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C E Wallis Lecture

Struggle Against Infection

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We think that man left his anthropoid cousins some two million years ago and that this cleavage was by no means abrupt. The study of disease has doubtless been going on since the time that mankind emerged as a thinking animal. The earliest evidence that we can trace is to be found in bones, carvings, paintings, tools, weapons and tombs. It is believed that the legendary Yellow Emperor, as far back as 2698 BC – before paper or books existed – had discussions with his medical and ministerial advisers, and the knowledge thus acquired was conveyed by recitation or carvings to be compiled later in one of the oldest medical treatises – the 'Su Wen' or 'Simple Questions'. In this work there are references to infections, with epidemics attributed to the wrath of supernatural powers. It is interesting to read in other early Chinese works the descriptions of 'locality diseases' and to find in them a strong resemblance to the writings of the later Greek school.

In Egypt, one of the chief centres of the civilized world at that time, there is reflected the reasoning that springs from a cultured people. While they knew nothing of the nature of infection, they introduced principles of hygiene. Certain of the Egyptian medical texts contain references to infection of wounds and diseases of women and cattle. The Ebers papyrus of 1550 BC gives accounts of infections which we recognize as coryza, mastoiditis, parasitic diseases and abscesses.

Fourteen centuries before Jesus was born, Moses, who displayed considerable knowledge of the laws of health – knowledge he acquired in Egypt – made the Israelites follow a code of regulations which preserved them in health and vigour for the forty years of their wanderings in the wilderness and remained a heritage of health to them afterwards. This is one of our earliest records of preventive medicine.

The centres of medical enlightenment in classical Greece were the rival schools located on the islands of Cos and Cnidus, and it was from here that scientific medicine began. In the Hippocratic corpus there are chapters on 'Air, Water and Places' but no clear reference to contagion. Hippocrates was said to have exterminated the plague of Athens by lighting fires as an atmospheric corrective. In 'The Aphorisms', the most famous book with which the name of Hippocrates is linked, there are a few brief generalizations related to infection, but it would appear that the association was not fully realized; for example, 'Convulsions supervening on a wound are deadly' (referring to tetanus) and 'It is fatal for a woman in pregnancy to be attacked by one of the acute diseases'.

The physicians of the Greek school gave excellent accounts of many diseases. They studied the art of prognosis and the mode of termination, but of the actual causes of disease they appeared to know little or nothing, and it is said that any glimmerings of truth were obscured in a cloud of theory. Harsh critics say unkindly of Galen that he touched nothing he did not ornament with his learning and injure by his theories. Medicine in Cos considered the environment as of decisive importance in conditioning the behaviour and performance of the body, but had somehow failed to take into account the fact that other outside agents – such as microorganisms – constitute one of the most important factors of man's environment. There were others, however, about that time who recognized that diseases could be spread by direct contact and even by contact with the clothing and the dwelling house of a sick person. In Leviticus, precise instructions are given to the priest to isolate lepers, burn clothing, scrape plaster from walls and even to demolish their dwellings.

Cornelius Celsus, a nonmedical Roman of the first century AD, collected much of the knowledge of the time. The doctrine of the four cardinal signs of inflammation – *rubor*, *tumor*, *calor* and *dolor* – was enunciated by Celsus and to these Galen (AD 130–200) added a fifth sign – *functio læsa*. Celsus included descriptions of dental procedures; the wiring together of loose teeth, removal of tender and painful teeth, and also accounts of a few dental instruments – dental mirrors, extraction forceps and probes.

The results of the pronouncements of Hippocrates and Galen had a profound influence on subsequent thought and for hundreds of years the progress of medicine was impaired by the failure in the teaching of the Greek school to recognize contagion. The idea of contagion was non-existent through the dark ages and mysticism was prevalent amongst the people.

The words of Osler, written hundreds of years later, come to mind: 'In all things relating to disease, credulity remains a permanent fact, uninfluenced by civilization or education.'

In the early middle ages great epidemics, such as the Black Death of 1347–48, ravaged Europe and there was a gradual strengthening of the belief that a sick person could infect others. An Italian physician and poet, Girolamo Fracastoro of Verona, is noted for his poem *Syphilis sive Morbus Gallicus* (Syphilis or the French disease). It was from a swineherd named Syphilis in this poem that the name of the disease was derived.

In 1546 Fracastoro published his celebrated *De Contagione* – a treatise on contagious diseases, amongst which he included syphilis. This work gave the death blow to the Galenic-Hippocratic dogmatism. He regarded infection as due to the passage of minute bodies from the infectious to the infected. These hypothetical minute bodies had the power of self-multiplication. The concept bore a striking resemblance to the modern germ theory of disease, although it was more than 130 years before bacteria were discovered. Fracastoro was the first to record the therapeutic value of mercury in the treatment of syphilis.

Others followed this lead: a Frenchman made an important contribution on the infective nature of whooping cough and the English physician Thomas Sydenham (1624–89), hailed as the founder of modern clinical medicine, published in 1660 his classical work 'The Method of Treating Fevers'. In a letter to the Royal Society in London in 1683, a Dutch maker of lenses – Antonj van Leeuwenhoek – gave the first description of bacteria from a smear which he obtained from the oral cavity. This man was an observer of genius and a very shrewd investigator. He constructed a simple microscope using lenses of exceedingly short focal length and with this he saw minute bodies which were not discernible to the naked eye. He referred to them as little animals.

In the middle of the eighteenth century, a young Scot, John Hunter, who had been an apprentice cabinet maker, left his native village of East Kilbride in Lanarkshire to join his brother William in London. Though handicapped by a poor education in youth, through unremitting energy and awakening of a latent genius, he contributed greatly to the good of humanity. His work on comparative anatomy, disease and infection, and the founding of a great museum, is preserved for posterity. His experimental work on infection even included a disease self-inflicted in the service of science, to which he was tragically a martyr in his death. Edward Jenner (1749–1823) was born at Berkeley Vicarage in Gloucestershire and was one of John Hunter's pupils. While practising as a country doctor, by inoculating with cow-pox, he became the forerunner of the study of immunity and the founder of an independent science.

The cholera outbreak which occurred in 1854 in England is referred to as the Golden Square outbreak. Within a period of ten days of the appearance of the disease there were 500 deaths at a distance not exceeding 250 yards from the Broad Street pump. John Snow's account of the outbreak survives as a classic of epidemiology. The source of infection was ascertained. It was the first outbreak of infectious disease in which water was incriminated as the vehicle of spread beyond all reasonable doubt. The vibrio of cholera was not identified till 1883, yet Snow marshalled the facts at his disposal to such purpose that he persuaded the vestrymen of St James' parish to take the handle off the pump which his reasoning had incriminated. His advice was amply vindicated, as almost at once new cases ceased to occur.

Scientists now accepted the role of organisms in disease but it fell to Pasteur – a chemist – to show his fellow men the way to fight them. It is acknowledged and abundantly evident that among the researches that have made the name of Pasteur a household word three are of the first importance: a knowledge of the true nature of fermentation, a knowledge of the chief diseases which have scourged man and animals, and a knowledge of the measures by which either the body may be protected against disease or the poison neutralized when once within the body. When a young student at the Sorbonne, Louis Pasteur became inspired by the eloquence and talent of Professor Dumas. Not only did Dumas open boundless horizons before the young man's mind, but he became his life-long friend and enthusiastic supporter.

In a letter dated December 9, 1842, Pasteur wrote: 'I attend at the Sorbonne the lectures of M. Dumas, a celebrated chemist. You cannot imagine what a crowd of people come to these lectures. The room is immense and always quite full. We have to be there half an hour before the time to get a good place as you would in a theatre; there is always a great deal of applause; there are always six or seven hundred people.'

While a research worker in chemistry, Pasteur was persuaded to turn his enquiring mind and energies from the study of tartrate crystals to the troubles which were affecting the wine industry of France. He first studied the age-old phenomenon of fermentation and satisfied himself that the souring of milk was due to the fermentation of lactic acid by multiplying bacteria. His early work on microbiology – a term originally used by Pasteur – made the fundamental observation that certain bacteria (which he named anaerobes) would grow only in the absence of oxygen – a monstrous discovery at a time when oxygen was still regarded as the essential elixir for all living creatures.

Later, his monograph 'The Study of Wines' and his demonstration of the value of differential heating – or Pasteurization as we now call it – revolutionized the whole wine and beer industry of Europe and established the importance of microbiology in industry. He perfected a method of brewing which produced a beer easy to keep and not liable to deterioration. Pasteur had demonstrated that the organisms which caused detrimental changes in beer were ones found in yeast as well as in the wort, and that these organisms were carried by dust in the air. In September 1871 Pasteur visited breweries in England and here taught the principles he had laid down. He showed that in the same way that wines could be preserved, bottled beer could escape the development of disease ferments by being brought to a temperature of 55°C.

Pasteur extended Jenner's work by the use of living attenuated cultures of pathogenic microbes against some important infections, including anthrax. His work on virology, chiefly on rabies, with his assistant Roux, led to the use of selective living tissue for the growth of viruses – which is today practised on an enormous scale – and to the production of the anti-rabies vaccine. On July 6, 1885 he applied his treatment to a youth exposed to rabies infection, with complete success.

Pasteur cultivated *Penicillium glaucum* and *Aspergillus glaucus* in a pure state. He proved that these moulds do not become transformed into alcoholic yeasts of either beer or wine. No one at that time was in a position to realize the significance of this.

At the beginning of 1873 Pasteur was elected a member of the Academy of Medicine – a rare honour for a nonmedical man. During the years which followed his election, he acquired the habit of visiting the hospitals of Paris and became interested in problems of puerperal fever, gangrene and other diseases which he already suspected of being the work of organisms comparable with his agents of fermentation. At his 70th birthday celebrations at the Sorbonne, on December 27, 1892, Lister and Pasteur met. Lister, who represented the Royal Societies of London and Edinburgh, brought to Pasteur the homage of medicine and surgery. 'You have', said he, 'raised the veil which for centuries had covered infectious diseases; you have discovered and demonstrated their microbian nature.'

The approach to the problem of infection by Lister, the surgeon, differed from that of Pasteur, the chemist. Lister's basic objective was to keep the organisms from reaching his surgical field. In the biography of Joseph Lister by his nephew, Rickman John Godlee, there is an account of how Thomas Anderson, Professor of Chemistry at Glasgow, while walking with Lister drew attention to the work of Louis Pasteur and suggested that his discoveries might shed light on the nature of the impurities which Lister suspected to be present in the air of hospitals. Lister saw in Pasteur's work on fermentation a possible explanation of the tragic fate that befell so many of his patients who were dying from hospital gangrene or 'blood poisoning' after injury or amputation.

In his book 'Joseph Lister, The Friend of Man' Sir Hector Cameron records: 'When on a morning in the spring of 1865, Joseph Lister, bearing in his hands the first crude sample of carbolic acid, stepped from his carriage at the gates of the Royal

Infirmary, Glasgow, and was met by the throng of eager dressers, modern surgery began.'

Lister, then Professor of Surgery in Glasgow, published in the *Lancet* a series of papers to expound the antiseptic principles. So great was the impact of his work that surgeons of this generation speak of the two eras of surgery – before Lister and after. His methods, which included the use of carbolic acid for preparation of surgeons' hands, instruments, dressings, patients' skin and also as a spray over the field during operation, produced a dramatic fall in mortality. The system was given its military application by French and German surgeons in the war of 1870.

In a letter dated February 13, 1874 Lister wrote to Pasteur enquiring whether the records of British surgery ever met his eye: 'If so, you will have seen from time to time notices of the antiseptic system of treatment, which I have been labouring for the last nine years to bring to perfection. Allow me to take this opportunity to tender you my most cordial thanks for having by your brilliant researches demonstrated to me the truth of the germ theory of putrefaction and thus furnished me with the principle upon which alone the antiseptic system can be carried out. Should you at any time visit Edinburgh, it would, I believe, give you sincere gratification to see at our hospital how largely mankind is being benefited by your labours.'

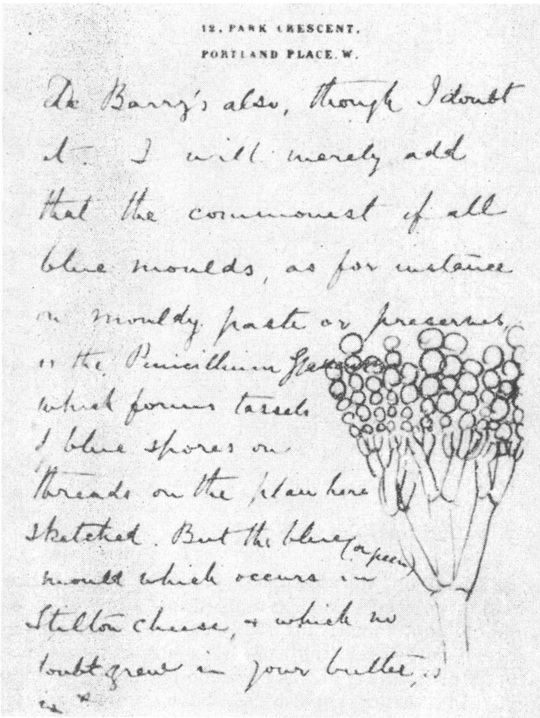
Lister had a predecessor – an exceedingly eccentric Viennese genius, Ignaz Semmelweis, who in 1846 succeeded in enormously reducing mortality from puerperal fever by insisting on sterilization of the hands of the operators. He maintained that infection was caused by decomposing animal matter transferred from the post-mortem room. Following acceptance of the Listerian system, the methods of Semmelweis were universally introduced into the practice of midwifery.

To Robert Koch (1843–1910) we owe the complete establishment of the germ theory of disease. His work on anthrax was a masterpiece, and from this he laid down his famous postulates. Now scientists and governments around the globe had a new awareness of the origin of disease and the cry in the struggle was 'find the organism'. New techniques, new culture media, new staining agents were all harnessed in the search and the results, though not all immediate, were rewarding. Typhoid bacillus, Klebs-Löffler bacillus, Koch's bacillus and many more were soon isolated. There were instances when fresh knowledge was discovered in the course of investigating the etiology of some diseases suspected of being caused by organismal infection. One notable example is beri-beri – a disease which reached epidemic proportions in the Far East. Fraser and Stanton, while working at the Institute for Medical Research at Kuala Lumpur, showed conclusively that the polishings of rice contained an essential food factor which prevented polyneuritis developing in fowls and beri-beri in humans. Later the name 'vitamine' was given to this substance obtained from the alcoholic extract of rice polishings. It was thus proved that beri-beri was a deficiency disease and not, as originally thought, due to an infection in the rice.

The part Joseph Lister played in the van of the fight against infection by first introducing carbolic acid has been given the prominence it so rightly deserves in the history of medicine, but some of his research work with the same goal has remained in comparative obscurity.

While Professor of Clinical Surgery to the University of Edinburgh, Lister recorded in his commonplace books experiments carried out in November and December 1871, referring to the inhibitory effect of *Penicillium glaucum* on the growth and motility of bacteria. The results were deemed to be inconclusive though Lister himself wrote: 'from the glass with profuse growth of Penicillium, bacteria were comparatively languid, multitudes were entirely motionless and there was not the same appearance of dense groups.' It is here that there was the introduction of the word 'antibiosis' to indicate antagonism between one organism and another.

Five letters from Pasteur to Lister are preserved. There is one in the library of this Society, and in it Pasteur identifies a mould which Lister had sent him as *Penicillium glaucum*, adding 'used for hundreds of years by the peasants in the steppes of Russia and the plains of Brittany and reputed to heal sores contracted in the fields'. When I discussed this letter with the late W J Bishop, for some years librarian of the Wellcome Historical Medical Library, he commented that he had acted as secretary to the European Librarians' Association and knew something of correspondence between Pasteur and a general practitioner in Quimper – a Dr Dufey – who worked in the practice earlier started by Dr René Laennec, inventor of the stethoscope. In the medical museum at Quimper there was the letter dated 1868, in which Pasteur wrote to Dufey identifying the mould sent to him from Quimper as *Penicillium glaucum*. The letter from Dufey is even more interesting, and he recounts how at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De Bary's also, though I doubt it. I will merely add that the commonest of all blue moulds, as for instance on mouldy paste or preserves, is the Penicillium Glaucum which forms tassels of blue spores on threads on the plan here sketched. But the blue (or green) mould which occurs in Stilton cheese, & which no doubt grew in your butter, is

Fig 1 *Part of a letter dated February 6, 1878, from Lister to Dr Albert Wilson.* (*Reproduced from Guthrie 1949, by kind permission*)

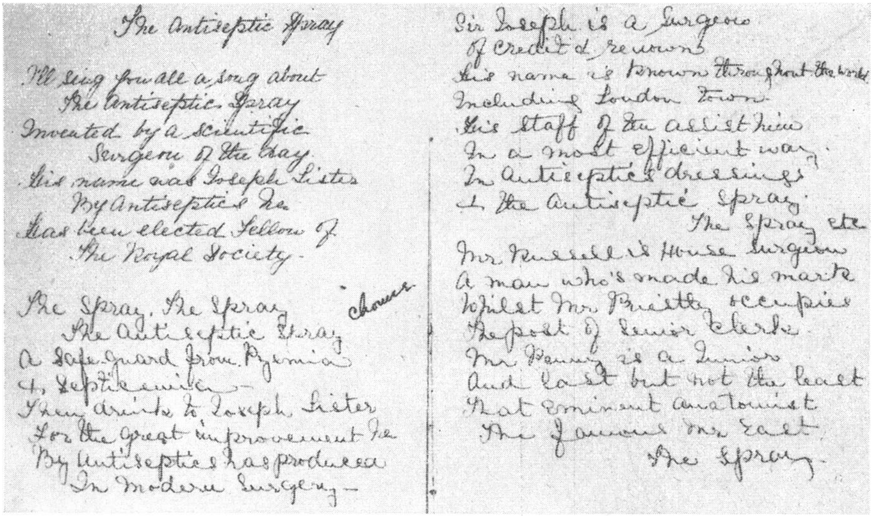
one time pots of bouillon were placed in the fields after harvesting and on this medium the mould grew. Later the same mould was found on the walls of old cellars, and the practice of putting bouillon in the fields ceased.

Lister's youngest brother, Arthur, who was a Fellow of the Royal Society, having worked for some years on the higher fungi, later specialized in the myxomycetes and was regarded as an authority on this subject. Many letters passed between the brothers on this and kindred matters in the years 1869–76. In a letter dated February 28, 1872, Joseph Lister says he is terribly busy, snatching time whenever he can to work on the organisms, but bewails the disproportion between the results and the efforts involved. In another letter in the same year he tells his brother of further work carried out on *Penicillium glaucum*. He refers to the hope of finding the ideal antiseptic – one which would inhibit or kill organisms, without affecting the cells of the tissues. Still later there is a brief reference to the possibility of its clinical application, and 'should a suitable case present I shall endeavour to employ Penicillium Glaucum and observe if the growth of the organisms be inhibited in the human tissues'.

A collection of 22 letters written by Lister to Dr Albert Wilson of Leytonstone, who also had a great interest in the study of bacteria, was presented to the University of Edinburgh in 1946. In one of the letters (Fig 1), dated February 6, 1878, Lister discusses the identity of various moulds and fungi and refers to the scanty literature on the subject which was available at that time. He continues:

'I will merely add that the commonest of all blue moulds, as for instance on mouldy paste or preserves, is the Penicillium Glaucum, which forms tassels of blue spores on threads on the plan here sketched. But the blue (or green) mould which occurs in Stilton cheese, and which no doubt grew in your butter, is Aspergillus Glaucus. As to the relation of bacteria to filamentous fungi, I cannot speak with anything like authority.'

In a paper given in Edinburgh to the British Association of Oral Surgeons during the Lister centenary year, I told how, during the treatment of an air raid casualty in 1940, interesting facts relating to the clinical use of *Penicillium glaucum* by Joseph Lister were revealed. The patient, while a probationer at King's College Hospital, was under the care of Lister after a street accident. On Christmas day 1884, *Penicillium glaucum* was used in treating a deep-seated gluteal abscess which was slow to heal. She had copied the words of the topical song (Fig 2), sung by the students on the Christmas morning, and on another page of her scrapbook she started to write the word


The Antiseptic Spray

I'll sing for all a song about
The Antiseptic Spray
Invented by a scientific
Surgeon of the day.
His name was Joseph Lister
By Antiseptics he
Has been elected Fellow of
The Royal Society.

The Spray. The Spray Chorus
The Antiseptic Spray
A safeguard from Pyaemia
& Septicaemia —
Then drink to Joseph Lister
For the great improvement he
By antiseptics has produced
In modern surgery —

Sir Joseph is a Surgeon
Of credit & renown
His name is known throughout the world
Including London town
His staff of [illegible] assist him
In a most efficient way.
In antiseptic dressings
& the Antiseptic Spray.
The Spray etc
Mr. Russell is House Surgeon
A man who's made his mark
Whilst Mr. [illegible] occupies
The post of Senior Clerk.
Mr Penny is a Junior
And last but not the least
That eminent anatomist
The famous Mr East
The Spray

Fig 2 *Topical song sung by students of King's College Hospital on Christmas Day 1884*

Penicillium – lest she forgot it. Mr Russell, the house surgeon mentioned in the song, noticed she was having difficulty and though she wrote the first few letters, he actually finished the word for her – writing it 'Penicillim' (Fig 3).

This matter was discussed with Professor George Grey Turner, who was attached to Hammersmith Hospital at that time, and also with Professor Alexander Fleming. Some time later, in a letter to the President of the Royal College of Surgeons, Fleming writes of Lister:

'What a pity that his experiments of 28th, November 1871 did not come off. He had the idea of penicillin but he had the wrong mould or the wrong bacteria or both. If fate had been kind to him medical history might have been changed and Lister might have lived to see what he was always looking for – a non-poisonous antiseptic. From the time of Pasteur and Lister, workers have been trying to kill one microbe with another – the idea was there but the performance had to wait until Fortune decreed that a mould spore should contaminate one of my cultures and then for a few more years until chemists busied themselves with the products of this same mould to give us pure penicillin. Lister would indeed have rejoiced to have had such a thing.'

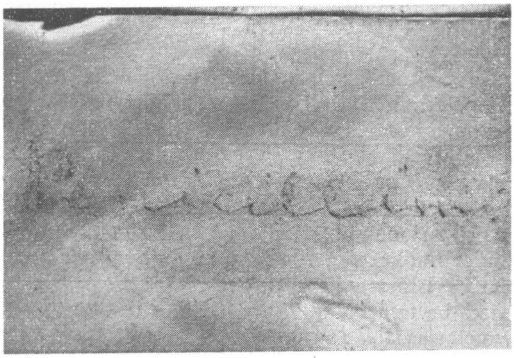


Fig 3 *Note made by patient during her treatment by Lister in 1884*

In the records of King's College Hospital, Volume 42, 1884, there is the entry (Fig 4) that Ellen Jones (the patient's maiden name) was admitted to Ferguson Ward under the care of Sir Joseph Lister on November 2, 1884: 'While going down Gt. Queen St, she was knocked down by a cab...' In addition to the gluteal abscess this patient had a fractured mandible. Difficulty was evidently experienced in retaining the fragments in position and eventually Sir Joseph wired the mandible with a thin silver wire. The ends were left protruding through the skin beneath the chin. After a few weeks the wires were removed.

It is of historical interest to record that modern chemotherapy began with the publication by Domagk in 1935 of the effectiveness of the first sulphonamide in the treatment of experimental streptococcal infection. However, in 1907 Ehrlich had established the principle of chemotherapy when he introduced salvarsan 606 – a word which actually meant 'saving with arsenic'. Almroth Wright was anxious to rename it pharmacotherapy but the word chemotherapy had already been accepted.

It should be mentioned that during his researches Fleming discovered lysozymes and published five important papers in the years

1922–27. In a lecture at the Royal Dental Hospital, Leicester Square in 1931, he spoke of the protective mechanisms in the body and described the mechanical resistance of the integument and an antibacterial ferment, lysozyme, which is present in great concentration in some human secretions, including saliva and tears. Fleming showed by simple experiments on a culture plate thickly implanted with bacteria, how human saliva completely inhibited growth on incubation. It is known that in Fleming's laboratory Petri dishes with cultures were often left for days uncovered and exposed to the atmosphere. This may well have been by design. In reading of the accidental discovery of *Penicillium notatum* by Alexander Fleming in 1929, one recalls the words of Louis Pasteur as quoted by Radot in 'The Life of Pasteur': 'In the fields of observation chance favours the mind that is prepared.'

Fleming's knowledge of mycology was limited, and from books he decided that the mould he found on one of his cultures was penicillium of the genus chrysogenum. Two years later Charles Thom, an eminent mycologist from America, identified the fungus as *Penicillium notatum.* On studying Thom's book on mycology, Fleming then discovered that *Penicillium notatum* had originally been recognized on a specimen of decayed hyssop by Westling, a Swedish chemist. Hyssop is a plant of the mint family; this may remind you, as it did Fleming, of Psalm 51: 'Purge me with hyssop and I shall be clean.' Surely this is the first known reference to the action of penicillin.

Sir Alexander Fleming's visit to the Pfizer laboratories in the USA had been well publicized in advance, and the benches had all been scrubbed and the instruments polished in readiness for his arrival. Looking around him at the vast and gleaming surfaces on which there was not so much as a speck of dust he said 'If I had been working in these conditions I should never have found penicillin'.

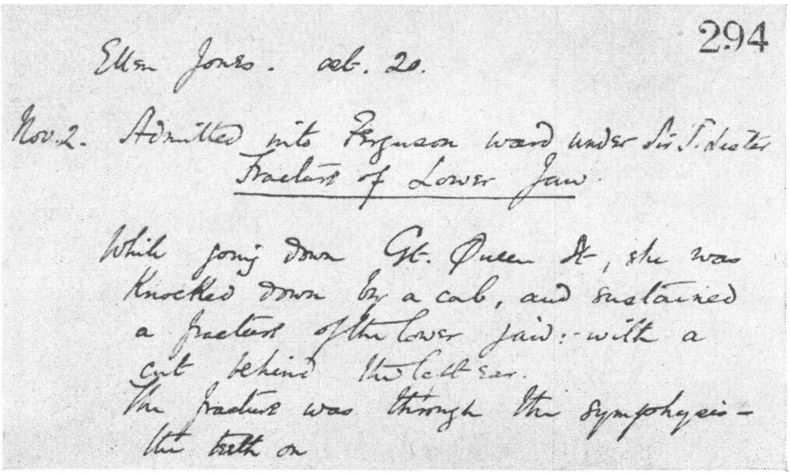
The part played by Florey and Chain in preparing the mould for therapeutic use and the work of Park and others in investigating its mode of action, have all been published in recent times. It soon became apparent that penicillin was only the forerunner of antibiotics, and that this valuable method of treatment was to be greatly extended.

In the sphere of odontology there are numerous instances of success in the field of infection. I mention but two in which antibiotic therapy is valuable:

Vincent's stomatitis was named after the French bacteriologist Jean Hyacinth Vincent, who in 1896 described the two organisms present and advanced the theory of their symbiotic action. This condition has been known and described from early times, and it affected the troops retreating from Persia in the time of Xenophon (401 BC).

In the *Lancet* of October 19, 1935, Professor C C Okell and Dr S D Elliott demonstrated the frequency of a transient bacteriæmia following dental extractions. They summed up:

'At least the direct observation of such an invasion of blood as we have described provides a tentative explanation of how streptococci reach the heart valves in cases of subacute bacterial endocarditis and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Ellen Jones. aet. 20.

Nov. 2. Admitted into Fergusson ward under Sir J. Lister
Fracture of Lower Jaw.

While going down Gt. Queen St., she was
knocked down by a cab, and sustained
a fracture of the lower jaw:- with a
cut behind the left ear.
The fracture was through the symphysis –
the teeth on

Fig 4 *Extract from records of King's College Hospital* one in agreement with views which are widely held on theoretical grounds.'

Although antibiotics have greatly improved the prognosis of subacute bacterial endocarditis, it is still a lethal disease with a mortality rated high by some authorities. Recent publications give statistics which support the contention that extraction of all teeth helps in the prevention of relapse.

In the past few decades great advances have been made in our knowledge of infections and in how to prevent and fight them. We have many additional therapeutic agents to help in overcoming them.

The triumphs of antibiotics have unfortunately been followed by certain difficulties. It is now apparent that some strains of organisms are resistant to the action of antibiotics. A few resistant ones may multiply rapidly and offset the destruction of all the other strains during an apparently successful course of treatment by a selected antibiotic. It may be that the antibiotic produces a mutation in the organism, as a result of which strains are produced which differ in their metabolic processes from the parent strain. The true explanation for this has yet to be found, and it may well involve the science of genetics.

In treating infection today we are conscious of the debt we owe to our predecessors, not only to those of the immediate past but to those also of relatively remote time. In lectures on moral philosophy, Sydney Smith stated: 'To whatever height we may carry human knowledge, I hope we shall never forget those energetic and enterprising men who met the difficulty in its rudest shape.' How valid is the ancient maxim, 'If I had not lifted up the rock, you had not found the treasure'.

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