagious and spread fast – first across Southeast Asia, then the world, including Australia, Africa, Europe and South America, reaching the US via troops returning to California from Vietnam in October 1968. *The Wall Street Journal* reported that corpses were being stored in Berlin underground tunnels and binmen were recruited to bury bodies due to undertaker shortages across West Germany. The virus is also reported to have infected prominent individuals including US president Lyndon B. Johnson, who said it was the worst he had felt in his life and NASA astronaut, Frank Borman – who fell ill to a flu-like illness while orbiting the moon on board Apollo 8.

On the frontline

Elizabeth Clyde, 77, is a retired GP who was working as a trainee doctor in her early twenties in Edinburgh during the Hong Kong flu pandemic. "A few weeks after the start of my GP training in an Edinburgh practice there was a recurrence of flu," she says. "We were very busy visiting ill patients and I, being the youngest and fittest, was allocated visits in tenements."

On her rounds, Elizabeth would enter several patients' flats every day and was not provided with any type of personal protective equipment. "We had no protective equipment and I didn't worry because I was in my twenties and I knew that most people in that age group would get over it. I got the flu a few weeks after treating patients and recovered quickly."

Upon arriving at the patient's home, Elizabeth would assess the general condition of the patient before checking for Hong Kong flu. "I'd enquire about cough and sputum, examine the chest and when you listened, a lot of them had very early chest symptoms."

In severe cases, the virus would weaken the lungs enough to allow opportunistic secondary bacterial infections to take hold – frequently pneumonia, leading to hospitalisation and, in some cases, death.

"A lot of people got over it without any treatment. If there was the slightest doubt they were getting a chest infection, I would prescribe a course of broad-spectrum antibiotics to the very elderly, diabetics, smokers, and those who would be shielded these days were prescribed prophylactic oral antibiotics even though their chest was clear," says Elizabeth.

"There were no antiviral drugs at that time and the flu vaccine was in its infancy. The hospitals were absolutely full of patients who started with flu and developed pneumonia. Ambulances had to check which hospitals had free beds."

The concept of self-isolation and social distancing wasn't as well developed or universally enforced as with the current pandemic. Asked about the social distancing and lockdown measures in place at the time, Elizabeth said: "Although I did say to people who had flu and other members of their family to stay in until their risk of infection was over, there were no general instructions to people to stay at home."

As Hong Kong Flu began to subside, Elizabeth was immediately faced with a new major threat: "As the flu gradually died out, I remember there was a measles epidemic after that and I was quite busy with that, as there was no immunisation against measles in those days". BMS

IMAGES: ALAMY/GETTY/©DR. FRED MURPHY-CDC

VITAMIN K DEFICIENCY: A CASE STUDY

Alison Hadfield, a Healthcare Science Section Leader in core haematology from the Newcastle upon Tyne Hospitals NHS Foundation Trust, presents a vitamin K-deficiency patient case study.

Bloods were received into the laboratory of a 73-year-old male about to have a re-do of an aortic valve replacement. Coagulation screen results showed a prolonged prothrombin time (PT) of 111 seconds (NR=10-13 seconds) and a prolonged activated partial thromboplastin time (APTT) of 109 seconds (NR=27-39 seconds) with a normal fibrinogen. The previous coagulation results a month before were normal, although the PT was prolonged by one second. Further tests, including mixing studies, thrombin time and a protamine time, were performed, and the results were phoned urgently to the cardiac theatre team.

Bleeding

The laboratory then received a phone call from the Consultant Haematologist. The patient was not on any anticoagulants, and was on the theatre table undergoing cardiopulmonary bypass when the abnormal results were phoned. Vitamin K dependent factors (II, VII, IX and X) were requested and performed urgently, and the consultant had advised theatre staff to give a bolus injection of vitamin K and transfuse fresh frozen plasma (FFP) as required.

Surgery went ahead, but when the patient was returned to intensive care they were bleeding into their drain – 375mL in the first 30 minutes, and then a further 175mL in the next 30 minutes. Further FFP, plus red cells and platelets, were transfused, and protamine and tranexamic acid administered in an attempt to stem the bleeding. After the patient had drained 1250mL in three hours, a decision was made to return to theatre to look for a source of bleeding.

No source was found, the patient returned to ICU where their condition deteriorated and they passed away a few hours later. In total, the patient received 20 units of packed red cells, 11 bags of FFP and 2 bags of platelets.

Looking back

The results of the factor assays confirmed that the patient was suffering from vitamin K deficiency. All of the vitamin K dependent factors were below 10%. The Factor VIII was normal, proving that the issue was vitamin K-related. In hindsight, a Factor V should also have been performed to prove that the patient was not suffering from liver failure, although there was no indication of this in the patient's notes and his liver function tests were normal pre-operatively.

Looking back in the notes there were clues that the patient was suffering from a bleeding disorder. It was noted eight days pre-op that the patient had a large haematoma, where blood samples had been taken the previous day. The day before surgery bloods could not be taken due to "bruising from previous cannulation causing hardening and causing him pain". The patient also had a tracheostomy in place following laryngeal cancer 16 years previously and the site of this was bleeding.

However, no coagulation tests were sent to the laboratory until a pre-operative thromboelastography was performed in the cardiac theatres and revealed some abnormalities, such as a prolonged R (reaction) time.

Causes of deficiency

There are a variety of causes of vitamin K deficiency, although it is more common in babies and is relatively rare in adults.

IMAGES: GETTY/ISTOCK

TABLE 1. TEST RESULTS

	Result	Normal Range
Prothrombin Time	111 seconds	10-13
Activated Partial Thromboplastin Time	109 seconds	27-39
PT-derived Fibrinogen	4.6 g/L	2.1-4.8
Thrombin Time	17 seconds	12-16
TT with Protamine added	13 seconds	10-16
PT 50:50 mix with normal plasma	15 seconds	
APTT 50:50 mix with normal plasma	Not performed	
Actin FS (Lupus insensitive aPTT)	127 seconds	22-33
Factor II	7%	50-150
Factor VII	4%	50-150
Factor VIII	233%	50-150
Factor IX	8%	50-150
Factor X	3%	50-150

All neonates should receive a vitamin K injection shortly after birth to prevent vitamin K deficiency bleeding, although parents have the right to refuse this. Newborn infants are at an increased risk for a number of reasons, including: breast milk being very low in vitamin K, not producing their own vitamin K in the first few days of life, and an immature liver not using the vitamin efficiently.

In adults the most common causes are dietary deficiency, prolonged use of antibiotics, and fat malabsorption syndromes, such as coeliac disease or cystic fibrosis. This particular patient had been prescribed antibiotics over three weeks prior to his death for infective endocarditis, which eventually led to him requiring surgical intervention. He was also described as having a poor dietary intake.

These factors almost certainly led to him becoming vitamin K deficient. Because of the short half-life of the relevant factors, deficiency in the right circumstances can develop relatively quickly.

Vitamin K is fat-soluble, which is a critical part of the coagulation cascade. It is a co-factor for y-carboxylation, which is required for the synthesis in the liver of factors II, VII, IX and X, as well as the anticoagulant proteins, protein C and S. As both the intrinsic and extrinsic pathways of coagulation are affected, both the PT and APTT are affected, although the PT more so.

Lessons learned

This case study is a lesson for all involved on the importance of extensive note and history taking of patients and monitoring during a hospital stay, particularly if there is prolonged antibiotic use. Although rare, the development of vitamin K deficiency during an inpatient stay can have profound consequences, as this case study demonstrates. BMS

MY IBMS NEWS

HSST PROGRAMME

ENHANCED FLEXIBILITY FOR TRAINING

The IBMS and a range of other bodies have announced changes that enhance the flexibility of training for senior healthcare scientists.

The move means a broadening of the eligibility criteria for the Higher Specialist Scientific Training (HSST) Programme. The changes will have a direct and positive impact on newly eligible IBMS members who wish to undertake the programme.

IBMS Council member Dr Jane Needham, the IBMS lead on this project, said:

"This is really wonderful news. It provides a career pathway and an exciting opportunity for our biomedical scientists to apply and develop their clinical and scientific knowledge and expertise through the consultant-level HSST training programme, with the key benefit of improving and enhancing the clinical care and services we provide to our patients."

→ For more information on the changes, visit bit.ly/2Zxc3KD

SUPPORTING MEMBERS

Comment on replacing PHE

The IBMS has issued a comment in response to the government's announcement that it is replacing Public Health England (PHE) and transferring some functions to the newly established National Institute for Health Protection.

It says: "The IBMS recognises that the current lack of clarity on how the new institute will be structured is causing a great deal of anxiety amongst many of our members who are employed in PHE laboratories and laboratories providing public health support.

"The absence of any details around the new institute that is proposed to replace PHE and Track and Trace leads us to assume that the laboratory staff will still be key to the delivery of the new organisation. To support our members at this time, the IBMS will continue to work with our partners in pathology to highlight any concerns that arise from the government's plans.

"PHE laboratory staff have been working tirelessly during the pandemic, along with NHS laboratories, and the IBMS thanks our members for the vital contributions they have been making."

IMAGES: SHUTTERSTOCK

SAVE THE DATE

THE BIOMEDICAL SCIENTIST LIVE

A live four-day digital event has been announced, which is free for all IBMS members to attend.

The CPD event is called The Biomedical Scientist Live and is set to take place from 16 to 19 November.

A packed programme will be announced in the coming weeks and will include workshops, seminars, discussions and demonstrations.

It will feature some of the biggest names from the profession and industry.

The dedicated event website will be live soon and will include more information on how to sign up and the programme of talks. Members will be notified when the website is live.

IBMS STATEMENT

ASSESSING COVID TESTS

The IBMS has published a document outlining and assessing the principal testing options currently available for the SARS-CoV-2 virus (COVID-19).

This statement aims to support scientists and other laboratory professionals in selecting and advising on the most appropriate testing route for patients.

The information is based on known clinical need, the requirement to support the management of patients within different care settings, and the limited supply of rapid testing kits.

→ To download a PDF, visit bit.ly/3bTH3d0

JOURNAL-BASED LEARNING EXERCISES

Institute of Biomedical Science Continuing Professional Development

Please select your choice of correct answers and complete the exercises online at: **www.ibms.org/cpd/jbl**

DEADLINE WEDNESDAY 6 JANUARY 2021

A comparison of the HAIN Genotype CM reverse hybridisation assay with the Bruker MicroFlex LT MALDI-TOF mass spectrometer for identification of clinically relevant mycobacterial species.

O'Connor JA, O'Reilly B, Corcoran GD, O'Mahony J, Lucey B. *Br J Biomed Sci* 2020; **77** (3): 152–5. doi: 10.1080/09674845.2020.1732639. Assessment No: 090120

01	*Mycobacterium avium* can be isolated from immunocompromised patients.	11	According to the authors, Genotype CM does not require mycobacteria to be pure.
02	The authors of this study concluded that MALDI-TOF MS could be a potential replacement for the HAIN assay for *Mycobacterium tuberculosis* complex but not for non-tuberculous mycobacteria.	12	It is felt that MALDI-TOF MS may offer an appropriate replacement for traditional methods used in a routine diagnostic mycobacterial laboratory.
03	The authors quote Bruker as stating that a log-score value of 2.0 or more is considered a high-confidence identification.	13	Of the three isolates that failed to identify by MALDI-TOF, all had log-scores of >1.7.
04	According to the authors, MALDI-TOF MS does not require mycobacteria to be pure.	14	All samples used in the study came from either patients or UKNEQAS.
05	Few non-tuberculosis species are considered environmental contaminants.	15	In the study, only 45% of all *Mycobacterium tuberculosis* complex isolates had a log-score of greater than 2.0.
06	The authors conclude that MALDI-TOF offers advantages over Genotype CM if high throughput of samples offsets the initial capital cost.	16	The authors quote previous research as showing that MALDI-TOF MS was superior in identifying mycobacteria from primary liquid culture as compared to a solid medium subculture.
07	In the study, all MTB complex isolates identified by Genotype CM were also identified as such by MALDI-TOF MS.	17	The Genotype CM system is unable to identify *M. xenopi*.
08	One MTC isolate that had been identified by the HAIN system was a slow-growing isolate that MALDI-TOF MS failed to identify.	18	It is recognised that rapid identification of mycobacteria facilitates early therapeutic measures.
09	The authors suggest that when choosing an empiric therapy for *M. chelonae* knowing the species is critical.	19	In the study, all *M. abscessus* isolates identified by Genotype CM were also identified as such by MALDI-TOF MS.
10	The *Mycobacterium* genus encompasses >170 species.	20	The MTC isolates used in the study included 66 *M. tuberculosis* strains.

REFLECTIVE LEARNING

01	Within your own laboratory, reflect on the methodology presently used to identify mycobacteria and whether on balance it represents the best approach.

DEADLINE WEDNESDAY 6 JANUARY 2021

Digital morphology analyzers in hematology: ICSH review and recommendations.
Kratz A, Lee SH, Zini G, Riedl JA, Hur M, Machin S. International Council for Standardization in Haematology. *Int J Lab Hematol* 2019; **41** (4): 437–47. doi: 10.1111/ijlh.13042. Assessment No: 090420

01	It is easy to access secondary consultations when using manual microscopy methods.	11	According to this article, the DI-60 is a fully integrated system involving two Sysmex XT analysers, the SP-10 Sysmex slide making/staining device and a CellaVision instrument.
02	The Diffmaster Octavia was the predecessor to the current CellaVision models.	12	WBC classification by the DI-60 was considered acceptable for normal and abnormal samples, although user verification improved performance.
03	According to Kratz's review of the DM96 at the preclassification stage, eosinophils were 29.3% less accurately identified than neutrophils.	13	For malaria diagnosis, the DI-60 has the potential to become the new gold standard.
04	According to Rollins-Raval, the DM96 had difficulty in reliably identifying immature granulocytes, plasma cells and blasts.	14	Depending on patient population, 80–90% of cases using CellaVision analysis do not require manual microscopic review.
05	Eilertsen's 2017 study of blast cell verification using the DM96 demonstrated significant differences in blast cell counts pre- and re-classification.	15	Average review times on the Nextslide system were 8.87 minutes shorter than for manual microscopy.
06	Using the DM96 ARBCA for shistocyte counting, Hervent reported a very high specificity but poor sensitivity.	16	Correlation coefficients were higher for basophils, atypical lymphocytes and bands using the Nextslide compared with the same cells using the CellaVision.
07	Direct comparisons of studies of the ARBCA can be difficult as red cell cut-off values can be manually adjusted.	17	Roche cobas M511 high-magnification module utilises a dry 50x lens for morphologic assessment.
08	In their review of the DM96, Guliati *et al.* found the sensitivity of detection of platelet clumps varied from 61.6 ± 21.2% depending upon whether the user looked for: (a) platelet clumps or fibrin strands in the WBC display only, or (b) searched all the WBC and PLT screens.	18	Agreement between the Roche cobas M511, manual microscopy and the Sysmex XN was good.
09	When examining body fluids using the DM96, Riedl *et al.* reported the correlation coefficient for post-classification accuracy of CSF analysis was 0.83–0.98 and for other fluids was 0.92–0.99.	19	Yagi and Gilbertson have published six recommendations to standardise digital image analysis.
10	According to the evidence presented in this article, the use of the DM96 for the identification of paediatric blasts is contentious.	20	For laboratories planning on introducing digital imaging, at least 100 slides covering all cell types, including abnormal cells, should be evaluated.

REFLECTIVE LEARNING

01	Using section 2.7.1 of this article as a starting point, critically discuss the practice-based opportunities that arise from research utilising digital morphology analysers.	02	Evaluate the use of digital morphology analysers in the education and training of biomedical scientists.

EVENTS AND TRAINING COURSES

More training courses, CPD and local events and activities are available on the IBMS website.

DATE	TITLE	VENUE CONTACT
October		
5-6 Oct	**Introduction to Practical HPLC Course**	Rochester I stuart@laserchrom.com
7-8 Oct	**Agilent HPLC Equipment Servicing Course**	Rochester I stuart@laserchrom.com
7-8 Oct	**Intermediate Practical HPLC Course**	Rochester I stuart@laserchrom.com
12-14 Oct	**Practical HPLC Method Development Course**	Rochester I stuart@laserchrom.com
14 Oct	**Mohs Introductory Webinar**	Online I cpt@ukneqas.org.uk
14 Oct	**UK NEQAS Cellular Pathology Technique Mohs workshop**	Gateshead I cpt@ukneqas.org.uk
15 Oct	**UK NEQAS Cellular Pathology Technique Renal workshop**	Gateshead I cpt@ukneqas.org.uk
17 Oct-31 Jan	**Biomed online learning courses**	Online I c.e.ronan@gre.ac.uk
November		
1 Nov	**Scottish Pathology Network Annual Event**	Edinburgh I NSS.SPAN@nhs.net
4 Nov	**UK Standards for Microbiology Investigations – Chairs Strategy Working Group Meeting**	London I Public Health England
9-13 Nov	**Advanced Practical HPLC Course**	Rochester I stuart@laserchrom.com
11 Nov	**UK NEQAS Cellular Pathology Technique Non Gyn Cytology Beginners/ Refresher Workshop**	Gateshead I cpt@ukneqas.org.uk
12 Nov	**UK NEQAS Cellular Pathology Technique Non Gyn Cytology Intermediate Workshop**	Gateshead I cpt@ukneqas.org.uk
16 Nov	**UK NEQAS Cellular Pathology Technique BMT workshop**	Gateshead I cpt@ukneqas.org.uk
25 Nov	**UK NEQAS Cellular Pathology Technique TEM workshop**	Leicester I cpt@ukneqas.org.uk
26-27 Nov	**Advances in Transfusion Medicine**	London I tanya.whyte@rcpath.org
27 Nov	**Ortho Clinical Diagnostics Transfusion Medicine User Group Meeting**	East Midlands I hayley.thomson@orthoclinicaldiagnostics.com
28 Nov	**Tissue Morphology and Tissue Recognition Part 1 Webinar**	Online I cpt@ukneqas.org.uk
29 Nov	**Tissue Morphology and Tissue Recognition Part 2 Webinar**	Online I cpt@ukneqas.org.uk
December		
2 Dec	**UK Standards for Microbiology Investigations Joint Bacteriology and Virology Working Group Meeting**	London I Public Health England
14-15 Dec	**Advanced Agilent HPLC Equipment Servicing Course**	Rochester I stuart@laserchrom.com
2021		
June		
16-17 Jun	**Beginners Immunohistochemistry**	Sheffield I l.baxter@sheffield.ac.uk
July		
14-15 Jul	**Advanced Immunohistochemistry**	Sheffield I l.baxter@sheffield.ac.uk

HERE TO HELP

VIRTUAL TRAINING EVENTS

Evis Ciri and **Jocelyn Pryce** from the IBMS Education Team outline new online sessions that have been launched.

As a result of the pandemic, we took the decision to introduce virtual methods for our assessments. The feedback we have received has been extremely positive, therefore, we have been developing ways of carrying out virtual training events too. A number of training and update events had been planned to be hosted at our offices in Coldbath Square and around the country this year. With the continued restrictions, we have decided to move our events online.

By adopting this new way of training and learning, we are able to accommodate a much larger audience without the usual barriers of travel or time. Therefore, we are planning a number of sessions for both new and experienced verifiers and examiners. These sessions will cover the processes involved in each type of assessment, different types of evidence and how to manage challenging cases.

For training day updates, information on when these events will take place and how you can access them, please keep an eye on our website's events calendar. For any queries you have, email the Education Team (registration@ibms.org).

The Education Team provides support for members and non-members alike, but there are some common themes in the questions they are asked. In response, they have collated these frequently asked questions and will be offering short online sessions to address them. These will include sessions on how to approach the laboratory approval process and applying for a non-accredited degree assessment. In the sessions on applying for laboratory approval, we aim to focus on issues commonly encountered by first-time applicants, as well as renewal applications resulting in follow-up requests before approval can be granted, thereby reducing the turnaround time in granting different levels of training approval.

Once confirmed, all arranged events will be advertised on our website events calendar ensuring members have the opportunity to take part. Please be sure to keep an eye on our website's events calendar, accessible from the homepage, for upcoming verifier and examiners training days and CPD events hosted by the IBMS.

Recently, we have also held individual training sessions for new, non-accredited degree assessment assessors and we were pleased to see how many of you expressed an interest. This has allowed us to increase our pool of assessors to deliver a more efficient and prompt process, reducing potential delays in providing candidates with their outcomes. Further training will be available online for those interested in becoming a non-accredited degree assessment assessor. If you would like to express your interest in becoming an assessor for this route, please email degreeassessment@ibms.org for further information on the requirements.

These member roles offer opportunities for continued professional development, so why not consider stepping up for one or more?

On behalf of the Education Team ,we thank you for the continued support and encouragement. As always, we welcome your feedback and comments as they help us to help you.

IMAGES: GETTY

THE BIOMEDICAL SCIENTIST LIVE

IBMS Institute of Biomedical Science

Save the date

16-19 NOVEMBER 2020

Our first virtual CPD event, ***THE BIOMEDICAL SCIENTIST LIVE***, will take place between **16-19 November 2020**.

Featuring a packed line up of knowledge sharing sessions, including seminars, presentations, discussions and demonstrations.

REGISTER YOUR INTEREST: live.thebiomedicalscientist.net

MY LAB

A WHOLE NEW APPROACH TO ASSESSMENT

Leslie Ramos, Cellular Pathology Quality Manager, gives a guided tour of her lab and talks through a recent virtual UKAS assessment.

The COVID-19 pandemic has changed many aspects of healthcare in the UK, including how the histology and mortuary department, which is part of our cellular pathology service, has had to adapt to manage our assessments in the last few months.

The service, based at University Hospital, Coventry and part of the Coventry and Warwickshire Pathology Services (CWPS), is one of the largest networked pathology service providers in the country. Our vision is to provide a safe and responsive service through innovation and efficiency. CWPS is a managed network of laboratories hosted by University Hospitals Coventry and Warwickshire (UHCW) NHS Trust. CWPS provides services to South Warwickshire NHS Foundation Trust (SWFT), George Eliot Hospital NHS Trust and Queens Hospital in Burton, as well as the surrounding clinical commissioning groups, with histology laboratories based at UHCW NHS Trust and SWFT, which were both included in the assessment.

The histology department processes over 300,000 slides a year and was due an on-site UKAS surveillance visit earlier this year, but the COVID-19 pandemic meant the assessment had to be carried out virtually using Microsoft (MS) Teams.

To meet the needs of this new approach we submitted our pre-assessment documents via Dropbox. While attaching and labelling a folder's name was complicated at first, after a few you find the system user-friendly in the end.

The remote assessment was certainly very different to having an on-site visit and my one piece of advice is to wait for the "official" MS Teams invitation from the UKAS assessor to prevent having multiple invitations on the same day and time. We had instances where staff were waiting to join the unofficial MS Teams meeting, while others were already on the right meeting. We also had to ensure rooms were available for technical assessment and all technical equipment – such as laptops, cameras, speakers and headsets – was available for the key staff. Mobile phones and iPads were also available to use for live recording requests.

Staff were invited to the opening meeting on the first day and this was followed by smaller meetings with the technical and quality management system assessor in separate rooms. Live recording for microtomy and embedding were also requested. This worked well using mobile phones.

Although the assessment review was carried out over several hours for a couple of days, it was relaxed and flowed well with any questions easily answered. The department was able to demonstrate the changes that had been made and introduced in previous visits and the team shared a screen to view the documents.

Whilst this was a very challenging time for the department, we were able to carry out the assessment with ease. Although there were slight issues with frozen screens and patchy calls during MS Teams meetings, the department felt the accreditation has been beneficial in these unprecedented times.

The team is delighted to have retained accreditation status for another year, and it was pleasing to hear the assessors say they could see a massive improvement since the last visit and that our lab is "a very good lab and quality assured".

The retention of this accreditation status represents a significant achievement by the entire team and could not have been reached without the commitment from every member of the whole network cellular pathology team (mortuary staff, UHCW NHS Trust and SWFT histology clinical, lab and secretarial staff), even more so during the current situation. BMS

DGreadernet

Advance to an automated experience for manual gel testing

Scalability

- Works as stand-alone system or as a true scalable solution when combined with fully automated instruments: Erytra and Erytra Eflexis

Flexibility

- Use lab space efficiently thanks to a compact and simple design that fits in any lab
- Combine different cards to perform a test, ensuring full use of cards

Intuitive Operations

- Improved and intuitive software
- Simple management
- Minimal maintenance
- Wi-Fi connection and remote access

TYPING

Grifols UK Ltd
Byron House
Cambridge Business Park
Cambridge CB4 0WZ
Tel: +44 0 845 241 3090
Fax: +44 0 845 241 3314

GRIFOLS

I KNOW WE ARE SAVING LIVES

THE POWER OF KNOWING

Roche Diagnostics gives you The Power of Knowing that you're using accurate information to make the right decisions today, so your patients can experience a healthier tomorrow.

Roche