

**THE LISTER INSTITUTE OF
PREVENTIVE MEDICINE**

A CONCISE HISTORY



LESLIE COLLIER

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2000

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CONTENTS

<i>Foreword by the Chair of the Governing Body</i>	vii
<i>List of illustrations</i>	x
<i>Acknowledgments</i>	xi
<i>Author's preface</i>	xiii
1: <i>The founding of the Lister Institute: A new venture for Britain</i>	1
First steps	2
2: <i>Scientific activities 1893-1978</i>	8
Early days at Chelsea and Elstree	8
The Lister in two World Wars	12
The aftermath: new directions	15
Blood and blood products	16
Biochemistry	20
Experimental pathology and pathogenesis	21
Microbiology	22
Life at the Lister: the golden years	35
3: <i>The dark days</i>	39
Elstree goes it alone: A gallant try	41
The salvage operation	43

<i>4: A new beginning</i>	45
The Fellowship Scheme	46
DNA fingerprinting: a spectacular success story	51
(Not) in conclusion	53
<i>Annex A</i>	
Former Directors of the Lister Institute	55
<i>Annex B</i>	
Summary of important events	56
<i>Index</i>	63
<i>Supplement</i>	Insert

FOREWORD

by Dr Anne McLaren DBE, FRS
Chair of the Governing Body

So much has been written about the Lister Institute during the past century that the need for this book might well be questioned. But it was commissioned for a specific purpose and for a specific readership. The establishment of the Fellowship scheme created a new subset of people closely associated with the Lister Institute, namely the Fellows themselves. The Governing Body felt that they should be provided with adequate background information about the institution supporting their work, and accordingly commissioned this *Concise History of the Lister Institute of Preventive Medicine*. The author, Leslie Collier, worked in the Institute for a total of 30 years. He was Head of the Department of Virology from 1955 to 1974, Deputy Director of the Institute from 1968 to 1974 and Director of the Vaccines and Sera Laboratories from 1974 to 1978.

History is always interesting. When the history is still ongoing, and when it is written by someone who himself played an important part, it becomes fascinating. Imagine the scene at the end of the nineteenth century, with diphtheria killing thousands of children in this country every year, and rabies a dreaded, ever-present danger. In 1888, the Institut Pasteur was set up in Paris, followed by no less than forty similar establishments in other countries. Bacteriology and immunology were the hot research topics of the day, vaccines and antitoxins were becoming available, but in Britain almost nothing. Why? Government apathy, opposition to animal experiments, lack of funding, all seem (even then) to have played a part. But a happy

series of coincidences vividly described by Leslie Collier, and generous donations from various individuals and trusts, led finally to the gift of £250,000 by the Guinness family. In 1898 the British Institute of Preventive Medicine was formally established in a handsome building on the Chelsea Embankment. The British Institute changed its name to the Jenner Institute of Preventive Medicine in 1898 and finally to the Lister Institute of Preventive Medicine in 1903.

Over the next seventy-five years, including two World Wars, that building was to become a focus of some of the finest bio-medical research in the world. A production facility was set up at Elstree, turning out high-quality bacterial and viral vaccines, antisera and blood products, the sale of which was crucial to the funding of the Institute. The Lister was a one-off: it was neither a Government-funded institute, though it received many Government research grants and housed Research Council Units, nor was it a commercial enterprise in the modern sense. None of its products were patented (had they been, its history might have turned out differently), and indeed so apprehensive was the Governing Body of the stigma of vulgar commercialism that it refused to sanction a signpost in the main road for fear that it be construed as advertising.

The inevitable happened: finally, in 1975, the Institute in Chelsea closed, and Elstree could not long survive without the research back-up.

The closure of a world-famous Institute was unprecedented. But like a phoenix, the Lister arose from the flames. Eventually the Chelsea building was sold for a handsome sum, and the Governing Body far-sightedly decided to establish a 'virtual' institute of five-year Senior Fellowships distributed around the country. The first shortlist of twelve highly selected applicants was interviewed in 1982: I was on that first interview panel, and we were well aware of the importance of making the new scheme a success. Five fellows were funded, including Alec

Jeffreys, and about the same number of fellowships have been awarded in each year since – about ninety in total. The fellowships are prestigious, and at least 60% of former Fellows now hold Chairs.

Many of the Lister Fellows work on very basic biomedical problems: molecular, genetic, structural, developmental, immunological. But clinically oriented research is well represented too. In the early days of the Lister Institute, infectious diseases were the killers, while today less than 8% of mortality in rich countries is due to infections, and clinical emphasis has shifted to non-communicable diseases and genetic susceptibility. But among the world's poor, nearly 60% of mortality is still due to infectious diseases. Appropriately for an Institute of Preventive Medicine, we have had Fellows working on malaria, tuberculosis, HIV, gastrointestinal pathogens, meningitis and influenza, as well as genetically based conditions such as retinoblastoma and the Lesch Nyhan and Alzheimer's syndromes.

I feel very proud to have known such outstanding Lister personalities as Ashley Miles, Albert Neuberger, Gordon Roderick and Walter Morgan (who celebrates his 100th birthday this year). You will read about these and many more in the pages that follow. I feel very honoured to have chaired the Scientific Advisory Committee, and now the Governing Body. But today the Lister Institute is its Fellowship – defined in the dictionary not only as 'the state of being a fellow' but also as 'companionship' and 'society' (also as 'fitness and fondness for festive entertainments'). Companionship is an important part of the Lister today, and I hope that our Fellows, and many others who read this Concise History, will not only enjoy learning about the Institute's origins, but will also appreciate the extent to which companionship has been a feature of the Lister throughout its working life.

Anne McLaren
April 2000

ILLUSTRATIONS

PLATES

Between pages 34 and 35

1. Lord Lister.
2. Charles Sherrington with 'Tom', the pony immunized to make the first diphtheria antitoxin used in the UK.
3. Rupert Cecil Guinness, 1st Earl of Iveagh.
4. The Chelsea Laboratories.
5. Aerial view of the Elstree Laboratories.
6. The Staff, 1907.
7. Sir Charles Martin, Director.
8. Sir Arthur Harden.
9. Sir John Ledingham.
10. Sir Alan Drury.
11. Sir Ashley Miles.
12. The Staff, 1950.
13. *Left to right:* Douglas McClean, Charles Martin and Walter Morgan, mid-1930s.
14. Muriel Robertson examining leeches, Elstree, 1910.
15. Professor Albert Neuberger, Chairman of the Governing Body, 1970-1988.
16. Gordon Roderick, Secretary, Elstree Laboratories, 1958-1976. Secretary of the Institute and Clerk to the Governing Body 1976-1995.

ACKNOWLEDGEMENTS

I am glad to have this opportunity of thanking several people who contributed to the preparation of this book. First, I much appreciate Anne McLaren's kindness in providing the Foreword. I am also grateful to Winifred Watkins, Alec Jeffreys, Leon Vallet and Jean and Derek Dolby and Keith Cowey for sparing time to read the manuscript and amend where necessary the sections dealing with their own work. I should also like to express my gratitude to Mrs Lilian Neuberger for providing such a good photograph of her late husband and Mrs Lynne Roderick for the picture of Gordon. Keith Cowey and Freda Richards unearthed all the documents I needed with their usual promptness and efficiency. It is also a pleasure to thank Alec Just, our printer, for taking so much trouble to ensure that the appearance of the book would be worthy of its subject.

Edward Guinness acted as what a publisher would term the Commissioning Editor, and provided the interface between me and the Governing Body; he was throughout an unfailing source of advice and encouragement.

I have drawn upon the following principal sources of information:

War on Disease by Harriette Chick, Margaret Hume and Marjorie Macfarlane; André Deutsch, London (1971).

The Lister Institute's own archives, including Minutes of the Governing Body and its Annual Reports (which contained summaries by the departmental heads of the previous years' work, together with the Balance Sheets and Accounts).

The Commemorative Review published in 1991 to mark the Institute's Centenary. This contained an excellent *Summary of important events* by Gordon Roderick and I have reproduced it almost *verbatim* at the end of the *Concise History*.

A Special Report, also commemorating the Centenary, published by *The Times* on 25 July 1991.

An interview with Gordon Roderick tape-recorded by Edward Guinness in June 1999.

The Lister Institute Archive held at The Wellcome Institute for the History of Medicine.

Illustrations from the Wellcome Institute Library: the Archive of the Lister Institute of Preventive Medicine, Hall, Lesley & Morgan M. (1986) *Medical History*, 30: 212 – 215.

A number of articles on the history of the Institute written by members of staff, including two former Directors, A.N.Drury and A.A. Miles. In particular, several issues of *The Biochemist* published in the latter half of 1993 contained articles by former Heads of Departments giving personal and informative accounts of their time at the Institute.

Leslie Collier

AUTHOR'S PREFACE

I much appreciate the honour of having been asked by the Governing Body to write this *Concise History*. The invitation came as a pleasant surprise; and at first sight the task did not seem unduly difficult. After all, there was an abundance of readily available information, but in the event, its volume proved almost to be an embarrassment; the sifting of the vast amount of material, the many decisions needed on what to keep in and what to leave out and arrangement of the contents in some sort of logical order proved more difficult than I had anticipated. Nevertheless, I was well rewarded in terms of my own education, particularly about the earliest days of the Lister.

The period from the inception of the Institute in the 1890s to 1970 had already been covered in the excellent book entitled *War on Disease* by Harriette Chick, Margaret Hume and Marjorie MacFarlane, 'The Lister Ladies' as they were sometimes known. Miss Hume died before the work was completed. It is a cornucopia of information, entertainingly written, and I drew heavily on it in my own account. Other sources are listed under 'Acknowledgements'.

The final sections deal with the closure of the laboratories and the conversion of the Institute into a grant-giving trust – a gloomy story with a happy ending. Despite its high compression ratio, I hope that this book will succeed in its primary object of conveying to both former and present Fellows something of the achievements of those who preceded them.

Being primarily intended for the information of Fellows, the book must remain topical and hence is arranged in two

separate volumes: the main text, which is permanent, and the Supplement, which will be updated as needed. The latter lists the current members of the Governing Body and the Scientific Advisory Committee, and current and former Fellows.

Leslie Collier
April 2000

The founding of the Lister Institute of Preventive Medicine: A new venture for Britain

The story behind the early years of the Lister Institute is more complex than that of many other major scientific organizations; it is also of more than usual interest to the medical historian. Like similar establishments devoted to microbiology and immunology, it was formed amidst the ferment of new ideas and discoveries that took place in the latter half of the 19th century. In 1888, as a consequence of Louis Pasteur's development of a rabies vaccine, the French government helped to found the Institut Pasteur in Paris. Its researches covered not only rabies, but also diphtheria and tetanus, whose exotoxins were proving of major importance as tools for studying antibody-mediated immunity.

The success of the Pasteur Institute prompted the rapid setting up of no fewer than forty similar establishments in other countries; but despite Britain's early lead in preventive medicine, starting with Jenner's work on smallpox vaccine in the previous century and with the later investigations by Lister and

others on prevention of wound infection, there was no similar organization in Britain. All that existed was a College of State Medicine; although this was formed primarily to train Medical Officers of Health, it is relevant to our story since it later amalgamated with the British Institute of Preventive Medicine, later to become the Lister Institute of Preventive Medicine.

FIRST STEPS

By the end of the 1880s, then, there was still nowhere in the United Kingdom that offered immunization against rabies, a much feared disease still widespread in this and many other countries. Clearly, this situation could not be allowed to continue, and in 1886, a committee of six eminent scientists was set up to investigate Pasteur's claims: they included Lister (*Plate 1*), John Burdon Sanderson (the Oxford Professor of Physiology) and Victor Horsley, who was to become a famous neurosurgeon. After fifteen months, during which Horsley undertook laboratory tests to confirm the French findings, the Committee gave them its stamp of approval.

Not long afterwards, in 1889, the Lord Mayor of London, Sir James Whitehead, who had visited the Pasteur Institute, formed a Committee to study the possibility of collecting funds to support its work, but this modest objective was soon superseded by the notion of setting up a similar institute in Britain: indeed, Pasteur had already been asked by Whitehead to suggest a suitable director and had proposed M. A. (later Sir Armand) Ruffer, of mixed Franco-German birth, who had studied under Pasteur and qualified in medicine at University College, London.

There were three main obstacles to the project. First, objections were raised by some who considered that it would not be cost-effective and by others who vociferously opposed

the idea of animal experiments; but in the event, those supporting the establishment of a British Institute won the day. The second problem, that of finance, was more difficult to resolve. In the event, it was provided by, *inter alia*, philanthropic individuals and trusts, by the Worshipful Company of Grocers and by the Duke of Westminster, who made available a fine site on the Chelsea Embankment for a knock-down price of £6,000. In addition, a very useful contribution of £40,000 was received from the Trustees of a certain Mr R. Berridge, who had left a large sum for the furtherance of medical science. This bequest played a major part in determining the future of the new Institute, stipulating that it should be sited in London rather than Cambridge, the Committee's first choice. Thirdly, work could not begin without a licence to conduct animal experiments.

From the outset, it was agreed that the remit should not be confined to rabies. It should include research on a variety of infections, with a strong emphasis on their prevention by immunization and other means; and accordingly the new establishment would be named 'The British Institute of Preventive Medicine'. It was incorporated on July 25th, 1891.

This was all very well, but no work could be started without suitable accommodation, and the Chelsea laboratories would not be completed for some time to come. A solution was achieved in 1893 by amalgamating with the College of State Medicine, situated in a converted private house at 101 Great Russell Street, and by then in some financial difficulties. It did however possess the all-important licence for animal work.

The interim Director of this establishment was M.A. Ruffer. Under his direction, researches on bacteriology and serology were started. In 1893, the year in which von Behring published his development of an anti-diphtheria serum, the disease was rife, with over 3,000 deaths in the UK alone. In the following year, with the aid of Charles Scott Sherrington, then Director

of the Brown Sanatory (*sic*) Institute, Ruffer successfully immunized a pony ('Tom') with increasing doses of diphtheria toxin (*Plate 2*). Even as this procedure was still under way, Sherrington's own nephew became moribund with severe diphtheria; his life was saved by an injection of Tom's serum. This dramatic episode was followed by a great expansion of work on diphtheria and other infections, during which Ruffer himself contracted diphtheria and was also saved by the antitoxin.

Funding and organization

The new Institute was desperately short of money; but a fortuitous event set it on its feet: in theatrical parlance, its financial problems were solved by the appearance of an 'angel'. Lord Iveagh (*Plate 3*), head of the Guinness family and brewery, and a notable philanthropist, had made a donation to the Institute at its inception. In 1896, a worker on his estate was bitten by a rabid dog and had to be sent to Paris for anti-rabies injections. Lord Iveagh, dismayed by the lack of similar facilities in Britain, first visited the laboratories under construction at Chelsea and then the Pasteur Institute itself. These visits were followed immediately by a donation of £5,000 and, in 1898, by a gift of £250,000, the latter on condition that management by the existing unwieldy Council should pass to a Governing Body of seven trustees, three to be appointed by Lord Iveagh or his representatives, three by the Council and one by the Royal Society. This sum, the equivalent of around £15m today, was sufficient to complete the building and to assure the payment of some staff salaries and scholarships, at least for the time being.

It was now possible to start work in earnest; and a number of scientists later to become leaders in microbiology joined the staff, notably William Bulloch, George Dean and Arthur (later Sir Arthur) Harden. By 1897 there were 80 students, including 10 women, a small library and a Clinical Investigation

Department undertaking diagnostic tests for 30 hospitals.

In 1897, the Board of Governors of St George's Hospital, at the proposal of Lord Lister, commemorated the centenary of Jenner's discovery of vaccination by a public appeal for a memorial fund, with a target of £100,000, to be devoted to research at the British Institute of Preventive Medicine. In the event, only £5,770 was raised, of which £5,000 was contributed by Lord Iveagh, £600 by the Duke of Westminster and £100 by Lord Lister. It is sad to record that the Great British Public contributed only £70. The money was eventually used to endow a Jenner Memorial studentship in bacteriology, of which the first holder, in 1905, was Harriette (later Dame Harriette) Chick. In 1984 the endowment, now amounting to some £31,000, was amalgamated with the Institute's General Fund.

The public appeal having met with such a poor response, Jenner's name was instead honoured by changing the name of the British Institute to 'The Jenner Institute of Preventive Medicine'. This was unfortunate, because a small company making smallpox vaccine in Battersea, the Jenner Institute for Calf Lymph, successfully objected to the use of the name 'Jenner'. In the event, despite Lord Lister's diffidence about accepting the honour, the Institute was renamed 'The Lister Institute of Preventive Medicine', and so it has remained.

An independent foundation

The Institute is a registered charity and was incorporated as a company, limited by guarantee, on July 25th, 1891; in 1905 it became a School of the University of London. Its finances were however still a matter of concern; and during 1913-14 there was considerable debate over whether to amalgamate with the Medical Research Committee (later the Medical Research Council). In the event, the proposal was voted down by the Members of the Institute. This action was beneficial in that it

secured the much-valued independence that undoubtedly contributed greatly to the Institute's scientific successes; but in retrospect, it also laid the seeds of the financial problems that eventually brought about the closure of its laboratories.

Despite the decision to go its own way, relations between the Institute and the Council were good, as evinced by the formation of joint committees, financial support extended by the MRC to individuals, and the establishment of research units housed at the Lister.

As we have seen, the Institute was founded with generous donations, mainly from Lord Iveagh. With its expansion however, the income from these endowments was not enough to provide running expenses, and from early on it was intended that it should be supplemented by sales of vaccines and antisera made at its country laboratories; this arrangement was very similar to that at the Pasteur Institute. The third, and very important source of income was the grants awarded to the scientific staff in respect of their researches; their number and quality testify more than adequately to the standing of the Lister as a centre of excellence. There were far too many to list here in any detail, but they included grants from the Medical and Science Research Councils, the Wellcome Trust, the British Empire Cancer Campaign, various Government departments, notably those concerned with overseas development and the Fleming Memorial Fund for Medical Research. Arthur Guinness, Son and Co Ltd endowed both the Guinness-Lister Unit for studying bacterial genetics and the Guinness Chair of Microbiology, and the Wolfson Foundation provided a new laboratory block of *c.* 24,000 sq ft adjacent to the original building and containing a lecture theatre; the latter was donated by the Grocers' Company, benefactors of the Lister since its inception.

Eventually, however, economic difficulties forced the cessation of all laboratory work, first at Chelsea in 1975 and

three years later at the Vaccines and Sera laboratories at Elstree. Since then, with its transformation into a grant-giving trust, the Institute's functions and management have changed considerably: its present organization may be summarized as follows.

The Governing Body is responsible for general policy, administration and financial management. It elects its own Chairperson and Treasurer. The Scientific Advisory Committee advises the Governing Body on scientific policy and the appointment of Fellows. The Members are appointed by invitation of the Governing Body: they include senior members of the former scientific staff and all former Fellows who live in the UK; Governors, former Governors, past and current Scientific Advisory Committee members; and a few representatives of other bodies. They have the responsibility for considering and approving resolutions, reports, and accounts presented at the general meetings, the appointment or re-appointment of certain members of the Governing Body and the appointment or re-appointment of the Auditors and their remuneration.

Chairmen and former Chairmen of the Governing Body and Scientific Advisory Committee are listed in the Supplement. Former Directors of the Institute from 1893 to 1978 are listed in Annex A.

2

Scientific activities 1893-1978: A proud record

It cannot be over-emphasized that in a book of this size there is no space to do more than provide bare outlines of the major activities, both in research and production, that were pursued during the best part of a century. Given the comings and goings between Chelsea and Elstree, the discontinuance of researches in some fields and their resumption some years later, the following summary is necessarily a compromise between a chronological arrangement and one based on subject headings.

EARLY DAYS AT CHELSEA AND ELSTREE

For reasons unknown, Ruffer resigned in 1896 and went to Egypt, where he had a distinguished career in public health, tragically cut short when a ship on which he was travelling was torpedoed during the First World War. He was succeeded by A. Macfadyen, under whose directorship the new laboratories in Chelsea (*Plate 4*) were occupied in 1898. After the cramped conditions in Great Russell Street, they must have seemed

palatial, with spacious rooms, central heating, electricity and telephones. This event was a turning point in the Institute's history, providing as it did an adequate environment both for its scientific activities and for its function as the administrative headquarters.

As a result of Ruffer's work on diphtheria antitoxin, 56 horses for serum production were acquired and kept at a privately owned farm at Sudbury, near Harrow. Despite the successful preparation of diphtheria and tetanus antisera, this venture at first proved unprofitable; and in 1902, sale of the lease dictated removal of the serum department to Queensbury Lodge, an estate of some 27 acres near Elstree in Hertfordshire (*Plate 5*). In many ways, this was an idyllic location. Albert Riggs, who started at the Lister as a lab. boy and finished as a Senior Chief Technician, described it thus:

At 6 o'clock on a lovely August morning in 1903 I first saw the Lister Institute, or as it was then known locally, 'Queensbury Lodge', and now whenever it comes to my mind I see it now as I saw it then, the lovely tree-lined drive, the green fields and trim hedges, the old house with its rustic porch in front, the stables with its 18 horses and whistling stablemen, and the calm peace which reigned over everything.

This description held true for the next 70 years or so (except, on occasion, for the 'calm peace').

By the turn of the century the Institute's structure was set: predominantly basic researches at Chelsea, and predominantly production activities at Elstree. The qualification is important, because there were considerable overlaps in the activities of the two establishments.

At the outset, the staff at Chelsea (*Plate 6*) were engaged mainly on teaching and diagnostic work. There were however some useful researches, notably the demonstration by A. Macfadyen and S. Rowland of an endotoxin in the typhoid bacillus; J. E. Barnard's discovery of the lethal effect of ultra-

violet light on bacteria; and the pioneer work on bacterial metabolism by Arthur Harden. It seems that Macfadyen was not a great success as Director, and in 1901 it was announced that he would be designated as Secretary, responsible only for administration and for the Department of Bacteriology; henceforth, departmental heads would report individually to the Governing Body. However, this arrangement also proved unsatisfactory in the face of an increasing administrative load; and two years later we find in the Annual Report:

... the Governing Body feel that the time has now come for adding to their present staff a gentleman of scientific eminence, who shall have the title of Director of the Institute.

Such a gentleman was soon found in the person of Charles James Martin (*Plates 7 and 13*).

The appointment of Martin heralded a major expansion of investigative work in a number of important fields. He had previously spent 12 years in Australia, first in Sydney and then as Professor of Physiology in Melbourne, during which time he was elected a Fellow of the Royal Society. Something of a polymath, his own researches at the Lister ranged widely over the fields of human physiology, biochemistry, nutrition and bacteriology. The 27 years of Martin's directorship saw the flowering of the Lister Institute into the centre of excellence that it was eventually to become.

Pioneer researches in physiology and biochemistry

Physiology of diving

Before the invention of modern self-contained breathing apparatus, men working on the foundations of bridges, wrecks, etc. were lowered under water in diving bells or primitive suits, and were exposed to high air pressures. Over-rapid decompression on ascending caused liberation of dissolved nitrogen

into the bloodstream and joints, resulting in an illness, sometimes fatal, known as the 'bends'. In 1904, J. S. Haldane FRS, father of the better known J. B. S. Haldane, conducted a classic series of experiments on animals and volunteers (including himself) in a pressure tank at Chelsea; he worked out a scheme for decompression that superseded the current unsatisfactory systems and was eventually adopted worldwide.

Enzymes and co-enzymes

From its inception, biochemical studies were a major component of the Institute's activities. The earliest, starting in 1900, were those of A. Harden and his colleagues on alcoholic fermentation. In Germany, E. Buchner had recently demonstrated an enzyme (zymase) in yeast that catalysed the fermentation of sugar to yield alcohol and carbon dioxide. Harden's invention of a volumetric method for measuring the rate of evolution of CO₂ greatly facilitated the subsequent studies on fermentation pursued in collaboration with, among many others, W. J. Young, R. Robison, W. T. J. Morgan, and E. J. King. In brief, these culminated in the discovery of the first co-enzyme (co-zymase) to be identified; the mechanism of the phosphorylation of sugar in yeast juice; the isolation by Robison of the intermediate mono- and diphosphates of various sugars; and the characterization of bacteria by their ability to ferment sugars. For his leading role in these researches, Arthur Harden (*Plate 8*) was elected FRS, awarded a knighthood, and shared the Nobel Prize for Chemistry with H. von Euler in 1929.

Robison, still pursuing his studies on hexosemonophosphates, then turned his attention to the process whereby calcium is laid down in ossifying cartilage. With colleagues, he discovered that it was mediated by another enzyme, bone phosphatase; and, with Honor Fell at Cambridge, showed that normal cartilage cells produce it only at the appropriate stage in their development.

Much later, during the early 1950s, J. (later Sir James) Baddiley and his group added another chapter to the work on co-enzymes in their studies on the synthesis and modes of action of pyridoxal phosphate and pantothenic acid, concerned respectively with transamination and with the synthesis of fatty acids.

Vitamins

Elucidation of the role of vitamins in nutrition for long occupied workers in several countries, among whom those at the Lister made outstanding contributions. Indeed, the term 'vitamine' was coined in 1912 by a guest worker, Casimir Funk, who studied the factor in unpolished rice – vitamin B₁ – that protected against beri-beri, while Harriette Chick and her team did important work on the distribution and stability of the anti-scurvy factor, later identified as ascorbic acid. At the same time, A. Harden and S.S. Zilva found that the common practice of adding soda when boiling vegetables destroyed the factor, and devised a method for preserving it in concentrates.

THE LISTER IN TWO WORLD WARS

Most of the researches so far described were done during the Institute's first half-century, a period that saw both the full impact of the First World War (WW1) of 1914-18 and the start of the second (WW2) in 1939. Both conflicts had important effects on the Lister: in particular, WW2 marked the start of the modern era of biomedical research, a period of exponential development to which the Institute made many important contributions. At this point, we shall digress from the purely scientific story and describe some of the more important events of the war years.

The 1914-18 war

On the outbreak of WW1, many of the male scientific and technical staff joined the Royal Army Medical Corps (RAMC) or other organizations connected with war-time medicine and public health. Charles Martin, the Director, had foreseen the need for tetanus antitoxin and ensured that the Institute started preparing stocks even before hostilities began. He later served as a major in the Australian army medical service, making, *inter alia*, invaluable contributions to the control of typhoid, cholera and meningococcal meningitis; his work earned him two mentions in dispatches and the CMG. Harriette Chick took over the production of diagnostic antisera and Muriel Robertson investigated the anaerobic bacteria causing gas gangrene, a major hazard in the conditions pertaining on the Western Front. With colleagues in other laboratories, she succeeded in identifying the micro-organisms responsible.

J.C.G (later Sir John) Ledingham (*Plate 9*), chief bacteriologist to the Institute since 1908, served as a consultant in the RAMC and studied trench fever, an illness spread by the body louse that was highly prevalent in troops fighting in France and Belgium. His work, in collaboration with J. Arkwright and A. Bacot, contributed considerably to the study of this and other infections now known to be caused by rickettsias.

Another important contribution was the antiseptic hypochlorite solution devised by H. Dakin, a member of staff since 1902. It was used extensively for treating wounds, both during the war and up to the development of antibiotics.

In 1918, Mellanby published his work on the prevention of rickets by a fat-soluble factor in cod-liver oil. The relevance of this and related findings to the nutritional problems occasioned by the war prompted the formation in 1918 of an Accessory Food Factors Committee, which at the end of hostilities mounted extensive investigations into nutritional deficiency

diseases – scurvy, hunger osteomalacia, keratomalacia and in particular rickets – that were widely prevalent in war-torn Europe. The researches were funded jointly by the Lister Institute, which sent Harriette Chick, Margaret Hume and Elsie Dalyell to Vienna, and by the MRC. The most important finding of these controlled studies was that rickets could be prevented or cured by cod-liver oil or by ultraviolet light.

The 1939-45 war

The outbreak of WW2 entailed many changes in terms of scientific activities, redeployment of staff and dispersion of several of the Chelsea departments to Elstree and other establishments outside London. Most of the Chelsea departments and the library were re-located to Elstree or to institutions in Oxford and Cambridge. Some of the scientific staff were seconded to various government establishments, or joined the armed Forces. As might be expected, there was a general intensification of research on immunization and on the production of vaccines and antisera. Lister workers, still including Harriette Chick and Margaret Hume, advised the Accessory Food Factors Committee¹ on the best way of preserving the vitamin content of the wheat flour used to make the National Loaf, which contributed significantly to the health of the nation during the war years.

Sir John Ledingham retired in 1943, having served as Director since 1930; he was replaced by Dr (later Sir) Alan Drury (*Plate 10*), who, as Chairman of the MRC Blood Transfusion and allied committees, ensured continuation of the Institute's involvement in this field.

¹ This was a joint MRC-Lister Institute creation, the original members being Gowland Hopkins (Chairman), A. Harden, J. C. Drummond, E. Mellanby and Harriette Chick (Secretary)

THE AFTERMATH: NEW DIRECTIONS

As with many other organizations, the coming of peace saw changes in the management of the Institute, in its staff and in its scientific activities. The Director became *ex officio* a member of the Governing Body, which was now also joined by the Earl of Iveagh and by a representative of the scientific staff. The Department of Bacteriology did not survive the losses of senior staff due to secondment to wartime duties or death, and the National Collection of Type Cultures, hitherto housed at Elstree and directed by S.T. Cowan, moved to the Central Public Health Laboratory, where it came under the aegis of the MRC and the Ministry of Health. Other activities will be described in the following sections.

Early in the post-war period it became apparent that the Lister, like other similar Institutes, could not, as hitherto, finance individual workers. The small group, sometimes funded partly or wholly by outside bodies, became the typical unit of research, an arrangement that carried many advantages in terms of shared expertise, facilities and expensive equipment. Even so, some members of staff continued to be individually financed by organizations such as the Nuffield Foundation.

At about this time, both the techniques of biomedical research and the intellectual climate surrounding it started to change at an accelerating pace. These factors, together with the appointment of A.A. (later Sir Ashley) Miles (*Plate 11*) as Director in 1952, combined to start the Institute on a new and productive phase, while maintaining the tradition of giving the established scientific staff a wide measure of freedom in forming their own units to pursue lines of research of their own choosing. *Plate 12* shows the scientific staffs of both Chelsea and Elstree at about this time

The need for improving the Elstree laboratories, which had for long been short of funds, was a major problem.

Nevertheless, it was possible by 1953 to provide both a new smallpox vaccine laboratory and new animal houses; and a start had been made on the provision of a Blood Products Laboratory (see 'Biophysics and Blood Products', page 18).

We shall now resume the description of the Institute's activities in research and in the manufacture of biomedical products, dealing first with blood groups and blood products, which were major interests at both Chelsea and Elstree.

BLOOD AND BLOOD PRODUCTS

Blood group antigens

Walter Morgan (*Plate 13*) moved from Elstree to Chelsea in 1939. Professor Robert Robison died suddenly in 1941 and Morgan succeeded him as head of the Biochemistry Department. With the onset of WW2, and the setting up of the Emergency Blood Transfusion Service, his attention had turned to the nature of human blood group antigens, which were chemically unidentified at that time. He initiated a major programme on the chemistry and genetics of the human ABO and Lewis blood group systems, which, with his colleague Winifred Watkins, was to continue for the next 35 years. An antigen on O cells previously thought to be the product of the O gene in the ABO system was shown to be the product of an independent genetic system, named H, which forms the precursor of the A and B antigens. Work carried out on secreted glycoprotein blood group substances that had the same serological specificities as the antigens on the red cells revealed that the antigenic determinants were carbohydrate and that one of the component sugars was more important for specificity than the others.

Indirect methods of inhibition of haemagglutination and enzymic degradation disclosed that L-fucose, N-acetyl-D-galactosamine and D-galactose are respectively the immunodominant sugars for the H, A and B specificities; and that each of these sugars is joined by α -anomeric linkage to the adjacent sugar. Subsequently the complete determinant structures for A, B, H, and Lewis blood group antigens, Le^a and Le^b, were isolated and chemically characterised, and the relationships between them became apparent. Sequential degradation of the glycoproteins with exo-glycosidases revealed the loss of one specificity and the development of a new one; this finding led to the proposal that the oligosaccharide chains are built up sequentially and that the products of the blood group genes are enzymes – glycosyltransferases – that add the final sugar to complete the determinants.

Walter Morgan officially retired in 1968 and was succeeded by Winifred Watkins as Head of the department. With her colleagues she identified the glycosyltransferases in human tissues responsible for the biosynthesis of the A, B, H and Lewis blood group antigens. These fundamental studies laid the basis for an understanding of the roles of carbohydrate cell surface structures as ligands in cell-cell and cell-protein interactions related to inflammation, tumour progression and metastasis.

The work of the Lister investigators was well complemented by that of two Medical Research Council units – the Blood Group Research Unit and the Blood Group Reference Laboratory – that were housed at Chelsea from 1946 onwards. Since they were wholly supported by the MRC their work will not be described in any detail, but there is no doubt that siting them alongside the Lister workers was mutually beneficial.

These units were directed respectively by R. R. Race, working in partnership with his wife, Ruth Sanger, and by A.E. Mourant, the latter being succeeded by K. L.G. Goldsmith in 1966.

Biophysics and blood products

In 1935 A. S. McFarlane, who had spent a year in Svedberg's laboratory at Uppsala, joined the Institute to continue his work on the properties of protein molecules. The Rockefeller Foundation funded the purchase of a Svedberg ultracentrifuge and this was complemented two years later by the recently invented Tiselius electrophoresis apparatus. At the same time, R. A. Kekwick also joined the staff and studies of viruses and immunoglobulins were begun; but these activities were interrupted by the outbreak of war and the new Biophysics Department was evacuated to the London County Council's Serum Institute at Carshalton, in Surrey, where attention turned naturally to the practical problems posed by blood transfusion.

The Institute's interest in blood transfusion and blood products was greatly stimulated by the arrival of A.N. Drury as Director in 1943. As a member of the MRC external scientific staff at Cambridge, he had been largely responsible for developing the blood transfusion services in the UK; and with the return of the Biophysics Department to Chelsea in 1944, a joint Lister - MRC Blood Products Research Unit was established, with Kekwick as head of the Lister's Biophysics Division. There he was joined by Margaret Mackay, who had supervised the sterility of the plasma products at Carshalton and who had also worked in the MRC Serum Drying Unit at Cambridge.

There was an urgent need to develop a method for fractionating human plasma – initially to obtain fibrinogen, thrombin, immunoglobulin and albumin – by an alternative to E. J. Cohn's system of ethanol precipitation, the latter reagent being unavailable in war-time Britain. Kekwick and Mackay developed such an alternative using ether as a precipitant and brought it into production on a pilot scale.

By 1954, the demand for these products was such that the Unit moved into a new building at Elstree, becoming the Blood

Products Laboratory (BPL), a department of the Institute but funded by the Ministry of Health. W. d'A. (later Sir William) Maycock was Director and Leon Vallet took charge of physico-chemical and technical developments. To the original range of products, including dried plasma, were added others: immunoglobulins specific against various infections, and, initially using a method developed by Kekwick and P. Wolf, antihæmophilic globulin, the first clinically effective factor VIII concentrate. In 1963, at the invitation of C. (later Sir Cyril) Clarke² the BPL prepared the first anti-D immunoglobulin used in a trial of its efficacy in preventing sensitization of Rh-negative women bearing Rh-positive infants; its success prompted an intense effort to provide enough to protect all women at risk.

In 1960, M. Creeth succeeded Kekwick as head of Biophysics. The old Svedberg ultracentrifuge was replaced with a Spinco; and Creeth's work on the physical properties of the blood group-specific glycoproteins led to a major study, in collaboration with Lynne Reid of the Brompton Hospital, of the properties of mucus in obstructive airways disease.

Later, in 1967, the Institute assumed administrative control of the Plasma Fractions Laboratory at Oxford, as an adjunct of the BPL. Headed by Ethel Bidwell, this unit investigated and produced clotting factors. Other important successes at the BPL included the development by B. S. Combridge of the radio-immunoassay used nationally to screen blood donations for hepatitis B surface antigen; and by Vallet of quantitative gel filtration to replace ultracentrifugation for detecting aggregated and fragmented protein in immunoglobulin and albumin. This method was later included in the European Pharmacopoeia.

² Of the University of Liverpool; later a member of the Institute's Governing Body

The Oliver Memorial Fund

In the early 1920s Percy Lane Oliver, an employee of Camberwell Borough Council, set up what was to become Britain's first voluntary blood donor panel. This grew in size and with some support from the Red Cross, became a model for others elsewhere. Eventually, Oliver gave all his time to organizing donor panels until the national Emergency Blood Transfusion Service was created in 1939. After his death in 1944 the Oliver Memorial Fund was raised to commemorate his work; it makes an annual award to mark outstanding contributions to the field of blood transfusion. Eight individual awards have been made to Lister staff or to workers in units housed at the Institute. In 1991, the award was made to the Lister Institute itself in recognition of its standing as a centre for transfusion research.

BIOCHEMISTRY

The chemical basis of immunological specificity

This was a topic of importance to the Lister, involved as it was in the production of vaccines and antisera. During the inter-war years, W. T. J. Morgan, working variously at Elstree and Chelsea, isolated and characterized the polysaccharide that confers antigenic specificity on the Shiga bacillus. The antigen, which proved to be an oligosaccharide composed of D-galactose, L-rhamnose and N-acetylhexosamine, was extracted by a novel method using diethyleneglycol. During the following years, Morgan and co-workers showed that the oligosaccharide was a hapten that needed to be complexed with a conjugated protein in order to induce antibody formation *in vivo*, and that such complexes could be prepared artificially. Similar antigens

could be prepared from polysaccharides derived from other bacteria and even from vegetables. Artificial antigens made by coupling Shiga conjugated protein with purified blood group A and B glycoproteins were used to produce powerful rabbit anti-A and B grouping sera that were used by the Navy during the 1939-45 war.

The metabolism of starch and glycogen

From 1956 to 1964, W.J. Whelan and his team studied enzymes involved in the metabolism of carbohydrate macromolecules. Starting with studies on the amylases and transferases of starch, Whelan went on to investigate analogous enzymes in animal tissues; these researches determined their role in breaking down glycogen to glucose and the pathological consequences of their absence in certain rare congenital syndromes.

EXPERIMENTAL PATHOLOGY AND PATHOGENESIS

Mechanisms of inflammation

In 1952, A.A. Miles was appointed Director. One of the outstanding scientists of his generation, Miles was during the war Professor of Bacteriology at University College Hospital Medical School and Director of the MRC Wound Infection Unit at Birmingham. At the Lister, he, together with D.L. Wilhelm, established a new Department of Experimental Pathology, where he extended his researches on the non-specific defences that come into play during the earliest stages of bacterial infection. The infection fails if the bacteria cannot establish what was termed a 'primary lodgement' in the tissues. Miles and his colleagues demonstrated two distinct stages in the

inflammatory response to primary lodgement, the first of which is characterized mainly by increased vascular permeability, and the second, a few hours later, by increased exudation of proteins and phagocytes. The first stage is mediated by histamine and the second by a newly discovered class of globulin permeability factors that operate early in a cascade of precursor molecules, the end result being the release of small molecules termed kinins. It is these that are highly active in lowering blood pressure and increasing vascular permeability.

Later, W. E. Parish investigated the dynamics of eosinophils in allergic responses, their interactions with other leukocytes and the pathogenesis of allergic vasculitis.

Hyaluronidase

Observations by Duran-Reynals and Karl Meyer in the USA showed that testicular extract and some bacteria contain an enzyme that breaks down a mucopolysaccharide, hyaluronic acid, a cementing material found in various tissues. At Elstree, D. McClean confirmed these findings, and showed that the enzyme, termed hyaluronidase, acts as a spreading factor that enhances certain wound infections but can be neutralized by specific antiserum. Further studies with I. W. Rowlands (National Institute for Medical Research) suggested that hyaluronidase contained in sperm plays an important role in penetration of the ovum.

MICROBIOLOGY

Protozoology

Trypanosomiasis

From its earliest days, the Institute maintained an interest in trypanosomiasis. In 1905, E. A. Minchin was appointed to a

chair of protozoology endowed by the Colonial Office, and proceeded to work out in detail the complicated life cycle of a trypanosome in wild rats and fleas. At that time, the idea of an intermediate host was not generally accepted, but this mode of transmission was confirmed by Muriel Robertson, who joined the staff in 1907. She had previously shown that in trypanosomiasis of fish, the organisms are transmitted by leeches. On arrival at the Lister, she studied the trypanosome life cycle in the goldfish and leeches frequenting the pond at Queensbury Lodge (*Plate 14*). By this time, Sir David Bruce had implicated the tsetse fly in the transmission of African trypanosomiasis ('sleeping sickness'), and Muriel Robertson was despatched to Uganda. Here she worked out the life cycle of the causal trypanosome and, travelling through the bush by bicycle, undertook a field investigation of the disease in cattle.

These studies were interrupted by WW1, but were resumed in the Serum Department at Elstree in 1947 by B. G. F. Weitz, a veterinary scientist, who, as part of a wider investigation mounted by the Colonial Office, set out to identify the feeding habits of the tsetse fly and other insects. He designed a mobile laboratory for collecting blood samples from a wide range of animals, birds and reptiles. Using the sera in a highly accurate, semi-automated precipitin inhibition test, Weitz was able to identify the sources of blood meals in the intestines of various species of tsetse fly. These researches opened the possibility of controlling the flies, and thus the spread of infection, by eliminating from given areas the species of animal on which they prefer to feed. As part of the international malaria eradication campaign, Weitz also provided a centralized service for identifying the blood meals of mosquitoes.

Weitz and his team later studied the sequential development of exoantigens in *Trypanosoma brucei* infections of animals. Replication is inhibited, but not completely eliminated, by the antibody induced by the primary infection. The surviving

trypanosomes then release a mutated antigen that stimulates formation of a second antibody, which in turn partially inhibits the next round of replication. These cycles can be repeated many times, and explain why production of a vaccine is at present impracticable.

In 1966, D.G. Godfrey succeeded Weitz as head of trypanosomiasis research, for which large amounts of antigen were now needed. Trypanosomes could not at that time readily be cultivated and Sheila Lanham tackled the problem of producing the antigens by alternative means. By exploiting the difference in charge between the surfaces of red cells and trypanosomes, she was able to produce purified trypanosomes in quantity, using a column separation method.

Trichomonas

In addition to her work on trypanosomiasis (see above) Muriel Robertson's main interest was the immunopathology of *Trichomonas foetus* infections, which affect the genital tracts of both cattle and humans. These studies were done in close association with W. R. Kerr (Dept. of Veterinary Research, Ministry of Agriculture, Northern Ireland). Over a period of twenty years these workers conducted wide-ranging studies of the immunopathology of such infections in cattle, with particular emphasis on the role of antibodies, some of which occur naturally in cattle and other animals, whereas others are elicited only by infection or artificial immunization; local muco-antibody formation in the uterine wall seemed to be responsible for immunity to infection. In one of the intramural collaborations characteristic of the Lister, Winifred Watkins found that filtrates of *T. foetus* cultures provided by Muriel Robertson possessed at least ten enzymes that were useful in selectively removing sugar residues from blood group substances.

Muriel Robertson was elected FRS in 1947, being one of the first women thus honoured.

Bacteriology and Virology

Disinfection

Harriette Chick was the first woman to join the staff; in 1905 she was awarded the Jenner Memorial Research Studentship (see p. 5) and soon, with Martin, embarked on a classic investigation into the mode of action of disinfectants, and the kinetics of bacterial inactivation, neither of which was understood at that time. The current test for the efficacy of a disinfectant, devised by S. Rideal and J. T. A. Walker, involved comparison of its killing power with that of phenol. It was so unreliable that it was referred to in Topley and Wilson's *Principles of Bacteriology and Immunity* as 'at best a grossly oversimplified answer to a very difficult problem, and at worst little short of bacteriological prostitution'. In brief, Chick and Martin recognized that in practice disinfectants are used in the presence of organic material, and added 3% dried human faeces to the reaction mixture. The Chick-Martin test gave realistic results and was in general use for many years. These findings were extended widely to cover the kinetics of protein coagulation by heat and the separation of the immunologically potent pseudoglobulin fraction from the horse antisera used for passive immunization.

Harriette Chick made valuable contributions to the study of nutrition in both World Wars, remained on the staff until her retirement, and then continued as an honorary member. She was created DBE in 1949 and lived to the great age of 102.

Plague

A sailor just returned from the East yielded the first isolation of the plague bacillus (*Pasteurella pestis*) in the UK. This was done at the Lister (then still in Great Russell Street) and published in the Institute's *Transactions* in 1897. From then on, the Institute provided a plague diagnostic service. In the early 1900s there

were major epidemics in India and elsewhere, with mortality rates up to 80%. The only remedies available were a vaccine and an antiserum prepared respectively by W. M. Haffkine in Bombay and A. Yersin in Paris. Although both were of doubtful value, the authorities asked the Lister to prepare the antiserum at Elstree, where the necessary isolation facilities were installed. There was however, still no solution to the crucial problem of how plague is transmitted. This was tackled with characteristic vigour by Charles Martin, who established the Advisory Committee for the Investigation of Plague in India, in which Governors and staff of the Lister played a dominant part. In a monumental epidemiological and laboratory investigation, the Indian rat flea, *Xenopsylla cheopsis*, was incriminated as the vector between rats and humans, thus providing the rationale for the preventive measures still in use worldwide.

These researches were expanded by Arthur Bacot, a City clerk who had made himself an expert on insects, particularly fleas. At first an unpaid part-time worker, his observations on their propagation, longevity and reactions to different environments gained him the post of entomologist to the Institute. Among other contributions, he and Martin worked out how the plague bacilli were injected into the skin during biting. Sad to relate, Bacot later died of typhus when investigating this disease in Cairo. Plague itself claimed a victim actually working at the Lister: in 1909, an Australian researcher under Sydney Rowland contracted a laboratory infection and died within a few days.

Clostridia

Early in WW1, Muriel Robertson had turned her attention to the anaerobic bacteria causing gas gangrene, a severe infection of wounds with a significant mortality. By improving culture methods, she and other workers introduced order into the taxonomy, which was at that time confused, eventually defining

three species of *Clostridia* important in anaerobic wound infections: *welchii*, *oedematiens*³ and *septicum*.

The outbreak of WW2 saw a resumption of research in this field, when Marjorie Macfarlane and B. C. J. G. Knight traced the toxic action of *Cl. welchii* to a lecithinase that destroys cellular mitochondria, and that can be inhibited by antitoxin; this was the first demonstration that an enzyme could act as a bacterial toxin.

The efficacy of anti-gas gangrene sera in the field was still controversial; as Secretary to the MRC Anaerobes Sub-Committee, Marjorie Macfarlane therefore carried out a statistical analysis of the results of serum prophylaxis and showed that it was in fact effective in preventing gas gangrene in wounded men.

Mycoplasma

Emmy Klieneberger-Nobel and co-workers, notably Ruth Lemcke, studied the properties of various mycoplasmas causing pleuropneumonia in cattle and other mammalian species, including humans, and impairment of lactation (agalactia) in sheep. She showed that these infections are often latent, but can be reactivated by stress or during ageing. These studies assumed greater prominence when she and others discovered that mycoplasmas are causally related to certain sexually transmitted infections of humans. Emmy Klieneberger-Nobel was the first to recognize the existence of L ('Lister') forms of certain bacteria, which are variants lacking a cell wall and thus superficially resemble the mycoplasmas.

Chlamydia

In 1955, L.H. Collier was appointed Head of a new Department of Virology at Chelsea. His immediate objective was the isolation of the agent – then thought to be a virus –

³ Original designations

causing trachoma, a blinding disease affecting 400 million people. He also became Honorary Director of the MRC Trachoma Research Unit, with a small team at Chelsea and an expatriate worker, Josef Sowa, in The Gambia. The intention was for Sowa to collect eye swabs and send them to the Lister group for isolation studies; but before this scheme could be got under way, Tang Fei-Fan and co-workers reported the isolation in chick embryos of a psittacosis-like agent from the eyes of trachoma patients in Beijing. Collier and Sowa confirmed these findings in The Gambia; and, with colleagues at the Institute of Ophthalmology in London, proved, by inoculation of blind volunteers, the aetiological relationship of the isolates to trachoma. An ophthalmologist, Shiona Melville (later Mrs Sowa), was appointed to the Gambian laboratory, where, under Collier's direction, the Sowa and other members of the Unit carried out a major study of the microbiology, clinical features and epidemiology of trachoma and allied infections, including those with *Haemophilus spp.* The latter investigation was done in collaboration with Arthur Standfast and Jean Dolby at the Bacterial Vaccines Department, Elstree.

At Chelsea, the Trachoma Unit achieved the first isolations of chlamydias (now known to be intracellular bacteria) from the related sexually transmitted infections, inclusion conjunctivitis, cervicitis and urethritis, and succeeded in propagating them continuously in cell cultures. As well as blindness in the tropics, chlamydial infections are a major cause of sexual disability in the developed countries; they also cause respiratory and cardiac disease. The work of the Unit on the properties of chlamydias was of major importance to their subsequent study in the UK and elsewhere.

Bacterial variation and genetics

The tendency of some bacterial subcultures to produce irregular colonies with rough surfaces, rather than the normal smooth,

circular appearance was studied by J. Arkwright, who succeeded in separating the two variants. The rough (R) forms had lost both their virulence and their ability to be agglutinated by sera prepared against the smooth (S) type. Arkwright correctly surmised that these changes reflected alterations in the bacterial cell surface and showed that they were accompanied by a variation in the somatic antigens: antiserum directed against the S forms protected against infection with virulent bacteria, whereas antibody to the R forms failed to do so.

Many years later, Arkwright's researches were extended by A. Felix, well known for his work during WW1 on the Weil-Felix test for typhus. In the 1950s, he and Margaret Pitt produced a highly virulent strain of *Salmonella typhi* containing a new antigen termed 'Vi' (for virulence). This strain protected mice against infection, but, disappointingly, neither anti-Vi sera nor vaccines containing the antigen proved effective in preventing or treating typhoid in humans.

The basis of these antigenic changes was of course genetic; and the theme of bacterial genetics was resumed in 1953 with the creation of the Guinness-Lister Unit, established in 1953 under the directorship of B.A.D. Stocker. Endowed by Arthur Guinness, Son and Co, this unit became predominant in its field within the UK. While working with J. Lederburg at the University of Wisconsin, Stocker suggested that the motility of flagellated strains of salmonellas is a genetic character susceptible to direct observation. This tool was used to study the acquisition of motility by phage transduction and its inheritance in episomal form. The work of Stocker and his team on bacterial conjugation eventually led to the mapping of the whole of the salmonella chromosome.

1963 saw the establishment of the Guinness Chair of Microbiology, with Stocker as the first Professor. He was succeeded by G.G. Meynell in 1965, when the Guinness-Lister Unit was supplemented by other microbiologists on the

Institute's staff. The work on bacterial and bacteriophage genetics continued with emphasis on plasmids, particularly those coding for colicins. By examining the way in which colicins are transferred, Meynell and Alan Lawn, the Institute's electron microscopist, made the important discovery of a new bacterial structure, a sex pilus involved in conjugation. Sex pili were subsequently used in classifying bacterial plasmids, notably those conferring resistance to antibiotics. Meynell also used phages to analyse the kinetics of bacterial replication. A number of his investigations were done in collaboration with his wife Elinor, a member of the MRC Microbial Genetics Research Unit. During its researches the Guinness-Lister Unit acquired a large and very useful collection of bacterial mutants for use in studies of this nature. The Unit closed in 1972 on Meynell's appointment to the Chair of Microbiology at the University of Kent.

Virology

During the 1930s, the study of viruses was in its infancy and research was hindered by the inability to propagate them in artificial culture media. Ledingham, together with Russell Amies, initiated a long series of investigations on the pox and herpes viruses; these studies did much to associate their 'elementary bodies' (now known as virions) with infectivity and to confirm the relationship between on the one hand the viruses of the pox group and on the other, those causing chickenpox and herpes zoster.

During the inter-war years, foot-and-mouth disease of cattle, caused by a picornavirus, was investigated intensively by Arkwright in collaboration with MRC workers; they elucidated many of the physico-chemical and antigenic properties of the virus, but were unsuccessful in preparing an effective vaccine.

Later researches on vaccinia (and rabies) are described in the next section.

Biomedical products

Many of the activities so far described were carried out at Chelsea. The emphasis now shifts to Elstree, where the manufacture of vaccines and antisera took place. After WW2 there were three departments for which the Institute was wholly responsible: Bacterial Vaccines, Smallpox Vaccine and Serum, each of which also undertook researches related to its products. The Blood Products Laboratory is referred to above; and the National Collection of Type Cultures was transferred to the Central Public Health Laboratory in 1950 (see p.15).

The table below summarizes the vaccines and sera being made at the Elstree Laboratories during their final years. The following paragraphs describe some features of particular interest, including major research projects.

Bacterial Vaccines Department

This department moved from Chelsea to Elstree during WW2; it was headed by A.F.B. Standfast from 1946 until his retirement in 1972. Under his direction it became a major producer

Summary of sera and vaccines prepared by the Lister Institute, Elstree

<i>Antisera</i>	<i>Bacterial vaccines*</i>	<i>Virus vaccines</i>
Diphtheria	Diphtheria	Smallpox
Tetanus	Tetanus	Rabies
Gas gangrene	Pertussis	
Rabies	Cholera	
Scorpion	Typhoid & paratyphoid	

* These vaccines were available in a variety of formulations and combinations.

of diphtheria and tetanus toxoids and of pertussis whole cell vaccine, either as separate components, or more often combined as 'triple vaccine'.

Related researches With Jean Dolby and others, Standfast did much research on the immunogenicity, toxicity and other properties of pertussis vaccines. Comparison of the validity of intracerebral versus intranasal challenge for determining the immunogenicity of pertussis vaccines was an important aspect of the department's researches; somewhat surprisingly, the former method gave results that corresponded more closely with protection in the field, and in this respect was also superior to assays of other components of the organism, including its toxin, agglutinogens, haemagglutinin and histamine-sensitizing factor.

The department participated in a series of field trials, mounted by the Medical Research Council, involving more than 35,000 children, which contributed greatly to the selection of a suitable vaccine for routine immunizations.

In addition to his heavy responsibilities in the Bacterial Vaccine Department, Arthur Standfast was for many years Editor of *The Journal of General Microbiology*, at first with B. C. J. G. Knight, and then on his own.

Tetanus toxoid In adolescents receiving routine booster doses of tetanus toxoid, local and general reactions seemed to be reported more often after vaccination with an aluminium hydroxide adjuvant than after plain toxoid. In collaboration with workers at the Central Public Health Laboratory, L. H. Collier confirmed, in a trial involving more than 1000 children, that this was so; and showed that the antibody response to the plain toxoid was in fact greater and more durable than that induced by the adjuvant vaccine normally used.

Rabies vaccine From its early days to the closure of Elstree in 1978 the Lister continued to make rabies vaccine by a traditional method involving propagation of an attenuated strain of virus in rabbit brains and its inactivation by phenol. Its production in the Bacterial Vaccines Department rather than a virus laboratory seems odd at first sight, but was explained by the absolute prohibition on handling any virus other than vaccinia in the Smallpox Vaccine Department. The procedure was not without risk to the technical staff, since the potency test involved challenge of immunized mice by inoculation with a fully virulent strain. It is pleasing to record that during the many years in which this vaccine was produced, there was not a single accidental infection. Given the facility in which rabies virus was handled, primitive by today's standards, this record is a tribute to the meticulous attention to detail by the staff concerned.

Related researches Various workers, notably G.S. Turner and C. Kaplan, studied aspects of rabies vaccines, including the immune response, methods of purification and propagation in cell cultures. In particular, Turner, with workers from the MRC Clinical Research Centre and WHO, was involved in the successful clinical trials of a cell culture vaccine produced by the Mérieux Laboratories in France.

Smallpox Vaccine Department

The Institute provided almost all the smallpox vaccine (originally referred to as 'vaccine lymph') used in the UK and also exported large quantities. The methods of production were similar to those of other manufacturers. The eruption on the skin of a sheep inoculated with vaccinia virus was harvested, homogenised and treated with phenol to reduce the number of bacterial contaminants. Glycerol was then added to avoid freezing at the storage temperature of -15°C .

Related researches Like all such live preparations, the Lister product lost potency rapidly at temperatures above freezing, a major problem in hot countries; and in 1948 L. H. Collier was appointed to the Department with the specific remit of developing a thermostable vaccine.

He was eventually successful with a freeze-dried suspension of partially purified virus in 5% peptone, which both stabilised the virus and prevented 'salting out' of the phenol during drying. This vaccine was highly heat-resistant, with no loss of potency after two years at 45° C. Collier determined the minimum titre needed to achieve 100% successful vaccinations in children, and with this information and the data on thermal stability drew up a specification for the vaccine that was later adopted by WHO. Finally, he brought the preparation of the dried vaccine to production scale. Of the vaccines from five countries compared for heat resistance in WHO trials, the Lister product performed best, and the method was adopted for preparing the vaccines used in the WHO world smallpox eradication campaign.

Serum Department

The antisera prepared at Elstree were made by immunizing horses, about 40 animals being stabled on the estate at any one time. Their differing responses to the various antigens sometimes made the production of high-titre antisera more of an art than a science; in particular, the yield of anti-diphtheria serum depended very much on finding a responsive animal.

Scorpion antiserum production dated back to 1909; again, it was not easy to prepare, but its considerable sales in the Middle and Far East made it highly profitable.

Related researches The researches on trypanosomiasis carried out by this department are described on pages 22 and 23 under 'Protozoology'.

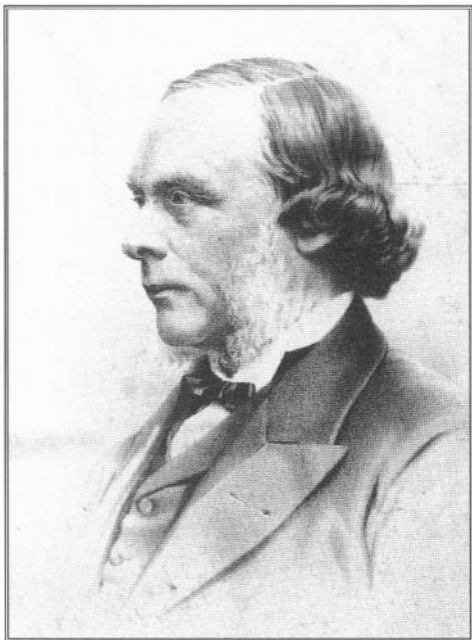


PLATE 1: Lord Lister
Courtesy Royal Veterinary College

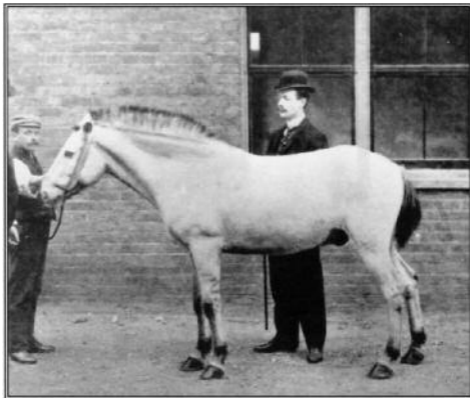


PLATE 2: Charles Sherrington with 'Tom', the pony immunized to make the first anti-diphtheria antitoxin used in the UK



PLATE 3: Edward Cecil Guinness, 1st Earl of Iveagh
From a portrait by Sir William Orpen



PLATE 4: The Chelsea Laboratories

Photograph by David Cockcroft



PLATE 5: Aerial view of the Elstree Laboratories



PLATE 6: The scientific staff of the Lister Institute, 1907

left to right:

Top: G. Cooper, E.L. Kennaway, J. Henderson-Smith, G.F. Petrie, H.W. Armit, J.C.G. Ledingham, S.Rowland, H.M.Woodcock, D.J.Reid

Centre: A.White Robertson, F.A.Bainbridge, J.A.Arkwright, G.Dean, C.J.Martin, A.Harden, E.A.Minchin, J.B.Leathes, H.de R.Morgan, W.J.Young

Front: Janet E. Lane-Claypon, S. Walpole, P. Hartley, Harriette Chick, W.E. Marshall

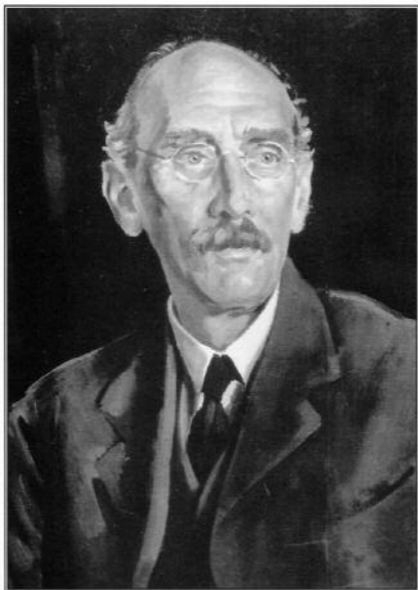


PLATE 7: Sir Charles Martin, Director, 1903-1930

From a painting by A.J. Murch, Adelaide, 1933

Wellcome Institute Library, London

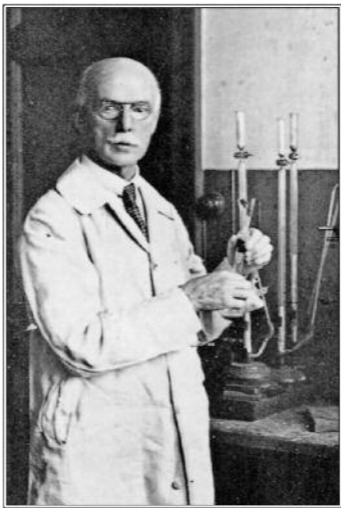


PLATE 8: Sir Arthur Harden, Nobel Laureate 1929,
in his laboratory



PLATE 9: Sir John Ledingham, Director, 1931-1942
From the portrait by Alexander Christie



PLATE 10: Sir Alan Drury, Director, 1943-1952



PLATE 11: Sir Ashley Miles, Director, 1952-1971



left to right from top row:

A.E. Pierce, P. Hartley,
 A.F.B. Standfast, D. McClean,
 E. Margaret Hume, R.A. Gibbons,
 Marjorie G. Macfarlane, Gillian
 Harris, Dorothy M. Parkin,
 A.P. Mathias, Margaret Nance,
 E.M. Thain, Ruth Sanger, Jean
 Walby, Elizabeth W. Ikin, Margaret
 E. Rowatt, Kathleen Cook, Jean
 Addy, Y.E.S. Gabr, B. Cinader,
 Winifred M. Watkins, Mary F.
 Kelleher, Margaret Blewett, Joan
 Thompson, E.A. Caspary,
 J.D. Feinberg, Jean M. Horton,
 L.H. Collier, A.P. MacLennan,
 Liza L. Lorenz, A.E. Mourant,
 L. Valliet, C.J.M. Rondle,
 M.J. Crumpton, K. Knox, J.O'Dea,
 J.G. Buchanan, F.K. Fox, Margaret
 E. Mackay, D.E. Dolby,
 W. d'A. Maycock, W.T.J. Morgan
 A.N. Drury, Muriel Robertson,
 R.A. Kekwick, J. Baddley, Emmy
 Nobel, S.A. White, B.G.F. Weitz

PLATE 12: The scientific staff of the Lister Institute, 1950



PLATE 13: *Left to right: Douglas McClean, Charles Martin and Walter Morgan in the mid-1930s*
From The Biochemist 15:5, 1933 (with permission)



PLATE 14: Muriel Robertson examining leeches, Elstree, 1910
Wellcome Institute Library, London

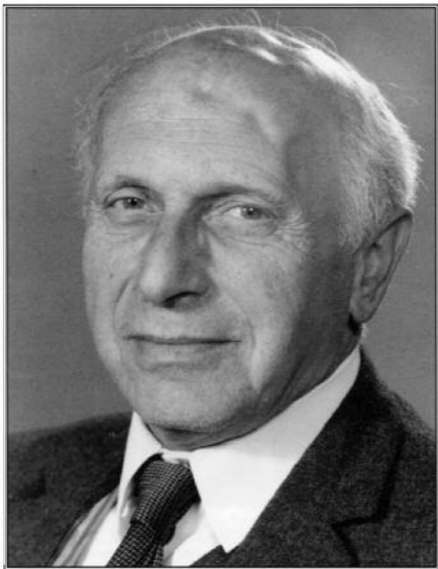


PLATE 15: Professor Albert Neuberger,
Chairman of the Governing Body, 1970-1988
Courtesy of Mrs Lilian Neuberger

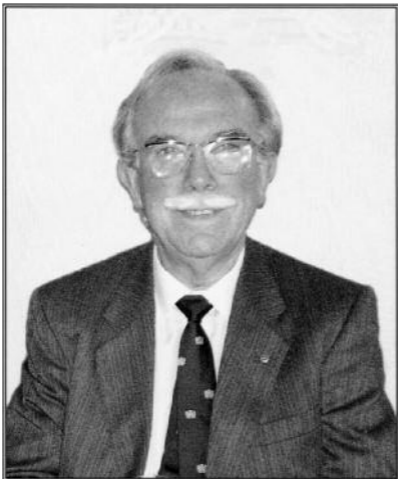


PLATE 16: Gordon Roderick
Secretary, Elstree Laboratories, 1958-1976
Secretary of the Institute and Clerk
to the Governing Body 1976-1995

Photograph by Mrs Freda Richards

‘Topley and Wilson’

This is a convenient point at which to take note of the Lister’s contribution to Topley and Wilson’s *Principles of Bacteriology and Immunity*, the indispensable ‘bible’ for generations of microbiologists in the UK and many other English-speaking countries. On becoming Secretary to the Agricultural Research Council, Topley could no longer participate and was replaced by A. A. Miles, then Professor of Bacteriology at University College Hospital Medical School and later Director of the Lister Institute. Wilson and Miles produced the next three editions of ‘Topley and Wilson’ on their own; that Ashley Miles was able to undertake this prodigious task alongside his many other responsibilities, including Directorship of the Lister and Biological Secretary of the Royal Society, almost beggars belief.

The association with the Lister was continued when L.H. Collier became co-editor of the eighth edition and then Editor-in-Chief of the ninth (1998), in five volumes covering the whole of microbiology, and with a large international panel of contributors. This edition, now entitled *Topley and Wilson’s Microbiology and Microbial Infections*, won the Society of Authors 1998 award in the Advanced Edited Book category.

LIFE AT THE LISTER: THE GOLDEN YEARS

The Institute’s 50th anniversary in the dark days of 1941 was marked only by an unwelcome gift – a bomb that landed behind the main building at Chelsea, narrowly missing the Svedberg ultracentrifuge, but destroying much material of historical interest. Nothing could have provided a greater contrast to the celebration of its Diamond Jubilee twenty-five years later, by which time the scene had changed beyond recognition. In 1966, the 75th anniversary of its foundation in 1891,

the Lister was at the peak of its activities; its scientific staff numbered 56, and included five Professors, one Reader and seven Recognized Teachers of London University. Though comparatively small, it was by now a centre of excellence in many areas of research and production; its international standing was appropriately recognized on the 9th November by an Open Day, an Anniversary Lecture by Lord Florey and an Anniversary Dinner attended by some 200 distinguished guests, including the Minister of Health as Guest of Honour. There was also a reception for over 270 past and present staff. It is pleasant to record that our French sister Institute contributed a handsome gift of wine from Pasteur's own vineyard.

By the time of its centenary, in 1991, the Institute was to look very different.

'Aren't we lucky!'

The high regard in which the Institute was held by the scientific community at large stemmed in no small measure from the respect, indeed affection, afforded it by its own staff. A bald account of its scientific doings cannot possibly give a flavour of what the Lister was like as a place in which to do research, or to convey an idea of the unique atmosphere created by successive Directors and their staffs, among whom were a number of colourful 'characters'. Not least among these were the Chief Technicians of the production departments, all of whom worked at the Institute for many years; few of them had had any formal training, but all knew their jobs inside out; and the first-rate safety record of Lister products owed much to their care and special skills.

As with other major laboratories, another important aspect of the Institute's activities was the hospitality extended to outside workers, many from overseas, and many internationally famous, who spent periods of days or months collaborating in

research projects or being trained in various techniques; the Lister always made both the results of its researches and its production methods freely available. The story of the thermostable smallpox vaccine provides a good example of the results of such a policy. As soon as the production technique had been perfected it was widely disseminated, not merely by publication, but by two-way training visits between Lister staff and those from overseas laboratories, often supported by WHO; patenting the process – or indeed any other method developed at the Lister – was never even considered. In a perfect world, this policy would have been admirable; but with hindsight, the potentially large revenues from patents might have contributed significantly to solving the financial problems that were ultimately to result in closure of the Institute's laboratories.

Avoidance of the stigma of commercialism went even further. The route to the Elstree laboratories lay down a small road, Dagger Lane, leading off the A41. For many years, the Governing Body refused to sanction the placing of a sign on the main road in case it could be construed as an advertisement, the result being a stream of telephone calls from visitors and delivery firms who had lost their way in the wilds of Hertfordshire.

It is probably true to say that the Lister was more free of internal politics than many similar establishments, and the generally excellent relationships between the various departments and their staffs were not the least of the factors responsible for its achievements; it may well be that the relatively small size of the various units and the absence of bureaucracy contributed to this happy situation. Furthermore, the scientific staff appreciated the privilege of working in an intellectual environment that could be relaxed without being lax. Writing in 1993, Sir James Baddiley commented that 'I shall remember with affection and gratitude the years spent at the Lister... to work at the Institute was an education'. Or as a remark overheard in the Chelsea canteen put it: 'Aren't we lucky to be working here!'

Thus ends the outline of the Lister's scientific achievements in its own laboratories. We have now arrived at the main watershed in the Institute's history, the point at which it underwent what might be termed a near-death experience followed by reanimation and metamorphosis.

The dark days

The funding of the Institute had proved reasonably adequate for many years; but in 1968 a new Medicines Act came into force, with far-reaching financial implications, primarily for the production departments but ultimately for the Institute as a whole. In brief, the Elstree Laboratories, although having an excellent safety record, were undeniably old-fashioned, and to comply with the provisions of the Act would need an injection of capital much larger than could be met from the Institute's liquid assets.

A second adverse factor was the general economic downturn of the 1970s, triggered by massive increases in oil prices with consequent inflation and high interest rates.

In addition to these concerns, there were changes in the Directorship around this time, which, although not affecting the outcome of the Institute's problems, were inevitably somewhat unsettling. In 1971, Sir Ashley Miles, Director for nearly 20 years, resigned, to be replaced by Professor (later Sir) David Evans, a member of the Governing Body since 1965. In the following year, however, Evans accepted the post of Director of the MRC Division of Biological Standards and Control, and was in turn replaced by Walter Morgan.

Apart from a brief note in the Annual Report for 1954 to the effect that expenditure was tending to exceed income, the

first public intimation that all was not well came in the Report of the Governing Body for 1972, when the Chairman, Professor Albert Neuberger (*Plate 15*), reported that the Governing Body had for some time been concerned about the serious financial position of the Institute: the previous five years had seen annual deficits of some £150,000, with consequent serious inroads on capital reserves, a situation that could not be allowed to continue. He announced that a special meeting of the Council had considered the available options and that the Governing Body would put forward proposals in the near future.

Events now moved swiftly. The first casualty was the Experimental Pathology Department at Chelsea, formerly directed by Ashley Miles, which was obliged to close in 1973, creating several redundancies. At Elstree, where production had for some time been steadily increasing, efforts to maximize income were redoubled; by this time, manufacture of almost every product surpassed all previous records, totalling 15 million doses of bacterial vaccines, and an issue of 7 million doses of smallpox vaccine. As a result of reorganization and heroic endeavours by the production staff, these figures doubled in the following year; but in the event it became apparent that even these efforts could not generate enough income to ensure the survival of both establishments. It was sad but understandable that around this time the normally good relations between the various departments were marred by resentment of some of the Elstree production staff at being asked, as they saw it, to work themselves into the ground in order to support a bunch of academics at Chelsea; and conversely, there were some at Chelsea who took the view that the main function of Elstree was to generate funds to support their research.

Because of the depressed state of the national economy it had proved impossible to attract public or private funds, and in 1975 it was announced that Chelsea would have to close

completely at the end of the year. An important factor in this decision was the danger to pensions and redundancy payments should the drain on resources continue.

ELSTREE GOES IT ALONE: A GALLANT TRY

All hopes were now pinned on the commercial side of the Institute. It was however generally appreciated that the Lister could not survive merely as a production facility. In the words of the Chairman, 'Without research there cannot be any long-term future for Elstree'. But for the time being, such thoughts took second place to increasing the output of vaccines and anti-sera.

We must now take a closer look at the organization of Elstree and its senior management.

There were two main establishments on the estate: the Vaccines and Sera Laboratories (VSL) and the Blood Products Laboratory (BPL), for both of which W. d'A Maycock was responsible as Superintendent from 1954 to 1973. The BPL was funded entirely from Government sources and was not directly affected by changes in the situation of the VSL. In 1974, L. H. Collier, Deputy Director of the Institute since 1968, was appointed to head the VSL on the resignation of W. E. Parish, Maycock continuing as Director of the BPL.

From 1974, the VSL was managed by a small Committee consisting of the Director (Leslie Collier); the Secretary (Gordon Roderick) (*Plate 16*); and the current Production Manager. Gordon Roderick played such a key role in the affairs of Elstree – and indeed, of the whole Institute – that he deserves special mention at this point.

Roderick was appointed to Elstree as Secretary and Estate Manager in 1958. He was directly accountable to the Director of the Institute for the general administration of the estate,

which included the BPL – together with the Plasma Fractionation Laboratory at Oxford – and a number of houses occupied by members of staff. He was also responsible for the sales and marketing of vaccines and sera. It is difficult today to imagine one person taking on such a wide spread of responsibilities with a minimum of assistance; indeed, it is doubtful if anyone could have filled this post without his talent for administration backed by a phenomenal memory.

In the early 1960s, Roderick was asked by the then Director, Ashley Miles, to make visits to various Middle East countries with the object of boosting sales. He was very successful in securing new contracts; and with the later help of a London-based agency, export sales increased considerably. Home sales of ‘triple vaccine’ – diphtheria, tetanus and pertussis – were also very healthy. The annual income eventually reached nearly £1m; but this was not enough even to support Elstree alone, particularly in view of the demands of the Medicines Act 1968, which were now beginning to bite in earnest.

Everyone concerned was acutely conscious that both the actual manufacturing facilities and the infrastructure of the estate – roads, buildings and utilities – needed major capital investment. But this was not all. With the exception of the dried smallpox vaccine, the Institute had not put out a new preparation for many years. Some of its existing products would have to be phased out sooner or later, and the development of even one replacement would cost £2m at a conservative estimate. Realistically then, at least £4m would be needed just to survive and remain competitive, and much more again to mount any significant research effort.

With the appointment in 1975 of a new and energetic Production Manager, Mike Campbell, considerable improvements to both the production and quality assurance laboratories were effected; but it was now a case of ‘too little, too late’. In the following year, the Institute applied to the

Department of Health and Social Security (DHSS) for grants-in-aid totalling some £500,000, most of which was needed to upgrade the laboratories. Shortly afterwards, however, DHSS officials reported unfavourably on the facilities, and the application was declined.

This was the death knell for the Lister's Elstree laboratories. In 1978, the Governing Body, supported by the Council and Members, unanimously decided that the Vaccines and Sera Laboratories had to close. The BPL would however, continue as before, but within the National Health Service, run at first by the North-West Thames Regional Health Authority, and eventually by the Central Blood Laboratories Authority.

The melancholy task of dismantling the Lister involved a great deal of time and effort on the part of Walter Morgan, the then Director, and particularly of Gordon Roderick, both of whom were closely involved in all the arrangements, both financial and physical, that now had to be made. The first priority after the closures of both Chelsea and Elstree was to minimise as far as possible the inevitable hardship caused to staff. The Treasurer, Robert McNeile, as Joint Chairman and former Managing Director of Arthur Guinness, was very familiar with staff management and welfare; he arranged a generous redundancy scheme and ensured that the interests of members of the Institute's pension scheme were fully protected. With few exceptions, all the scientific staff soon found satisfactory posts, and the Governing Body provided several of the senior people with one-off grants to help in continuing their researches until they were fully established in their new institutions.

THE SALVAGE OPERATION

As a result of astute management by successive Treasurers, the Institute had a healthy portfolio of investments. Its main fixed assets were the Elstree estate, the valuable stocks of vaccines

and sera, and the buildings at Chelsea. It was vital to dispose of these, especially the latter, on the best possible terms, not only to ensure survival of the Lister in some, as yet undefined, reincarnation but also to meet its redundancy and pension commitments. In the event, the Elstree estate was bought by the DHSS and most of the stocks of biomedical products were sold to other manufacturers. Chelsea was a major problem, since any sale depended on obtaining a change of use certificate, and the estate agents first employed placed an unacceptably low value of £500,000 on the property. However, after a number of abortive negotiations, conducted mainly by the Chairman, Albert Neuberger, and by Gordon Roderick, Chelsea was sold in 1980 for the very satisfying sum of £2.7m. The purchaser, a property company, converted the buildings to a private hospital, which still bears the name of Lister. With the successful sale of the Institute's fixed assets, and now with a useful amount of money at their disposal, the Governing Body could start detailed planning for the future.

A new beginning: The Lister Institute Research Fellowships

Throughout the stormy period described above, the paramount need for continuing to contribute in some way to biomedical research was a constant theme in the Chairman's annual reports. During 1978-79, the Governing Body, in particular the Chairman and the Secretary, Gordon Roderick, gave much thought as to how to achieve this aim. It became apparent early on that the most favoured option would be to transform the Institute into a grant-giving trust; but until the sale of its assets had been completed it would not be possible to say on what scale such a body could operate. In the first place, and in addition to those made to former members of staff, grants of about £200,000 were made to two workers at the Institute of Neurology for research on motor neurone disease. Their applications were originally submitted to the Wolfson Foundation, but, being judged of sufficient merit, were taken over by the Lister in recognition of the funding of the Wolfson Wing. These grants did not however form part of the Fellowship scheme that was later to materialise.

The period between the closure of the laboratories and

disposal of the Institute's material assets was put to good use in crystallising thoughts about the form and function of the new organization. It is a tribute to the perspicacity of Albert Neuberger and his colleagues that the remarkably successful scheme described in the next section so closely followed the ideas they formulated at that time.

With the successful sale of Chelsea in 1980, the Chairman was able in the following year to make the momentous announcement that a Scientific Advisory Committee, separate from the Governing Body, was being formed to consider applications for support for research in various branches of biomedical science. The Governing Body would elect one of their number to chair the Scientific Advisory Committee, allocate funds for it and approve its general grant-giving policy. The Committee would consist of six eminent scientists, with power to seek specialist advice from outside when needed; each would serve for a period of six years on a rotating basis. At the same time, other administrative changes in the organization of the Institute were effected. In particular, Council was abolished, its members becoming Members of the Institute; and the Memorandum and Articles of Association were revised to take account of the altered structure.

The new Committee was launched with the appointment of Geoffrey S. Dawes CBE, FRS, Director of the Nuffield Institute for Medical Research, as its first Chairman; and by 1982 it had its full complement of six other scientists, all distinguished in various branches of medical science (see Supplement).

THE FELLOWSHIP SCHEME

At the outset, the Governing Body had identified a need for support of post-doctoral scientists with a good record of research in some aspect of biomedical science. Such a person

would typically have completed one or more grant-aided projects, and would now be poised to consolidate and expand a line of work that showed promise of being highly productive. Although there have been a few alterations in the conditions attaching to these Fellowships since their inception, the scheme is substantially unchanged. The terms on which they are awarded are listed in the Supplement; the main provisions are as follows.

- The Fellowships are competitive and are awarded annually by the Institute on the recommendation of the Scientific Advisory Committee. The candidate placed first in order of merit is nominated the Lister Institute-Jenner Research Fellow.
- Candidates must have at least two years' postdoctoral research experience in a biomedical or clinical field.
- Fellowships are normally for five years, during which time the Fellow remains an employee of his or her institution. A permanent post temporarily vacated to take up a Fellowship must be protected by the employing institution.

A flying start

The first advertisements for the Fellowships appeared in 1982 and attracted 44 applications; their generally high standard was an encouraging foretaste of things to come. The first five projects to be approved were characteristic of those that followed, first in their strong emphasis on molecular biology, which, together with studies at the cellular level, was also to be a dominant theme in succeeding years; and second, in the academic distinctions subsequently attained by these new Fellows. Three of the five gained professorial chairs, and one, Alec (later Sir Alec) Jeffreys, was to make a major contribution not only to the discipline of genetics, but also to the reputation and finances of the Institute. The continuance of these successes, from the inception of the

scheme until the present, is a tribute to the expertise of the Scientific Advisory Committee in hand-picking the winners from among so many worthy runners. The lists of present and former Fellows (see Supplement) specify their projects.

Some facts and figures

- There has been an average of 55 applicants each year, of whom 12 are short-listed and interviewed by the Scientific Advisory Committee and five finally selected for Fellowships. In 1999 there were 80 applications, the highest number since the inception of the scheme.
- From 1982 to 1999 inclusive, 85 Fellowships have been awarded.
- As at May 2000, more than 60% of former Fellows held Chairs; and many have gained other prestigious awards and distinctions.
- At the end of 1998 the gross income for the year was £1.43m and there was a balance of nearly £34m in the capital and funds accounts. The direct charitable expenditure on grants was £1.28m. In a Wellcome survey of national biomedical research institutions (*Mapping the Landscape*, 1998) the Lister Institute ranked 12th in terms of acknowledgements in peer-reviewed journals.

The Gordon Roderick Travel Scholarship

In their Report for 1996, the Governors announced the inauguration of a travelling scholarship, to the value of £1000, in recognition of Gordon Roderick's contribution to the Research Fellowship scheme. The recipient is the Lister Institute-Jenner Research Fellow appointed each year, and this money can be used at any time during the five years of tenure for attending one or more conferences relevant to the Fellow's research.

The Fellowship Weekends

Early in the Fellowship scheme Gordon Roderick had suggested that Fellows should meet the Governing Body and Members at a reception held after the Annual General Meeting. Impressed with the success of these informal get-togethers, he then proposed a weekend at an Oxford or Cambridge college, so that Members, Fellows, former Fellows, Governors, members of the Scientific Advisory Committee and former scientific staff could meet in pleasant and convivial surroundings, present and discuss projects, and relax over an excellent and delightfully speech-free dinner. The first of such meetings was held in September 1985 at St John's College, Cambridge and was so successful that they have become eagerly anticipated annual events. The venue has varied, but the format has remained largely unaltered: presentation of projects on a Friday afternoon, reception and dinner in the evening, and more papers next morning, followed by lunch.

Such occasions must surely be unique in the hard-nosed world of grant-giving trusts!

One hundred, not out

During the depressing period following the closure of the laboratories, few would have bet on the Lister attaining its centenary, let alone celebrating it in a style comparable with the sparkle and zest of its Diamond Jubilee. But by 1991, the turn-around in its fortunes enabled it to do just that.

On 25th July of that year, the anniversary of the Institute's incorporation, *The Times* published a four-page supplement describing some of the highlights of the Institute's scientific achievements, the Fellowship scheme and the grant of the Queen's Award for Technological Achievement in 1990. The occasion was further celebrated by a Dinner at the Royal

College of Surgeons attended by, *inter alia*, Members of the Institute, Fellows, former Fellows, scientific colleagues from other establishments and spouses; the Guests of Honour were Baroness Hooper (Ministry of Health) and Alderman Sir Hugh Bidwell, a previous Lord Mayor and deputy for the current one. A particularly welcome guest was Professor Maxime Schwartz, Director of the Pasteur Institute, who gave an interesting talk on the collaboration and warm relationship that developed between Louis Pasteur and Joseph Lister. In view of his family's crucial role in the founding and subsequent support of the Institute, it was most appropriate that the toast to the Guests should have been proposed by Edward Guinness, a member of the Governing Body since 1969 and widely liked and respected for his personal interest in the Lister and the welfare of its staff.

The White House

The loss of Chelsea in 1975 immediately raised the question of a centre from which administration of the remaining activities of the Institute could continue. The Chairman, Albert Neuberger, found temporary accommodation in the Charing Cross Hospital. Gordon Roderick continued for some years in premises leased from the Central Blood Laboratories Authority at Elstree, and thence temporarily to a Portakabin in the grounds of the Royal National Orthopaedic Hospital at Stanmore. Eventually, however, suitable office accommodation was found in Bushey Heath. Gordon Roderick negotiated its purchase in 1995 but never occupied it, retiring in that year to be replaced as Secretary by Keith Cowey. 'The White House' is now the centre from which the Lister Institute and its Fellowships are so efficiently administered.

* * *

DNA FINGERPRINTING: A SPECTACULAR SUCCESS STORY

The DNA fingerprints produced by minisatellite probes 33.6 and 33.15 are therefore sufficiently stable and individual-specific for use in human identification in, for example, forensic medicine ... They also provide a reliable method for paternity testing:
(Jeffreys AJ, Wilson V and Thein SL, *Nature*, 316 : 76-79, 1985)

This short paper did much more than herald a new technique in forensic medicine: it was to bring to Jeffreys greater honours and distinctions than could ever before have been awarded to a scientist of his age; and to the Institute not only a Royal award but also considerable financial benefit.

In 1984, Alec Jeffreys was Reader in the Department of Genetics at the University of Leicester. One of the first five Lister Fellows to be appointed, his project was listed as *Molecular analysis of the structure, function and evolution of developmentally regulated animal genes*. This somewhat non-committal title gave little clue to the work at the heart of the project, which accidentally resulted in what is now generally known as 'DNA fingerprinting' (or 'profiling'). The technique has been described often and there is no point in giving a detailed account here. In brief, Jeffreys created two DNA probes that hybridize to certain multiple hypervariable fragments in enzymic digests of human DNA. Each probe produces a very different pattern of hybridization in the same subject, so that the use of both in parallel identifies a far greater range of differences between individuals than would one alone.

Although development of the Jeffreys technique demanded a high degree of technical expertise, its beauty is that it can be used to test very small samples by any suitably equipped laboratory. Crucially, its ability to discriminate between unrelated individuals is so high that its findings are as acceptable as actual fingerprints in courts of law; and it added a new dimension to the identification of tissue samples, blood and other body fluids

in, for example, criminal and paternity cases.

This novel test was eminently patentable. Long gone were the days when the Lister shied away from any hint of commercial exploitation! Until the necessary patent was secured, nothing could be published, a frustrating situation familiar nowadays to many scientists. Soon, however, the key paper (*op. cit.*) appeared, marking the moment at which DNA fingerprinting and all that followed from its invention really took off.

Patent applications for other countries soon followed. The first approaches from commercial firms came from the United States, but from the outset, the Governing Body took the view that the technique should be exploited in the UK. Several British firms showed no interest, but then Gordon Roderick learned that ICI were about to open a new diagnostics unit, and would be interested in developing the technique commercially. It was eventually settled that this would be done both at the ICI Cellmark laboratories at Abingdon and at another ICI unit in Maryland, USA, each established specifically for DNA fingerprinting, with an agreed sharing of royalties between Alec Jeffreys himself, the Lister Institute and the University of Leicester.

Meanwhile, the Prime Minister had learned of these events and Gordon Roderick was asked to prepare a report on the exploitation by industry of research findings emanating from British academic institutions. As might be imagined, Margaret Thatcher was adamant that intellectual property of this sort should not be lost to other countries, and as a result, all universities were instructed to appoint industrial development officers.

In 1990, the Lister was honoured by being awarded, jointly with ICI, the Queen's Award for Technological Achievement, the Institute being represented at the ceremony by Alec Jeffreys, Gordon Roderick and David Hobson, the then Treasurer.

The rewards gained by Alec Jeffreys himself were immense.

He was elected a Fellow of the Royal Society in 1986 at the remarkably young age of 36; and in the year following, in addition to a Personal Chair, was awarded the Society's Davy Medal and the Bicentenary Medal of the Linnaean Society. In 1991 he was appointed the Royal Society's Wolfson Research Professor, and was knighted in 1994. He was also made an Honorary Fellow of the Royal College of Physicians, an Honorary Member of the Institute of Biology and a Freeman of the City of Leicester.

Jeffreys resigned his Fellowship in 1991 and was elected a member of the Institute's Scientific Advisory Committee in the same year. He became a Governor four years later.

(NOT) IN CONCLUSION

The end of this Concise History is, happily, not the conclusion of the Lister story. During its physical existence, which lasted for the best part of a century, the Institute served the nation well in its many important contributions to biomedical science, in training junior scientists, in service to outside institutions, boards and committees, and in the supply of vaccines, antisera and blood products. With the closure of its laboratories in 1978, it underwent a profound and probably unique change in direction, converting itself to a facilitator of biomedical research, mostly at a basic level, but always innovative and of high quality.

What were the keys to the survival of the Lister in its new incarnation? Perhaps first and foremost, the correct identification of an area in which research funds could be applied with a high probability of success; second, the awarding of Fellowships as much on the basis of the candidates' potential as on the merits of their projects; third, the lack of bureaucracy, stemming from a compact and economical organization and

freedom from dependence on outside funds; and fourth, the excellent relationship between the Fellows and those who administer their researches. To these may eventually be added the building of new and profitable relations with industry, on the lines so successfully pursued with the DNA fingerprinting project.

With such a propitious start, and with nearly two decades of successful researches already behind it, there is every prospect that, well into the new millennium, the reborn Lister Institute will continue the traditions of the past as a centre of scientific excellence.

ANNEX A

FORMER DIRECTORS OF THE LISTER INSTITUTE

- 1893 -1896 Dr M. Armand Ruffer (interim Director)
- 1896 -1903 Dr Allen MacFadyen (interim Director)
- 1903 -1930 Sir Charles Martin CMG, FRS
- 1930 -1943 Sir John Ledingham CMG, FRS
- 1943 -1952 Sir Alan Drury CBE, FRS
- 1952 -1971 Sir Ashley Miles CBE, FRS
- 1971-1972 Professor David Evans CBE, FRS
- 1972 -1975 Professor Walter Morgan CBE, FRS

ANNEX B

SUMMARY OF IMPORTANT EVENTS

- 25 July 1891 Institute incorporated as The British Institute of Preventive Medicine.
- 1893 Purchase of the Chelsea site.
Amalgamated with the College of State Medicine, 101 Great Russell Street, which became the temporary home of the Institute.
- 1893 -1896 Dr M. Armand Ruffer as Hon Secretary and interim Director.
- 1894 Establishment of the Serum Department at Sudbury, Middlesex.
Therapeutic diphtheria antitoxin produced (first in UK).
Early researches included:
- the testing of mallein and tuberculin in animals
 - work on the ringworm organism
 - the chemical analysis of various samples of ice cream
 - an enquiry for Derbyshire County Council into an alleged outbreak of hydrophobia
 - the preparation of antitoxins
 - the examination of water and water supplies.
- 1894 Evening classes in bacteriology started.
Courses continued in Chemistry and Physics for the Diploma in Public Health.
- 1896-1903 Dr Allen MacFadyen as Hon Secretary and interim Director.
- 1898 Donation of £250,000 from the first Earl of Iveagh
Name changed to The Jenner Institute of Preventive Medicine, on accepting donations raised during the Jenner centenary, 1896.

- 1898 *contd.* First stage of the Chelsea site completed.
Work of the Institute transferred from 101 Great Russell Street to Chelsea.
- 1902 Purchase of the Elstree estate.
- 1903 Name changed to The Lister Institute of Preventive Medicine.
Serum Department moved from Sudbury to Elstree.
Lord Lister, having retired from chairmanship, became President (holding office until his death in 1911).
- 1905 Institute admitted as a School of the University of London.
The rat flea proved by the India Plague Commission, under Sir Charles Martin, to be the carrier of bubonic plague.
- 1906 The Colonial Office endowed a Chair of Protozoology which continued until the First World War (1915).
- 1908 Investigations into the circumstances attending accidents in deep sea diving concluded, and the investigation for the Royal Commission on Mines also completed, and published.
- 1913 Proposal that the Lister Institute should form the core of a new National Institute of Medical Research.
- 1914 General Meeting of Members of the Institute rejected proposal to amalgamate with the Medical Research Council (MRC).
- 1914 -1918 Many of the staff joined the forces during the First World War; the remainder continued in work of national importance.
- 1919 Lord Iveagh resigned from the Governing Body, assigning his place and responsibilities to the Rt Hon Walter Guinness MP (later Lord Moyne).
- 1919 -1921 A team including Dr (later Dame) Harriette Chick from the Lister Institute collaborated with the MRC in work on rickets and scurvy among the peoples of central Europe and established that vitamin D deficiency was the cause of rickets.
- 7 Oct 1927 Death of Lord Iveagh.

- 1929 Professor (later Sir) Arthur Harden, Head of the Biochemistry Department, awarded the Nobel Prize in Chemistry for his researches on alcoholic fermentation.
- 1936 The first ultracentrifuge in the UK installed in the Biophysics department for work by Dr A. S. McFarlane on viruses and proteins.
- 1938 Dr (later Professor) Walter Morgan's fundamental studies on bacterial antigens demonstrated for the first time that a bacterial endotoxin was a conjugate of protein and lipopolysaccharide.
Dr Emmy Klieneberger-Nobel made the important discovery of filterable forms (L. forms) of bacteria of the pleuropneumonia group.
- 1939 -1945 World War II. Apart from those serving in the Forces, the staff were engaged in work of national importance.
- 1940 Work on the bacillus of gas gangrene by Drs Marjorie Macfarlane and B.C.J.G. Knight led to the first identification of a bacterial exotoxin as an enzyme.
- 1940 & 1941 Bombing of Chelsea site.
- 1940-1965 Pioneering work by Drs Walter Morgan and Winifred Watkins on the biochemistry of the antigens associated with the classical ABO blood group system culminated with the establishment of the chemical structures, and proposals for the genetic control of the biosynthesis, of these biologically important characters.
- 1944 The MRC established a unit for research into blood plasma that was eventually to develop into the Blood Products Laboratory, Elstree.
Death of Lord Moyne; 2nd Earl of Iveagh inherited his rights of nomination to the Governing Body.
- 1947 The ether precipitation method developed by Drs Ralph Kekwick and Margaret Mackay was found to be suitable for large scale production of human immunoglobulins for therapeutic use.
- 1947 - 1975 The MRC's Blood Group Unit, newly set up under the direction of Dr Rob Race, was accommodated at

- 1947 - 1975
contd. the Institute. This Unit remained until 1975 and Drs Race and Ruth Sanger were to receive much international acclaim for their pioneering work in the field of human blood group genetics.
- The Blood Group Reference Laboratory of the Ministry of Health, under the direction of Dr Arthur Mourant, was also housed at the Institute. This Unit supplied essential blood grouping sera to the National Transfusion Service and Dr Mourant's research activities made valuable contributions to human anthropology.
- 1949 - 1955 Dr (later Sir James) James Baddiley and his colleagues made a series of seminal contributions to the chemistry of nucleotides, including the first chemical synthesis of adenosine triphosphate (ATP) and studies on the structure of co-enzyme A.
- 1951 - 1954 Dr (later Professor) Leslie Collier, whilst at Elstree, produced a freeze-dried smallpox vaccine which gave 100% successful vaccinations after storage at 45°C for two years. It thus became possible for vaccines of this type to be stored and used in tropical countries, leading by October 1977 to the eradication of smallpox from the world.
- 1953 Department of Experimental Pathology re-established as Professor Miles' own department.
- Guinness-Lister Unit established through the generosity of Arthur Guinness Son and Company. This unit played a predominant role in the development of microbial genetics in the UK.
- 1963 A new professorial Chair – the Guinness Chair of Microbiology – established.
- 1964 A gift of an electron microscope received from the Trustees of the Fleming Memorial Fund for Medical Research.
- 1964-1975 Several unsuccessful efforts made to obtain financial support from the government, the MRC and private foundations.
- 1968 - 1971 New buildings constructed on Chelsea site. Substantial grant towards their cost received from the Wolfson Foundation; the lecture theatre a gift from the Grocers' Company.

- Dec 1975 Closure of the Chelsea Laboratories.
- June 1978 Closure of Vaccines and Sera Laboratories, Elstree.
- 1979 Sale of the Elstree site.
 Administrative responsibility for the Blood Products Laboratories transferred to the Department of Health (via NW Thames Regional Health Authority).
 Sale of the Chelsea site.
 Three-year research grants awarded to several senior former members of staff.
- 1980 In consultation with the Wolfson Foundation, substantial Lister-Wolfson grants given by the Institute to two applicants to the Foundation for research into motor neurone disease.
- 1981-1982 Institute transformed from an organisation supporting research in its own laboratories to a grant-giving body supporting post-doctoral research in biomedicine.
 Memorandum and Articles of Association amended.
 Council disbanded, all members continuing to serve as Members of the Institute, including the representatives of Universities, Royal Colleges, BMA etc.
 Scientific Advisory Committee set up under the chairmanship of Professor Geoffrey Dawes.
- October 1982 First five Lister Institute Post-Doctoral Research Fellows appointed:
 Dr Judith P Armitage, University College London
 Dr G Marius Clore, NIMR, Mill Hill
 Dr Alec J Jeffreys, University of Leicester
 Dr Sai-Kit Alex Law, University of Oxford
 Dr Stephen J Perkins, Kennedy Institute of Rheumatology, London.
- 1984 Dr (later Professor Sir) Alec Jeffreys, one of the Institute's Research Fellows and, at the time, Reader in Genetics at the University of Leicester, discovered that no two people (apart from identical twins) have the same DNA 'fingerprint'. This invention is used to test

- 1984
contd paternity and to detect criminals from blood, hair, semen and other samples left at the scene of a crime.
Patents, world-wide, taken out by the Institute.
- 1985 Annual Fellowship Weekend Meetings started, the first at St John's College, Cambridge, attended by all fifteen Fellows, together with Governors, Members of the Scientific Advisory Committee and Institute Members.
- 1986 Entered into Agreement with ICI for the exploitation of DNA 'fingerprinting' in return for royalties. Royalties received by the Institute to be shared with Dr Jeffreys and Leicester University.
Dr Alec Jeffreys became the first Institute Fellow to be elected a Fellow of the Royal Society.
- 1987 ICI Cellmark Diagnostics set up at Abingdon to exploit the DNA 'fingerprinting' invention.
On the tenth anniversary of the eradication of smallpox from the world, dedication of a plaque at the London School of Hygiene & Tropical Medicine to commemorate the Institute's contribution.
- 1988 Sir James Gowans elected Chairman of the Scientific Advisory Committee in place of Professor Geoffrey Dawes.
- 1989 Dr Ann L McLaren elected Chair of the Scientific Advisory Committee in place of Sir James Gowans.
- 1990 Institute granted The Queen's Award for Technological Achievement 1990. Presentation at the Royal Society of Medicine by the Lord Lieutenant of Greater London, Field Marshal the Lord Bramall.
Professor Christopher Higgins the first former Fellow to be elected a Fellow of the Royal Society of Edinburgh.
- 20 Feb 1991 Presentation to the Queen at Buckingham Palace of Professor Alec Jeffreys, Mr Gordon Roderick and Mr David Hobson representing the Institute as winners of the Queen's Award for Technological Achievement, 1990.

- 25 July 1991 Centenary Dinner held at The Royal College of Surgeons, Lincoln's Inn Fields, London.
- 1991 Tenth award of a Chair to a former Fellow.
- 1993 Fiftieth Lister Institute Research Fellowship awarded.
- 1994 Professor Alec Jeffreys receives a knighthood in the New Year's Honours List.
 Dr Anne McLaren elected Chair of the Governing Body.
 Sir James Gowans re-elected Chair of the Scientific Advisory Committee.
- 1995 Retirement of Mr Gordon Roderick, the Institute's Secretary, who had played a key role in the development of the Fellowship scheme.
 Registered Office moves to new accommodation at Bushey Heath.
- 1996 Professor Stephen Yeaman elected a Fellow of the Royal Society of Edinburgh.
 Twentieth award of a Chair to Fellows and former Fellows.
- 1997 Professor W. V. Shaw elected Chair of the Scientific Advisory Committee.
- 1998 Professor Steven Homans elected a Fellow of the Royal Society of Edinburgh.
- 1999 Dr Rosa Beddington the second former Fellow to be elected a Fellow of the Royal Society.
 Thirtieth award of a Chair to Fellows and former Fellows.
 Dr Wendy Bickmore awarded a James S. McConnell Foundation Centennial Fellowship worth \$1million.

INDEX

- Accessory Food Factors
Committee, 13, 14
Amies, C. R., 30
Anti-D immunoglobulin, 19
Antigens, 116, 19, 29
Antigen, 'Vi', 29
Antihaemophilic globulin, 19
Anti-scurvy factor, 12
Antisera, diagnostic, 13
Anti-tetanus serum, 9
Antitoxins, *see* diphtheria, gas
gangrene, tetanus
Arkwright, J., 13, 29, 30
- Bacot, A., 13, 26
Bacterial & bacteriophage
genetics, 30
Bacterial conjugation, 29
Bacterial metabolism, 10
Bacterial Vaccines Dept, 28, 31-33
related researches, 32
Bacterial variation and genetics,
28-30
Bacteriology & Virology, 25-30
Bacteriology, Department of,
10, 15, 31, 32
Baddiley, Sir James, 12, 37
Barnard, J. E., 9
Behring, E. von, 3
Bends, The, 11
Beri-beri, 12
Berridge, R., 3
Bidwell, E., 19
Biochemistry Dept., 16
Biomedical products and related
researches, 31-34
Biophysics & blood products, 18-19
Biophysics Department, 18
Blood
donor panel, 20
Blood, *contd.*
transfusion (MRC c'ttee), 14
transfusion service, 18
Blood group
antigens, 16-17
Reference Laboratory, 17
Research Unit, 17
Blood Products Laboratory, 18-19,
31, 41-43
British Institute of Preventive
Medicine, The, (viii), 2, 3, 5
Bruce, Sir David, 23
Buchner, E., 11
Bulloch, W., 4
- Campbell, M., 42
Centenary Dinner, 49
Central Blood Laboratories
Authority, 43, 50
Central Public Health
Laboratory, 15, 31, 32
Chelsea laboratories, (viii), 3, 4,
7-9, 11, 14-18, 20, 28, 31, 35,
37, 40, 43-44, 46
Chick, Dame Harriette, (xi), (xiii),
5, 12-14, 25
Chlamydia, 27-28
Cholera, 13, 31
Clarke, C., 19
Clostridia, 26-27
Cohn, E. J., 18
Combridge, B. S. 19
College of State Medicine, 2, 3
Collier, L. H., (vii), (viii), 27, 28,
32, 34, 35, 41
Cowan, S. T., 15
Cowey, F. K., (xi), 50
Creeth, J. M., 19
- Dakin, H. D., 13
Dalyell, E., 14
Dawes, G. S., 46
Dean, G., 4

- DHSS, 43, 44
 Diphtheria (vii), 1, 4, 42
 antiserum, 9, 31, 34
 antitoxin, 9, 32
 Disinfection, 25
 Diving, physiology of, 10
 DNA fingerprinting, 51-52, 54
 Dolby, D., (xi)
 Dolby, J., 28, 32
 Drury, Sir Alan, (xii), 14, 18, 55
 Duran-Reynals, 22
- Elstree, (viii), 8-9, 14-16, 18, 20,
 22, 26, 31-34, 37, 40-41, 43-44
 Emergency Blood Transfusion
 Service, 16, 20
 Enzymes and co-enzymes, 11
 Eosinophils, 22
 Euler, H. von, 11
 Evans, Sir David, 39, 55
 Experimental Pathology Dept., 21
- Factor VIII concentrate, 19
 Felix, A., 29
 Fell, H., 11
 Fleming Memorial Fund, 6
 Foot & mouth disease, 30
 Funk, C., 12
- Gas gangrene, 13, 26-27, 31
 Godfrey, D.G., 24
 Goldsmith, K.L.G., 17
 Gordon Roderick Travel
 Scholarship, The, 48
 Great Russell Street, 8, 25
 Grocers, Worshipful Company of,
 3, 6
 Guinness, Arthur, Son & Co Ltd,
 6, 29, 43
 Guinness-Lister Chair of
 Microbiology, 6, 29
 Guinness, C.E., (xi), (xii), 50
 Guinness-Lister Unit, 6, 29
- Haffkine, W. M., 26
 Haldane, J.S., 11
 Harden, A., 4, 10-12
 Hepatitis B, screening for, 19
 Hobson, D., 52
 Horsley, V., 2
 Humc, M., (xi), (xiii), 14
 Hyaluronidase, 22
- ICI, 52
 Immunological specificity,
 chemical basis of, 20
 Inflammation, mechanisms of, 21
 Iveagh, Lord, 4-6, 15
- Jeffreys, Sir Alec, (viii), (xi), 47,
 51-53
 Jenner, E., 1, 5
 Jenner Institute of Preventive
 Medicine, The, 5
 Jenner Memorial Studentship, 5, 25
- Kaplan, C.A., 33
 Kerr, W.R., 24
 Kekwick, R.A., 18-19
 King, E.J., 11
 Klieneberger-Nobel, E., 27
 Knight, B.C.J.G., 27, 32
- Lanham, S., 24
 Lawn, A.M., 30
 Lederburg, J., 29
 Ledingham, Sir John, 13-14, 30,
 55
 Leicester, University of, 52
 Lemcke, R., 27
 Lister Institute, 20-21, 24-28,
 33-37, 39, 41-54
 Fellowship scheme, (vii), (viii),
 (ix), (xiv), 45-50, 53-54
 Fellowships awarded, 48
 Fellowship Weekend, 49
 funding and organization,
 an account of early, 4-6;

- Lister Institute, *contd.*
 Governing Body, 4, 7, 10, 15,
 37, 39-40, 43-46, 49-50, 52;
 Scientific Advisory Committee,
 (ix), (xiv), 7, 46-49, 53
- Lister, Lord, 1-2, 5, 50
- Lister Institute-Jenner Research
 Fellow, 48
- McClellan, D., 22
- Macfadyen, A., 8-10, 55
- McFarlane, A.S., 18
- Macfarlane, M., (xi), (xiii), 27
- Mackay, M., 18
- McLaren, Anne L., DBE, (ix), (xi)
- McNeile, R., 43
- Martin, Sir Charles, 10, 13, 25-
 26, 55
- Maycock, W. d'A., 19, 41
- Medical Research Council, 5-6,
 14-15, 17-18, 27, 32
 Blood Transfusion Committee,
 14;
 Clinical Research Centre, 33;
 Microbial Genetics Research
 Unit, 30;
 Trachoma Research Unit, 28;
 Wound Infection Unit, 21
- Mellanby, E., 13
- Melville, S., 28
- Meyer, K., 22
- Meynell, G.G., 29-30
- Minchin, E.A., 22
- Miles, Sir Ashley, (ix), (xii), 15,
 21, 35, 39-40, 42, 55
- Morgan, W.T.J., (ix), 11, 16-17,
 20, 39, 43, 55
- Mourant, A.E., 17
- Mycoplasma, 27
- Oliver Memorial Fund, The, 20
- Oliver, P.L., 20
- Parish, W.E., 22, 41
- Pasteur, Institut, (vii), 1-2, 4, 6,
 36, 50
- Pasteur, I., 1-2, 50
- Pathology, Department of
 Experimental, 21
- Pertussis vaccine, 31, 32, 42
- Physiology & biochemistry,
 pioneer researches in, 10
- Physiology of diving, 10
- Pitt, M., 29
- Plague, 25-26
- Plasma Fractions Laboratory, 19
- Protozoology, 22
- Queen's Award, 50, 52
- Queensbury Lodge, 9, 23
- Rabies, 1-4, 30-31
- Rabies vaccine, 33
 related researches, 33
- Race, R.R., 17
- Reid, L., 19
- Ricketts, 13-14
- Rideal, S., 25
- Riggs, A., 9
- Robertson, M., 13, 23, 24, 26
- Robison, R., 11, 16
- Rockefeller Foundation, The, 18
- Roderick, G.J., (ix), (xii), 41-45,
 48, 50-52
- Rowlands, I.W., 22
- Rowland, S., 9, 26
- Royal National Orthopaedic
 Hospital, 50
- Royal Society, The, 4, 35
- Ruffer, M.A., 2-4, 8-9, 55
- Sanderson, Sir John Burdon, 2
- Sanger, R., 17
- Neuberger, A., (ix), 40, 44, 46, 50
- Nutritional deficiency diseases,
 13-14

- Schwartz, M., 50
 Scorpion antiserum, 31, 34
 Sera & vaccines produced at
 Elstree, table of, 31
 Serum Department, 23, 31, 34
 related researches, 34
 Sherrington, C.S., 4
 Smallpox vaccine, 1, 31, 33, 34
 Department, 16, 31, 33
 related researches, 34
 Sowa, J., 28
 Standfast, A.F.B., 28, 31
 Starch & glycogen,
 metabolism of, 21
 Sudbury farm, 9
- T'ang, F.-F., 28
 Tetanus, 1, 31, 32, 42
 antisera, 9; antitoxin, 13;
 toxoid, 32
 Thein, S.L., 51
 Tom, the immunized pony, 4
Topley & Wilson, 25, 35
 Trachoma, 28
 Trichomonas, 24
 'Triple vaccine', 32, 42
 Trypanosomiasis, 22-24, 34
 Tsetse fly, 23
 Turner, G.S., 33
 Type Cultures, National
 Collection of, 15, 31
 Typhoid & paratyphoid vaccines,
 31
 Typhoid bacillus, 9, 13
 Typhus, 29
- University College London, 5
- Vaccine lymph, 33
 Vaccines & Sera laboratories,
 Elstree, 7, 31, 41, 43
 Vaccines, thermostable, 33-34
 Vaccinia virus, 33-34
- Vallet, L., (xi), 19
 Virology, 30
 Department of, (vii), 27
 Virus vaccines, 31
 Vitamins, 12
- Walker, J.T.A., 25
War on Disease, (xi), (xiii)
 Watkins, W., (xi), 16-17, 24
 Weil-Felix test for typhus, 29
 Weitz, B.G.F., 23-24
 Wellcome Institute, The, (xii), 48
 Wellcome Trust, The, 6
 Westminster, Duke of, 3, 5
 Whelan, W.J., 21
 Whitehead, Sir James, 2
 White House, The, 50
 WHO world smallpox eradication
 campaign, 33-34, 37
 Wilhelm, D.L., 21
 Wolf, P., 19
 Wolfson Foundation, 6, 45
 Wolfson Wing, Chelsea, 45
 World War I, 12, 25-26, 29
 World War II, 12, 14, 16, 21, 27, 31
- Yersin, A., 26
 Young, W.J., 11
- Zilva, S.S., 12