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Scotland's War on Germs

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Summary:

Bacteria are germs that can cause a multitude of diseases.

They are developing resistance to drugs, called antibiotics, that are used to treat them.

This antimicrobial resistance problem threatens many aspects of modern medicine.

Beyond re-awakening the threat of diseases like TB, cholera and typhoid, processes like surgery translation and childbirth are threatened too.

This is because bacteria able to grow in our bodies, that we can generally kill easily with antibiotics, may develop resistance too.

The first great medical leap forward against bacteria came in the mid-nineteenth century in Glasgow, where Lord Lister introduced antiseptic methods to kill bacteria in medical operating rooms.

In 1928, the Scottish doctor, Alexander Fleming, discovered penicillin – and triggered the age of antibiotics.

Scottish scientists, doctors, vets and public health officials remain at the forefront of research into ways to beat antimicrobial resistance today.

In this feature article we discuss the amazing contributions Scotland has made to the war on germs.

Is an antimicrobial resistance Armageddon upon us? Are the drugs that have kept infectious agents at bay for decades about to fail? A report by Lord Jim O'Neill in 2016 predicted that by 2050 we might be seeing as many as 10 million deaths globally caused by antimicrobial resistant infections which will also place an annual economic burden on societies running as high as a hundred trillion pounds per year. O'Neill's report has helped galvanise efforts to combat the threat and Scotland is set to continue its role as a global leader in combating microbial disease.

SIR ALEXANDER FLEMING: THE SCOTSMAN WHO DISCOVERED PENICILLIN

For over 60 years we have taken it for granted that we are unlikely to be killed by bacterial infections. Just 100 years ago, diseases like tuberculosis, typhoid, cholera, bacterial pneumonia and sepsis accounted for around half of all deaths. Average life expectancy is now twice what it was back then. This change can be attributed, in part, to a serendipitous discovery by a young Scottish doctor, Alexander Fleming, from Darvel in Ayrshire, who is credited with discovering a class of chemicals that we now call antibiotics. In the summer of 1928, while working at St Mary's hospital in London, he went on holiday and left an open plate of bacteria behind. Returning to work, he found a fungus growing on the plate. What's more, the fungus had killed the bacteria. Fleming realised that the fungus was secreting something that was toxic to the bacteria. He set about isolating this substance that he called penicillin. However, without the kind of chemical separation skills needed he found the task too tough and dropped it. It was nearly a decade later that a group in Oxford, working under the Australian pharmacologist and pathologist Howard Florey, purified penicillin, allowing its true potential to be realised.



Figure 1. Sir Alexander Fleming with his Petri dish. Source www.uk.businessinsider.com

The success of penicillin stimulated an era of “bioprospecting”

It is often reported that Fleming's original discovery was a fluke. A sloppy worker leaving the lid off his Petri dish, making a chance discovery that changed the world. However, Fleming had been seeking new ways to kill bacteria for many years. He was the first to discover another antimicrobial agent, a protein we produce in our tears and saliva called lysozyme that can weaken the cell walls of bacteria. Lysozyme is a key part of our own antimicrobial system. St Mary's hospital, where he worked, was among the world's foremost centres for research into antimicrobial interventions. Under the stewardship of the formidable Almroth Wright, the Institute had led the way in immunisation, the creation of vaccines and other immunological approaches to attack bacteria. Wright, for example, pioneered the development of a vaccine against typhoid, the awful diarrhoeal disease caused by *Salmonella* bacteria. Boiling large numbers of cultured bacteria to kill them prior to injecting them into people provoked immune responses to the dead bugs and those immune responses then protected against later infection with live *Salmonella*. Since the British army was frequently devastated by typhoid outbreaks it was in soldiers that early trials were conducted, for example during the second Boer war in South Africa. Wright was convinced by his method. Others less so, primarily because Wright was rather slapdash in what he did. Eventually another great Scottish physician-scientist, William Leishman, a graduate of Glasgow's medical school, was tasked with carrying out definitive tests on the use the typhoid vaccine. By using a reproducible dose of the bacteria, that had been boiled for a carefully controlled time, Leishman showed the vaccine really did work. By the time the first world war broke out the British army had been receiving inoculations and suffered a drastically reduced incidence of typhoid compared to their German counterparts.

Fleming was a relatively mild-mannered, quiet and slightly eccentric man. During the first world war, stationed in Boulogne, he gained a reputation for his brilliance in treating wounds infected with bacteria that cause gangrene - a horrifyingly common affliction in WWI.

Fleming showed that slapping anti-septics into wounds, in war circumstances, did nothing to kill bacteria. In fact, it was immune cells that were worst affected by these chemicals. Lord Lister, Professor of Surgery at Glasgow University in the 1860s, had introduced the concept of chemically sterilising surgical equipment and swabbing wounds to diminish microbial infection during routine surgery in hospital operating theatres. Unfortunately, the filth-filled and roughened wounds of war were impenetrable to the phenolic compounds that worked so well on equipment or cleaner kinds of abrasion, making the approach futile. This war work instilled a determination to work out other ways to defeat infection which stimulated Fleming's post-war work.

Fleming was eventually awarded the Nobel prize in Physiology and Medicine for his discovery. In truth, had not Florey, and in particular Ernst Chain, a German Jew who had fled Hitler's regime in 1933, unravelled the structure of the drug and worked on ways to produce it to scale, Fleming's original discovery might have rested undiscovered in the *Lancet* journal where he had published it in 1929. In fact, it was Almroth Wright who pushed relentlessly to assure his St Mary's colleague obtained credit. Since only three people can win a Nobel prize in any one year, Fleming joined Florey and Chain on the stage in Stockholm while Norman Heatley, another key member of the Oxford team, missed out.

Once war broke out, the race to produce penicillin in quantities needed to treat bacterial infections was on. The route to mass production was remarkably quick. Today it typically takes more than ten years to chaperone a drug through clinical trials to prove its safety and curative effect. In 1941, a policeman, Albert Alexander, was dying from septicaemia in the John Radcliffe hospital in Oxford. For some strange reason, the story of Constable Alexander has been given an apocryphal edge. The usual account suggests he was infected from a mild thorn prick whilst pruning his roses. His daughter, Sheila, however, recalls how he had, in fact, been seconded to Southampton during a sustained period of bombing, where he was injured during an attack and transfer-

red back to Oxford where his condition deteriorated badly. Florey gained permission to test the effect of penicillin. The response was remarkable with dramatic recovery overnight. Sadly, there was not enough drug to keep treatment going as long as needed. Chain desperately re-purified drug secreted in urine and this was injected, but supplies soon ran out and Constable Alexander died.

Despite the failure to save Albert Alexander, his temporary reprieve showed how efficacious penicillin could be, if only enough were available. Further trials proved the effect and Florey undertook a punishing tour of the USA, seeking companies who could scale production to levels needed to administer in massive quantities. By the end of the war tons of penicillin were being made, and contributing to the war effort. Treated allied service personnel were far less likely to die of wound infections when treated with this first wonder drug. The success of penicillin, a natural product made by one bug to kill others, stimulated an era of “bioprospecting” with scientists systematically seeking other antimicrobial agents produced by microbes found in soil. The most important of these was streptomycin, discovered by workers in the laboratory of Selman Waksman in the USA, in 1943, and able to kill the deadly tuberculosis bacterium which afflicted colossal numbers of the world's population. Waksman and his group found over 20 active antibiotics, a term that he coined to describe these agents that worked against bacterial life.



Figure 2. World War 1 Soldiers.
Source www.forces-war-records.co.uk

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"It is time to close the book on infectious diseases, and declare the war against pestilence won."
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- General William Stewart
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GEORGE ORWELL: SCOTLAND'S FIRST PATIENT TO BE TREATED WITH STREPTOMYCIN

The author Eric Blair, better known as George Orwell, aged 44, in December 1947 had been working peacefully on the western isle of Jura, on the novel that was to become his masterpiece "Nineteen Eighty-Four". He was afflicted with tuberculosis. As his condition deteriorated he was moved to Hairmyres Hospital near Glasgow and once there his physicians considered getting hold of the new wonder drug streptomycin. There was, however, barely any of the drug in the UK and no Scottish hospitals had been selected by the UK government as sites in which to test activity. What's more, Orwell was considered too old to be a participant in the trials. Only when David Astor, editor of the Observer and Orwell's friend, intervened did he receive some drug. Unfortunately, after some early positive response, the writer developed an allergy to streptomycin, and had to stop taking it. He moved to a sanatorium where he died in 1950.

THE GOLDEN AGE OF ANTIBIOTICS LOSES ITS SHEEN

The post war period saw an expansion in the development of new antibiotics. It appeared that mankind's battle against microbial infection would soon be won. Indeed, in 1969, the US surgeon General William Stewart, is credited as having said that "It is time to close the book on infectious diseases, and declare the war against pestilence won." Bacterial infections could be easily treated. However, it is important to note they never went away. Many parts of the world, where antibiotics were not available, continued to suffer a great burden from killers like TB, typhoid and cholera. What's more, cheap and easy-to-make antibiotics flooded societies. Not just to treat bacterial infections, but increasingly they found

inappropriate use, for example, being given in undiagnosed viral infections (viruses are a different kind of microbe and not vulnerable to antibiotics that act against bacteria). It was found that farm animals benefit from antibiotics not only when infected with pathogenic bacteria but at other times too they grow fatter and faster when on antibiotics. This is because all animals (including humans) naturally harbour trillions of bacteria. As those bacteria share our food, killing them means we gain more energy from what we eat, allowing us to grow faster. (These bacteria are increasingly understood to have many benefits to health too, but in the case of farm animals, rapid growth for milk and meat production rather than animal welfare has been the key economic driver in much of modern farming). What's more, with multiple cheap antibiotics available, and drug development costs becoming ever higher (it is estimated that today pharmaceutical companies are spending \$2bn every time they bring a new drug to the marketplace), the industry has steadily abandoned the quest for new antimicrobial drugs.

In the meantime, as Fleming himself had foreseen, bacteria were developing ways to survive treatment with drugs. Most of these were ancient mechanisms, that had evolved while bacteria were fighting each other in soil with those same compounds that Fleming, then Waksman and others, had discovered and mass produced to use in humans. Once genes encoding for resistance entered bacterial populations, these bugs were no longer susceptible to the antibiotics used to treat them. So, they spread, and also shared their genes with different bugs. Health officials have been growing increasingly concerned about the risk posed by antimicrobial drug resistance. Not only will we not be able to treat infections – other commonplace medical procedures, like surgery, transplantation and even childbirth, all of which bring serious risks of infection against which antibiotics are routinely given during the procedure to mitigate that risk, will once again become dangerous.



Figure 3. George Orwell. Source: Bookstr, 2018.

SCOTLAND'S ROLE IN ASSURING AN ANTI-MICROBIAL FUTURE

All of Scotland's leading research-led Universities have responded to international calls to reinvigorate efforts to combat the rising tide of antimicrobial resistance. The challenge isn't merely one of understanding the mechanisms by which bacteria become resistant to drugs, nor is it just about inventing new drugs that kill bacteria in ways they can't resist. We need to understand more about how resistance spreads from one bacteria to another and how those populations pass across and between populations, be it between humans, or animals or from animals to humans and back. This can then help policy makers diminish the risk of spread. What environmental pressures can contribute to resistance? Remember that antibiotics first came from soil organisms, and also that other soil organisms evolved the first measures to resist antibiotics. What happens, then, when unused antibiotics are disposed of in landfill sites? Can these act as super-selection conditions for antibiotic resistant genes that may then enter the bacteria that infect man? What about cows systematically filled with antibiotics, some of which pass in their faeces? Are our fields being turned into antibiotic resistance selection grounds as soil organisms evolve ways to combat these drugs to which they are unintentionally exposed? Networks of researchers are coming together to address these problems. Microbiologists are probing the ways by which resistance occurs and also finding new ways to target bacteria. Pharmaceutical chemists are returning with new compounds that can hit these targets in bacteria. Engineers are building devices that can diagnose when antibiotic resistant bacteria are infecting people; Economists are tracking the impact of the problem to enable Governments to know how high the stakes are by not intervening. Social scientists are trying to work out how patients can be dissuaded from demanding antibiotics when they are not appropriate, and also how health workers can be discouraged from their use when not needed. Veterinary scientists are seeking ways to preserve animal health and help farmers produce high yielding animals without resorting to the quick and easy, but ultimately damaging, use of growth-promoting antibiotics.

The Universities of Glasgow, Edinburgh and Dundee have all established networks bringing workers together across disciplines to help combat antimicrobial resistance. A new Antibacterial Drug Discovery Accelerator in Dundee has sprung from the Drug Discovery Unit whose initial focus on diseases of the developing world, primarily caused by parasites, is now expanding

to take in different bacterial infections too. Dundee has been recognised as the world's number one academic institution in pharmaceutical research. Professor Ian Gilbert, who has designed chemicals that are now being developed to treat diseases like malaria, leishmaniasis and African sleeping sickness acquired a great appreciation of the problems caused by infectious diseases during his time working in Zambia in Southern Africa. His experiences inspired him to devote his life's work to developing drugs to treat these diseases rather than following more lucrative pathways in the pharmaceutical industry.

Also in Dundee, Professor Dilip Nathwani, a physician specialising in infectious disease and President of the British Society for Antimicrobial Chemotherapy, worries that humanity's ability to exploit and abuse its resources, including antibiotics, could lead to disaster. Nathwani believes passionately in the need to preserve the antibiotics we have – and is working hard to create policies to assure antibiotics are only used when really necessary.

Mike Barrett, Director of the Scottish Universities Life Sciences Alliance (SULSA), himself an expert on antimicrobial resistance in parasites that cause disease in developing countries, says he has never seen a coming together of researchers from so many disciplines as seen in response to the antimicrobial resistance challenge. Barrett, based at the University of Glasgow, adds that the action has been invigorating and also timely. O'Neill's report, he says, offers predictions as to what is likely to happen if things don't change. These predictions will come to fruition if we continue to misuse existing drugs and don't work out new models to develop new ones, or introduce public health policies to help keep resistance and microbial infection more generally at bay. The great thing about the antimicrobial networks is that they offer a platform to form new ideas to help combat the problem. Whilst the Universities will provide the innovations to help address the problems, it will be necessary for companies to translate new ideas into products, and national agencies to implement new policy.

Scotland already has two prominent pharmaceutical companies devoted to developing new antimicrobial agents. In Aberdeen, Deborah O'Neil heads the company Novabiotics that focuses on a class of compound known as peptides, some of which are specifically able to kill bacteria (and also fungi) that cause disease and resist existing classes of drug. Novabiotics has raised millions in investor money in the last few years, and has also set up a branch in the USA to help bring their products through clinical trials and make them available for use.



Figure 4. Deborah O'Neil, Novabiotics
Source: twitter.com/debsoneil

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We need to understand more about how resistance spreads from one bacteria to another.

“Our small nation looks set to drive innovation leading to the third great antimicrobial push in the Twenty First Century”

Aberdeen University also houses one of the World's leading centres for research into medical mycology, the study of fungi that cause disease. There are relatively few antifungal drugs compared to antibacterials, and antifungal drug resistance is now undermining clinical options for the treatment of patients with deep seated fungal infections. The specific problem of antifungal AMR is exacerbated by the lack of any fungal vaccines and the work in Aberdeen, unravelling the complexities of fungal biology offers great hope towards designing new drugs to deal with fungal infections too.

In Glasgow another Company, MGB-Biopharma has taken technology developed by Professor Colin Suckling at the University of Strathclyde forward. Their compounds bind to DNA and different variations on their theme seem to be able to penetrate and bind DNA of different types of microbe. One compound is progressing through trials to kill the dreaded *Clostridium difficile*, a leading cause of serious diarrhoea that has been a growing problem across the UK and beyond. Also at Strathclyde, researchers are exploring diverse environments for microorganisms that produce new antibiotics. From such places as the Chilean Atacama Desert, Trinidadian rain forest, Antarctic marine sediments as well as Scottish peat and mining wastes, the Microbiology group in the Strathclyde Institute of Pharmacy and Biomedical Sciences are using advanced molecular tools to identify new antibiotics produced by newly isolated microorganisms. They have already discovered multiple strains that kill important pathogens. Once again, it is the inspiration of Fleming's original discovery of penicillin that is sending researchers back to nature to seek new generations of natural products that may be harvested to treat infection.

An Edinburgh-based company, Ingenza, renowned for its world-beating ability to exploit bugs to generate high value chemicals, is adding a twenty first Century twist to the quest that stemmed from Fleming's great discovery that bugs produce chemicals to kill

other bugs. Ingenza are engineering useful bacteria to make bacterioricins, a group of compounds also belonging to the peptide class that kill other bacteria. They have joined forces with the University of Plymouth and National Physics laboratory to do this.

Another company, Omega Diagnostics, based near Dollar, founded in 1987 by Andrew Shepherd, who handed over the top job at the company to Colin King at the end of last year, is leading the way in making cheap and easy to use diagnostic tests for a variety of infectious diseases including many bacteria. Omega Diagnostics is one of the UK's leading companies and has tests in the market place able to distinguish a variety of different infections to help assure that only appropriate drugs are used to treat patients.

Yet another company, Orbital Diagnostics, a spinout from the University of St Andrews, won a prestigious Longitude Prize Discovery Award in 2016 for their technology which enables detection of a bacteria's ability to resist antibiotic treatment in just 20 minutes instead of many hours as is usually the case.

Barrett believes that the success of companies like Novabiotics, MGB-Biopharma and Omega Diagnostics will stimulate more activity in this area and that innovations emerging through the Universities will find routes to market. This extraordinary galvanisation of Scotland's research community into AMR-networks offers unprecedented opportunities to deal with the problem.

Hence the small nation which led the first great intervention against microbes with Lister's introduction of antiseptic approaches in the nineteenth Century, then the second through Fleming's discovery of penicillin in the Twentieth, looks set to drive innovation leading to the third great antimicrobial push in the Twenty First Century.



Figure5. Omega Diagnostics.
Source: Herald Scotland

The Scottish Universities Life Sciences alliance will be hosting a two-day Antimicrobial Resistance Conference on Thursday 26 - Friday 27 April 2018 at the University of Strathclyde.

The Scottish Universities Life Science Alliance (SULSA) is a strategic alliance between nine Scottish Universities that was founded by the SFC in 2008. Created alongside 10 other research pools, as a result of the SFC's greater research pooling initiative, the pools were developed to encourage researchers across Scottish higher education to pool their resources and respond to increasing international competition.

Since its inception in 2008, SULSA has leveraged over £400m from its initial £27m investment from the SFC. During this time, SULSA has brought dozens of new Life Sciences researchers to Scotland and has helped to underpin new research angles.

SULSA continues to bring Scotland's Life Science researchers together, helping to assure the country continues to be a world leading environment for research into biological and biomedical science.

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