

THE EVOLUTION UP TO THE FIRST
WORLD WAR OF SCIENTIFIC THERAPEUTICS
FROM MATERIA MEDICA

WILLIAM ALEXANDER SOUTER, M.B., Ch.B.
(Honours) (1957) F.R.C.S., (Edin.)



"Therapeutics will be a science only when it has established the relationship existing between the remedy used and the cure of the sickness".

Claude Bernard (1865)

"Introduction a l'Etude de la
Medecine Experimentale".

"We must learn to make magic bullets which, like those of the ancient fable, will not miss the mark and will destroy only those pathogenic agents they are aimed at".

Paul Ehrlich (1854-1915)

Introduction

Therapeutics must probably be regarded as the oldest branch of medicine. Certainly its origins appear to be dimly discernible in remote prehistoric time in the person of the witch doctor, who constitutes a phenomenon common to all primitive peoples. The earliest record of such "a medicine man" is probably a drawing on the wall of the Trois Frères Cave in the Pyrenees, attributed to the Aurignacian race living about 15,000 B.C. (Guthrie 1958). With the dawn of history in the valleys of the Euphrates and the Nile, we have evidence of considerable systematisation of medical knowledge and by 1500 B.C., approximately 900 prescriptions were to be found in the Ebers Papyrus. The great bulk of the therapeutic agents were, however, completely worthless and magic, sorcery and superstition played an enormous part in the art of the medicine man. Moreover, the absence of truly specific remedies for most diseases was to persist until comparatively recently. So accustomed are we today to the wielding of drugs of great efficiency and potency, that it is difficult for us to realise that this modern pharmacy is a mushroom growth dating only from the second half of the 19th century.

As late as 1860, Oliver Wendell Holmes was to write: "Throw out opium, which the Creator himself seems to prescribe, for we often see the scarlet poppy growing in the cornfields, as if it was foreseen that wherever there is hunger to be fed, there must also be pain to be soothed; throw out a few specifics which our art did not discover..... throw out wine, which is a food and the vapors which produce the miracle of anaesthesia and I firmly believe that, if the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind - and all the worse for the fishes".

A similar note is to be heard in a quotation (Thomson 1959) from "The Times" of April 3rd 1858: "There is so much guesswork in the (medical) profession that the president of the College of Physicians is nearly on a level with the meanest herbalist The result of the longest, most varied and most profound medical experiences is so often a discussion of the worthlessness of medicine".

It is intended in this essay to review the various factors which explain the sudden blossoming of scientific therapeutics in the second half of the 19th century and the development of this science up to the First World War.

Many factors coincided to effect this progress and chief among these was the general advance of medical knowledge especially with regard to the accuracy of diagnosis and the discovery of the aetiological factors responsible for many diseases. To a lesser extent progress was facilitated by the advances in chemistry which occurred in the late 18th and in the 19th centuries, together with the development of pharmaceutical chemistry and the science of pharmacology.

The Advance of Medical Knowledge up to
approximately 1850.

Therapeutics must be regarded as the culmination and *raison d'être* of all medical science. A rational system of therapy must be derived from a synthesis of our knowledge of normal anatomy, physiology, pathology and bacteriology and a resultant awareness of the exact aetiology of any given disease. Not until this was achieved, was it possible for treatment to evolve on a scientific basis.

The medical thought and practice of primitive man was largely conditioned by the basic concept that disease was produced through the influence of some malevolent deity or because of actual demon possession. Hence the therapeutics of that time were essentially designed to protect or release the individual from such influences. The witch doctor by his spells and incantations would attempt to frighten demons away, or again, the patient might wear an amulet or charm with similar intent. This was the era of magic and superstition. It is important, however, at this point to make it clear that scientific therapeutics should not be regarded as the eventual offspring of magical medicine. Its line of descent may be regarded as of quite different origin. Primitive man

did not interpret every happening of life in terms of the supernatural. Natural causes did play a considerable part in his philosophy. Where natural causes were obviously responsible for an injury or illness, natural methods of cure were attempted. For example, a broken limb was splinted. Such techniques were based on observation, experiment and meditation. Primitive man's thinking was not by any means illogical. It was to lead him, as the ages rolled by, to discover quinine, curare, opium and digitalis and he was to learn to splint fractures and to practise surgery.

The first great revolution in medical thought was to come with the Greek civilisation. While the cult of psychotherapy and the ritual of suggestion persisted in the followers of Aesculapius, Hippocrates (c.460-355 B.C.) based his teaching on the natural causation of disease, thus separating magic and philosophy from medicine. Disease itself was regarded as a physico-mental disharmony and nature herself as the chief healing agent, though at times, it was granted that nature might fail and then the Hippocratic school agreed that it was necessary to have recourse to medication e.g. the use of beef liver in anaemia.

The other two great contributions made by the Greeks were in the realm of medical ethics,

with the formulation of the Hippocratic Oath, and in the stress they laid upon the importance of clinical observation.

The work of the physicians of the Roman world was mainly one of consolidation of medical knowledge, as the classical era drew to its close. Celsus about A.D. 30 was to write his great medical classic "De medicina", a work encompassing a remarkable field of medical knowledge. Galen (c. 131-200 A.D.), through his dogmatic teaching and voluminous writings was to achieve such a position of pre-eminence in the medical world, that he was to remain virtual dictator of medical knowledge for the next 1200 years.

During the Middle Ages, medical science regressed rather than advanced. Disease was regarded as due to some undesirable humor or to the visitation of some extraneous factor. Cathartic therapeutics in the form of blood letting, cupping, purging and enemata was the order of the day. Man was obsessed by fear of plagues and fear of God. The revival of alchemy and astrology revitalised belief in zodiacal and magical bonds between men, stars and the world. "As medicine passed into the hands of the Church, prescription became combined with sermons and medicines with relics" (Martí-Ibáñez, 1958). The torch of medical learning, however, was kept burning in the medical centres of the Arab world,

in the monasteries, in the schools of Salerno, Monte Casino, Bologna and Montpellier and later in the Universities of Paris and Padua. These were to be the channels from which the medical Renaissance was to come.

The publication in 1543 of Andreas Vesalius' (1514-64) great work, "De Humani corporis Fabrica", inaugurated the era of modern medicine. This first great work of scientific literature not only provided a magnificent textbook of Anatomy but in addition, it dealt a death blow to the autocratic portion of Galen, and, in place of blind acceptance of the dogmas of the classical master, created a tremendous stimulus to original thought. What Vesalius had done in the field of Anatomy, William Harvey (1578-1657) was to do for physiology with his publication in 1628 of "De motu cordis et sanguinis". Considerably later, Giovanni Battista Morgagni (1682-1771) was to awaken the medical world to the importance of pathological research by the publication of his fine volume work "De sedibus et causis morborum" in 1761. These three tremendous works were to be the foundation stones of the three basic medical sciences of anatomy, physiology and pathology, yet centuries of slow, groping progress had to pass, before these disciplines had yielded a sufficient harvest of knowledge to enable the clinician to elucidate

the aetiology of disease. The rise of the scientific approach to medical research had indeed been reflected in the new Hippocratic clinicians, epitomised in Thomas Sydenham (1624-1689) who was justly sceptical of most of the therapeutic armament of his time, yet this scepticism tended to result in therapeutic nihilism rather than in any therapeutic progress.

If we imagine for one moment that we are in a situation in which we have been ~~benefit~~ of all knowledge of bacteriology and pathological histology, and at the same time are faced with the macroscopic appearances of, say, advanced tuberculosis, we can appreciate how utterly baffling such a pathological picture must have been to the observers of the 17th and 18th centuries, and we can realise how impossible it was for them to achieve even an aetiological hypothesis which would enable them to pursue a rational line of therapy. Not until the microscope had been fully applied to the elucidation of pathological processes, could the problem of disease causation be tackled in any satisfactory fashion. It was Marie François Xavier Bichat (1771-1802) who took the first step when he removed the spot light of research from macroscopic pathology of whole organs to the microscopic study of tissues, and

this evolution of thought was carried still further when Virchow (1821-1902) in 1858 finally introduced the concept of cellular pathology.

Further insight into pathological processes had to await the foundation of the fourth basic medical science viz. bacteriology. The epoch-making work of Pasteur in establishing the germ theory of disease provided a complete explanation of a vast field of disease processes. Moreover, the 19th century witnessed a further series of tremendous advances in physiology. Claude Bernard had by his researches blazed the trail of the experimental method and had added greatly to our knowledge of the physiology of the gastro-intestinal tract. Moreover, he had discovered the vasomotor activity of the autonomic nervous system and had dimly discerned the new science of endocrinology when he propounded his theory that all organs produce an internal secretion through which they influence 'the milieu interne', the composition of which they tend to keep invariable. The physiology of the cardio-vascular system had been further elucidated by Starling and before the century was out Haldane in the realm of respiratory physiology and Sherrington in the realm of nervous integration were to have begun the researches which laid the basis of all modern concepts in these branches of physiology.

The Advances in Chemistry and in Pharmacology

Parallel to the development of medical knowledge, there had been great progress in other fields which were to prove of considerable significance in the future progress of scientific therapeutics. Chief among these was the advance in chemistry.

Robert Boyle (1626-1691) has been called the father of modern chemistry. He put an end to the useless questing of the alchemists, and established chemistry as a fundamental science concerned with the observation and study of a certain class of phenomena. Progress was at first slow and, save for the preparation of certain elements and simple compounds, little advance was made until a break through occurred when Lavoisier in 1777 elucidated the true nature of combustion. Thereafter chemistry advanced with gigantic strides and, with the coming of the 19th century, a great cavalcade of famous chemists passed across the stage of history, among them, Black, Cavendish, Davy, Dalton, Gay Lussac, Avogadro, Faraday, Thomson, M. Curie, Bohr, and Rutherford. Within 50 years of Lavoisier's achievement, Wohler had succeeded in synthesising urea, thus destroying the previously held concept that the complex organic substances of the body required some

factor inherent in living tissue for their manufacture.

The new strides in chemistry were reflected in the augmented interest exhibited in drugs, and, especially, in the active principles of vegetable drugs, viz. the alkaloids and glucosides. Furthermore, much more rigid criteria began to be employed in the evaluation of the efficacy of a drug. During earlier centuries, a drug had often acquired its reputation on account of some spectacular recovery in a notable personage, quite irrespective of whether such a recovery might have been achieved spontaneously, had no drug been administered. During the 19th century, the value of drugs began to be assessed more objectively and the concept of control groups appears in the organisation of such experimental trials. One of the earliest examples of the experimental study of drugs is Magendie's researches in 1809 on arrow poisons. Further progress along these lines was made by his pupil Claude Bernard (1813-1878) in his researches on curare.

The main advances in pharmacology at this time, however, were achieved by German chemists. Rudolf Buchheim (1820-1879) directed the first purely pharmacological laboratory and developed the science as an independent part of physiology. Among other drugs, he studied the alkaloids and

ergot, while Oswald Schmeideburg (1838-1921) contributed important research on digitalis and muscarin.

Meanwhile the isolation and purification of these vegetable drugs was proceeding rapidly. In 1818-19, strychnine and brucine were isolated, followed by quinine, cinchonine and caffeine in the next two years. Atropine and hyoscyamine were obtained in pure form in 1831-33 by Geiger and Hesse, while Neumann isolated cocaine in 1860. Of the glucosides, salicin was prepared in 1839 and Digitalin in 1851.

With the formation of the Pharmaceutical Society of Great Britain in 1841 and later of the Institute of Chemistry in 1877, the regulations for the preparation and marketing of drugs were greatly tightened up. Furthermore, the researches of Arthur Hill Hassall in 1851 showed how the microscope could be effectively utilised in the detection of adulteration of food and drugs. Hence, with these new advances and regulations, the clinician or laboratory scientist could rely on much purer drugs being available than had hitherto been the case.

The final stage in this development was the introduction of a system of biological standardisation for drugs which could not be isolated or synthesised in pure form. The pioneer work in

this field, as in so many others, was done by Ehrlich during his investigation of diphtheria antitoxin but was not finally perfected until the Pharmaceutical Society established its own laboratories for this purpose in 1926.

With the combination of the new knowledge of normal function and of cellular pathology, coupled with the new science of bacteriology, the aetiology of a vast field of disease processes began to be apparent. With the concomitant advance of chemistry and the knowledge of the nature and action of drugs, the time was ripe for the therapeutic awakening of the latter half of the 19th century.

The Dawn of Scientific Therapeutics

Having now reviewed the various factors which led to the great advances in therapeutics during the past century, we must turn to consider the main lines of progress along which the new therapy evolved, but before doing so, let us look briefly at the therapeutic armament which was available by the earlier part of the 19th century. Mention has already been made of the reaction which the scientific renaissance had upon the clinicians of the 17th and 18th centuries in that scepticism became widespread with regard to the efficacy of the polypharmacy then rampant and an atmosphere of therapeutic nihilism prevailed. On the otherhand, as has been stressed by Professor Toynbee in his studies of human history, no historical epoch can ever be defined accurately and the old practices and social customs live on in uneasy companionship with the new. Thus we find that polypharmacy was still much practised even by the end of the 17th century. Haggard (1929) quotes an astonishing account by a Dr. Scarborough of the therapeutic "torture" to which Charles II was subjected on his death bed in 1684, after having suffered what would appear to be a cerebro-vascular accident. So extreme is the degree of polypharmacy recounted in this passage, that it is worth quoting in full.

"As the first step in the treatment, the King was bled to the extent of a pint from a vein in his right arm. Next his shoulder was cut into and the incised area "cupped" to suck out an additional eight ounces of blood. After this homicidal onslaught, the drugging began. An emetic and purgative were administered and soon after a second purgative. This was followed by an enema containing antimony, sacred bitters, rock salt, mallow leaves, violets, beet root, camomile flowers, fennel seed, lin seed, cinnamon, cardamom seed, saphron, cochineal and aloes. The enema was repeated in two hours and a purgative given. The King's head was shaved and a blister raised on his scalp. A sneezing powder of hellebore root was administered and also a powder of cowslip flowers, "to strengthen his brain". The cathartics were repeated at frequent intervals and interspersed with a soothing drink composed of barley water, liquorice, and sweet almond. Likewise, white wine, absinthe and anise were given, as also were extracts of thistle leaves, mint, rue and angelica. For external treatment a plaster of Burgundy pitch and pigeon dung was applied to the King's feet. The bleeding and purging continued and to the medicaments were added melon seeds, manna, slippery elm, blackcherry water, an extract of the flowers of lime, lily-of-the-valley, peony, lavender and dissolved pearls. Later came gentian root, nutmeg, quinine and cloves. The King's condition did not improve, indeed it got worse, and in the emergency 40 drops of extract of human skull were administered to allay convulsions. A rallying dose of Raleigh's antidote was forced down the King's throat; this antidote contained an enormous number of herbs and animal extracts. Finally bezoar stone was given. Then says Scarburgh, "alas! after an ill fated night, his

serene Majesty's strength seemed exhausted to such an extent that the whole assembly of physicians lost all hope and became despondent: still, so as not to appear to fail in doing their duty in any detail, they brought into play the most active cordial". As a sort of grand summary to this pharmaceutical debauch, a mixture of Raleigh's antidote, pearl julep and ammonia was forced down the throat of the dying King".

It must not be thought, however, that the therapeutic canvas presented a completely impenetrable gloom consisting of therapeutic nihilism on the one hand and cathartic polypharmacy on the other. The vista was lightened by the ray of certain specific remedies most of which had been culled on an empirical basis from folk medicine. These specifics included iodine, opium, colchicum, digitalis, ergot, cinchona bark, ipecacuanha and mercury.

Iodine in the form of certain seaweeds, had been used as a cure for goitre from remote antiquity being in fact recorded in Chinese literature as early as 1600 B.C. and this therapy was introduced to Europe by Roger of Pallerno as early as 1180.

Opium too was probably used from very early periods in the medical cultures of Egypt, Assyria, Crete and Cyprus. It has been identified with "Chesit gum" in the Ebers Papyrus. By the Middle Ages, it had been prepared in tincture form and was one of the few drugs strongly recommended by Sydenham. Robert Boyle was to attempt the extraction of its active principles but this was not achieved until the early 19th century. In 1803, Charles Derosne (1780-1846) a Parisian, apothecary, produced a crystalline salt from opium. This was supposed at first to be the active ingredient, but was later recognised as narcotine. In the following

year, Séguin isolated the real active principle "morphium" but his results were not published until 1814. Meanwhile, a German apothecary, Adolf Serturmer, (1783-1841) had been accurately investigating opium and announced in 1806 the discovery of "opium säure" (meconic acid) which was linked to an alkaline base closely analagous to ammonia. The active principle "morphium" was finally isolated by him in 1817. Serturmer's work is of special importance since he was the first to determine the true chemical nature of the alkaloid group of drugs, and indeed it was he who first called them by this name.

Digitalis purpurea had been known to some of the herbalists of the medieval period and was recommended in the German and English herbals of the 16th and 17th century. It was, however, put to no particular use until William Withering (1741-1799) of Birmingham, introduced it to scientific medicine in 1785 after he had observed its use as the chief ingredient of a folk medicine for dropsy. It was not appreciated at the time that the diuresis was secondary to its cardiac action. However, William Cullen (1710-1790) in 1789 and Ferriar (1798) recognised its cardiac action. It was, however, not until 1905 that its main indication in cases of auricular fibrillation was fully appreciated by Sir James Mackenzie (1853-1925). Ergot is a remedy of very ancient lineage and was used in Chinese midwifery at a very early date. It may also have been known to the Arabs and was undoubtedly in vogue in German folk medicine, as it is mentioned as an obstetric drug in Adam Lonicer's "Kreuterbuch". Its real entry into scientific therapeutics was, however, delayed until the start of the 19th century, when in 1818, Prescottt gave a paper in Boston entitled "Medicinal Efforts of Ergot". This awoke fresh interest in Europe in this drug

and by 1836, it appeared in the official Pharmacopoeia of the London College of Physicians.

Ipecacuanha was introduced to Europe after the discovery of the New World. It had long been used by the natives of Brazil in the treatment of diarrhoea and tropical dysentery. The first European to study its effect was Manuel Trestno (1589-1617) who was acting apothecary at the port of Brazil. The principle alkaloid of the drug, viz. emetine, was eventually isolated in 1820 by Pelletier and Magendie, and 24 years later was prepared in an absolutely pure form by Paul and Cownley.

The other remedy obtained from the folk medicine of the New World was, of course, cinchona bark. The romantic legend of how in the early 17th century the Countess of Chinchon was cured of malaria by the use of this remedy and thereafter introduced it to Europe, is now regarded as being definitely suspect, (Haggis, 1941), and it appears more likely that the drug was introduced into Europe by Jesuit missionaries. Indeed, it was for long known as Jesuits' bark. It also appears that this name was really applied in the first place to the product of the Myroxylon tree which yielded Peruvian balsam but, in a comparatively short time, the original source was exhausted and the more plentiful cinchona bark came to be utilised. In 1709, F.R. Torti (1658-1741) published his classic work on the use of cinchona bark in intermittent fever, "Therapeutice specialis ad febres periodicas perniciosas." In the early part of the 19th century, much interest was shown by chemists in the alkaloid group of drugs, following, as has already been mentioned, Sertürner's pioneer work on the opium alkaloids. In 1820, Pelletier and Caventou isolated quinine from cinchona bark and, within three years, this drug was being officially manufactured in this country by the firm of

Howards.

Of all the specifics in vogue by the beginning of the 19th century, only one would be claimed as having been originated by the medical profession. This was the use of mercury in the treatment of syphilis as advocated by Paracelsus (1493-1541). The latter was responsible for quite a revolution in the therapeutics of his day in that he advocated a departure from the purely vegetable drugs and, instead, attempted to explain disease in terms of chemistry, and, as a corollary, to employ inorganic chemicals as drugs. It is also of interest that his name is associated with the doctrine of "signatures", later to be more fully developed by della Porta (1588) in his "Phytognomonia". "Every natural substance which possesses any medicinal merit indicates by an obvious and well marked character, the disease for which it is a remedy or the object for which it can be employed". For example, as the leaf of cyclamen resembled the human ear, this plant was considered to be effective in diseases of the ear. Similarly the extracts of yellow flowers were thought to be of value in jaundice, while Euphrasia, which bears flowers with a black central spot resembling the pupil, was thought to be applicable to ophthalmic disorders. It is of interest historically that this doctrine, which may be taken as epitomising man's dream of specific remedies for the different diseases, was to reappear centuries later in a rather different form in the homeopathic doctrine of Samuel Hahnemann (1755-1843) "similia similibus curantur", but as we shall see, the dream remained unfulfilled until Paul Ehrlich pointed the way to new horizons in the shape of the science of chemotherapy.

The Therapeutic Advances of the second half of the 19th century and of the early 20th century

It is impossible and would indeed be tedious in an essay of this type to detail all the advances which were made in pharmacology and therapeutics in the second half of the 19th century. Rather is it important to delineate the broad lines on which the new science developed. It is in fact in the fields of immunology, chemotherapy, vitaminology and endocrinology that the greatest triumphs of the period were achieved.

Immunology

Immunology, which was to constitute the spearhead of the new scientific era in therapeutics, can trace its roots to the ancient medicine of China, where inoculation against smallpox was achieved by the rather hazardous technique of nasal insufflation of dried crusts from a smallpox patient. Inoculation was introduced into England in 1717 by Lady Mary Wortley Montague, wife of the British Ambassador in Turkey. The technique used was to make a small incision on the patient's arm and to draw through the wound, a thread, soaked in the fluid from a smallpox pustule. Similar techniques had been popularised in Europe by Emmanuel Timoni in the early 18th century.

The first major advance on the primitive technique was the epoch making discovery by Edward Jenner (1749-1823) that inoculation with pus from a cowpox lesion would confer satisfactory immunity against smallpox, and furthermore this technique was entirely safe. The vital experiment proving this theory was carried out in 1796 and Jenner officially published his researches in a small book, bearing the grandiose title "An Inquiry into the Causes and Effects of the Variolae Vaccinae, a Disease discovered in some of the Western Counties of

England, particularly Gloucestershire and known by the name of "The Cow Pox'."

The practical importance of his discovery was immediately recognised but a true appreciation of the scientific significance of his observation had to await the genius of Pasteur. The latter, having begun his study of bacteria and having established the germ theory of disease, immediately recognised that in cowpox, Jenner had been dealing with the organism of smallpox, rendered less virulent by passage through a series of unusual host animals. He accordingly set himself the task of finding out how other bacteria of deadly virulence could be similarly attenuated so that vaccines against these germs could also be prepared. In his study of the anthrax bacillus, he had noted that birds were relatively immune to this germ and he suggested and proved that this was due to their higher body temperature. By growing the anthrax bacillus at as high a temperature as possible, he was able to produce in 1882 an attenuated strain of the organism suitable for use as a live vaccine. Similarly, in the case of rabies the vaccine was achieved by partial drying of the organism.

For many years it was considered that live organisms were necessary for a satisfactory vaccine, but that this was not necessarily so was proved right at the end of the 19th century by Haffkine who showed that immunity against plague could be produced with a killed culture of plague bacillus.

The next major advance in immunology stemmed from the discovery in 1888 of the exotoxins of the tetanus and typhoid bacilli. It became clear that certain of the manifestations of these diseases were due to the toxins and not to the organisms perse. In 1890, Emil von Behring (1854-1917), a Prussian Army Surgeon, and Shibasaburo Kitasato (1852-1931) showed that

it was possible to achieve a Passive Immunity against tetanus by inoculation with serum from an infected animal. For the first time the word 'antitoxin' appeared in the medical literature. Von Behring immediately followed the above observation by showing that immunity against Diphtheria could similarly be conferred by injecting serum from an animal previously injected with living cultures of Diphtheria bacillus. This was applied successfully in a child at the Berlin Clinic in 1891.

It was at this point that Ehrlich entered the field of immunological research. His aid had been sought in an attempt to evolve a method of producing the diphtheria antitoxin in sufficient quantity, ^{and} of a sufficient standard of potency to be used therapeutically. His great ingenuity is shown in his approach to this subject. In order that he might study the antigen-antibody reaction more easily, he made use of the plant protein ricin to stimulate antibody formation. Thereafter he was able by means of a precipitation reaction, to study the neutralisation of the toxin and to assess the antitoxin from the quantitative standpoint, in vitro. These results could then be used to facilitate his 'in vivo' studies on the diphtheria antitoxin. By 1897, he was able to publish a monograph entitled "The Assay of the activity of the diphtheria curative serum". As has already been mentioned, this was an event of outstanding importance, as it provided the first demonstration of the possibility of establishing a fixed basis for the measurement of a potent remedy, the active constituent of which could not be separated in pure form or quantitatively measured by any chemical test. Furthermore, Ehrlich's researches enabled him to produce a working hypothesis of the nature of the antigen-antibody reaction, known as his 'Side Chain Theory' and although this has had

to be modified in the light of advancing knowledge, it provided a most important stimulus to immunological thought.

Ehrlich's main practical work had been with passive immunity, while more recent research has tended to concentrate on methods of achieving active immunity by the use of modified toxins or toxoids as antigens. Yet even in this branch of the subject, Ehrlich's influence is to be detected for it was he who had discovered the naturally occurring toxoids and had studied their properties. Sir Henry Dale (1956-60) suggests that their development might well have been impossible without the quantitative methods for measuring the activity of an antitoxin and using it as a standard for determining the combining powers of toxin and toxoid as Ehrlich so early discovered.

In 1891 Kitasato prepared antitetanus serum which some twenty years later was to prove of inestimable value in the Great War. Prior to the introduction of its routine administration to all wounded personnel in 1914, the incidence of tetanus among the wounded was 16/1,000. After immunisation was introduced, the incidence fell to 2/1,000.

Quite apart from its immediate applications in the treatment and prophylaxis of infectious disease, the study of the antigen-antibody reaction i.e. the inevitable response of the introduction into the body of any foreign protein, has had very far reaching consequences. It has been possible to utilise it in bacteriological investigations both with regard to immediate diagnosis, as in the Wassermann and Widal reactions, and in the more complex typing of organisms, as was shown by Neumann and Handel in 1909 in the course of the pneumococcus and by Lancefield in 1928 in the case of streptococci. Furthermore, at the present time

this whole field of research has once more sprung into prominence in view of the current interest in transplanting tissues. Much thought is now being given to methods of modifying the reaction so as to avoid the total rejection of the donated tissues.

It was undoubtedly the growing knowledge at the turn of the century of the nature of the antigen-antibody reaction that enabled the next great therapeutic advance to be achieved viz. blood transfusion.

Blood transfusion had been attempted as early as the 17th century and in spite of a continuous series of failures, the principle had never been completely forgotten. The opening of the 19th century saw a revival of interest in this type of therapy. Bichat tried unsuccessfully in 1805 and further abortive attempts were made by Prevost and Dumas in 1821 using defibrinated blood and by Blundell in 1824 using the indirect syringe technique. Apparent success in animal experiments kept interest alive and in 1874 O. Hasse even suggested the use of lamb's blood in preference to defibrinated human blood. Failure was, however, bound to attend all these efforts until Landsteiner in 1900 discovered the four main blood group antigens. In the light of Ehrlich's researches, the presence of these antigens clearly explained the previous failures and pointed the way to a logical approach to the problem. Crile (1906) was one of the first to make practical use of the discovery with his direct method of transfusion by suturing the donor's artery to the recipient's vein. However, with the discovery by Albert Hustin (1914), Luis Agote in Buenos Aires in 1914 and R. Lewisohn (1915), that coagulations could be prevented by the addition of sodium citrate, the indirect method of transfusion was introduced. Still

later the storage of blood was successfully achieved by Rous and Turner (1916) and by D.N. Belakin (1925) of Moscow.

Chemotherapy

We must now turn to one of the greatest advances in the whole history of mankind viz. the conquest of infectious disease. In his pioneer work in this field, Ehrlich stands out like a Colossus. "There are men who leave behind them both great actions and great written works, men who soar to towering heights leaving in their wake a glorious scar on the face of the earth. Such a man was Paul Ehrlich of whom it can be said - as was said of Claude Bernard in connection with physiology - that he was not a chemotherapist, but chemotherapy itself". (Martí-Ibáñez 1958)

Even from his early days as a student, Ehrlich had been fascinated by dyes and histological staining techniques and in 1878 he produced his doctorate thesis on the use of aniline dyes in histology. By applying these techniques to the staining of blood films he laid the whole basis of practical haematology.

It was some time later in the 1880's, when using methylene blue as a histologic stain, that Ehrlich noticed the great affinity of this dye for nerve cells and axons. He noticed also that this dye had the effect of blocking nerve conduction. In his reaction to these observations, we already see that the therapeutic motive was a powerful influence on his line of research, for he conceived the idea of using intravital staining of the living nerves as a means of relieving neuralgia. Furthermore, even at this early stage in his career, he conceived what is now a fundamental technique of modern pharmacological chemistry viz. the alteration of the methylene blue molecule in an attempt to obtain a derivative

which would retain its neurotropic affinity while having a stronger depressant effect on whatever vital processes might be involved in nerve conduction.

A few years later, Ehrlich observed that this same dye had an affinity for the malarial parasite and in co-operation with Professor Guttman of Berlin, Ehrlich attempted to test the remedial action of this drug in two patients suffering from malaria. Although the immediate results were not strikingly successful, it is of interest that methylene blue is still used in the Balkans in the treatment of cases of malaria which are resistant to quinine. Moreover, it is of significance that Bayer, in the development of the antimalarial drug Atebrin, took the methylene blue molecule as their starting point.

Part of the cause of Ehrlich's early failure in the field of chemotherapy, was the absence of a successful technique for transmitting a protozoal infection through an animal reservoir suitable for experimental research and drug trials. This problem, was, however, solved by Laveran and Mesnil in 1903 when they successfully achieved the transmission of certain trypanosomes through several series of animal subjects (rats and mice). Just about this time, Ehrlich himself, having completed his researches on diphtheria anti-toxin, was once again casting his mind to the problem of specific therapy for infectious disease. It would seem in retrospect that this apparent change in the object of his researches was merely an extension of his side chain theory of the antibody reaction. The latter theory was originally put forward to explain the formation of antitoxins and led him to the idea of completely overcoming

a toxin or bacteria by using a drug instead of an antitoxin i.e. chemotherapy was to be a completion and fulfilment of immuno-biology. Moreover, his previous observation of the specific affinity of methylene blue for certain tissues and parasites gave him the idea of evolving a compound exhibiting a special affinity and toxicity for the invading organism while being relatively non-toxic to the patient's own tissues.

Along with Shiga in 1903 and using the benzopurpuric dye 'Trypan red', he attempted to achieve a cure for trypanosomiasis. This dye was definitely curative in mice but success was rather limited in man and the higher mammals. However, once again in later years, Bager was to take up this problem and by modification of the molecule was to produce 10 years after Ehrlich's death, Bayer 205 (Suramin) still the most effective of the purely organic remedies for trypanosomiasis.

Ehrlich next turned to the organic arsenicals as possible therapeutic agents. Of the ones at his disposal, a toxyl was the most promising and by repeated modifications of the molecule, he attempted to achieve his objective. At first only failure was his lot. The compounds capable of killing the organism were too organotropic or, on the other hand, the non-toxin derivatives were not sufficiently parasitotropic. During these experiments there emerged the concept of a chemo-therapeutic index i.e. the ratio of the minimum therapeutic dose to the maximum tolerated dose, a ratio which has been of immense value in assessing the chemotherapeutic value of recently discovered antibiotics. Eventually at the 606th attempt success was achieved. In 1907, Compound 606 or Salvarsan was found in monkeys to be a spectacular cure for not only trypanosomiasis but also syphilis. Two years

Two years later, the drug was successfully used in human syphilitic patients. Ehrlich had at last forged and fired his 'magic bullet'. Sir Henry Dale (1956-60), in discussing Ehrlich's discovery, calls it "The culminating practical achievement of his career of research. In reaching it, he had laid down the principles for further development of the method. And the observance of these has led others, long after his death, to successes which even he might have regarded as ~~impossible~~ - to the discovery of remedies for malaria of an effectiveness beyond all earlier expectation, to the discovery of the sulphanilamide drugs and of penicillin and the still growing series of antibiotics, as direct curative agents which have transformed the prospects of recovery for sufferers from a still widening range of the bacterial and Rickettsial infections and even for the patient with syphilis, so that the directly practical importance of Ehrlich's Salvarsan has been very greatly diminished, even while the historical significance of its discovery has been steadily increasing.

Ehrlich's work also defined certain broad principles which have been applied in later chemotherapeutic studies and in other fields of pharmacology. When in 1903, he had been studying the effect of trypan red on trypanosomes, he noted that although the organisms "swam merrily" in the dye in vitro, they had lost the power of causing disease when they were injected into mice. This in fact proved to be the first observation of the bacteriostatic action of a chemotherapeutic agent in contra-distinction to a bacterial effect. In the eventual development of antimicrobial drugs, it has ^{been} found that the great majority achieve their effect by this bacteriostatic action.

Again Ehrlich with insight, decades ahead of his time, had noted as early as 1909 the ability of organisms to achieve resistance to chemotherapeutic agents.

Mention has already been made of his technique of altering a drug molecule in an attempt to enhance or decrease some property of a drug. This technique has of course been widely applied in many fields of pharmacology e.g. in the development of cocaine substitutes and in the very large numbers of barbiturates which are now available. In the case of the latter group of drugs, it has been found that alterations in the molecule greatly affect the duration of activity of the drug, so that it has been possible to produce drugs of extremely evanescent action such as thiopentone, suitable for use as general anaesthetics, while at the other end of the scale are long acting sedatives such as phenobarbitone itself.

Vitaminology

From the 15th century onwards, with the increasing length of the voyages of discovery, scurvy had become an increasing occupational hazard to seamen. Lord Anson in his voyage round the world (1740-1744) had lost 75% of his ship's company from the disease. Though the nature of the disease was to remain obscure for many a long decade, a few percipient souls put forward the suggestion that it was the absence of fresh fruit and vegetables from the diet which was responsible for the condition. Such a prophetic mind had James Lind (1716-94) when he produced his medical classic "A Treatise of the Scurvy", in 1753. Similarly some 20 years later, Captain Cook in his voyage to Australia, advocated the eating of fresh citrous fruits. Much later in 1881 and 1905, N. Lunn and C.A. Pekel having respectively put forward the hypothesis that certain "accessary food factors were necessary

for health." No experimental evidence of this was produced, however, until Sir F. Gowland Hopkins during the years 1906 to 1912 showed that young rats failed to grow on purified nutriments but would recover if they were given skimmed milk. It was later shown in America that at least two substances must be involved, one water soluble and one fat soluble. The term "vitamine" was coined by C. Funk in 1911.

Over the years, an enormous expansion in this field has occurred and now more than 30 vitamins are known. The discovery in 1933 that many of these substances are intimately involved as co-enzymes in the metabolic activities of the living organism provided yet another impetus in this branch of medicine.

Endocrinology

The final therapeutic field which blossomed in the latter part of the 19th century and has developed in the succeeding decades into ^a science of staggering complexity, was endocrinology. Yet once more, we find that in a blind, empirical or more often superstitious way, man has practised organotherapy from remote times e.g. the ancient Chinese records reveal that cretins were fed on sheep's thyroid gland. Warriors of primitive tribes ate the liver and heart of their opponents killed in battle in an attempt to obtain their warlike virtues. Again, among the prescriptions of the Eber Papyrus, we find glandular extracts cited.

Leaving the therapeutic angle for a moment we must also note that the clinical syndromes now known to be associated with disease of the ductless glands, were recognised in very early times. In the Ayurveda - Veda of Susruka (1400 B.C.) a case of goitre is described, while Hippocrates made a study of the condition of hypo-orchidism. Aretaeus (2nd

century A.D.), the Cappadocian, described diabetes and the Greeks and Romans too were undoubtedly well acquainted with the disease, Celsus noting the three features of polyuria, polydypsia and emaciation. However, in spite of the recognition of these clinical syndromes and on the other hand of the anatomical study of the ductless glands, there was a failure to appreciate the secretory role of these organs until the latter part of the 19th century. Nevertheless, it is of interest to quote the view expressed by Theophile de Bordeu of Montpellier in 1755 in his "Analyse médicinale du sang" that all organs produce specific substances that pass into the blood and are useful to the organism; that the deficiency symptoms of castrates may be caused by a lack of the humeral substances produced by the sex glands, and that the anomalies of humeral secretion play an important part in pathology".

The three great events in the development of scientific endocrinology occurred in 1849, 1891 and 1899.

In 1849, Addison published his original report in the London Med. Gazette of a clinical syndrome characterised by anaemia, bronzed skin emaciation and a pathological lesion of the adrenals. Six years later, urged by John Hilton and others, he published his famous monograph, "On the Constitutional and local effects of Diseases of the Suprarenal Capsules". Later research has shown that in fact Addison had confused two conditions, viz. pernicious anaemia and true Addison's disease, yet this confusion is not surprising when we consider that detailed haematological investigation had to await Ehrlich's researches on staining techniques.

In the same year as Addison first

formulated his preliminary report on this condition, Barthold de Göttingen~~in~~ (1849), indicated that the testicles produced an internal secretion and proved that it was possible by castration to destroy secondary sex characters in cocks and to stimulate their subsequent development through testicular implantation.

Goitre had long been noted to be an endemic disease in certain mountainous areas of the world, notably Switzerland. It was not surprising therefore that it was here that the technique of thyroidectomy was perfected by Kocher (1841-1917). The study of thyroidectomised patients showed that in some cases a clinical syndrome could develop which was indistinguishable from myxoedema and, furthermore, it was noted that the latter had certain resemblances to the condition of cretinism. Moritz Schiff of Berne (1823-1890) showed in 1884 that the undesirable results of the removal of the thyroid gland could be avoided if the animal were fed on thyroid gland extracts. Consequently in 1891, Murray in England successfully treated a case of myxoedema in man by administering thyroid extract, thus inaugurating one of medicine's greatest triumphs and yet another field of specific therapeutics.

Finally in 1899 with Brown-Sé^quard's suggestions of the existence of a mechanism of endocrine integration in the organism quite independent of and different from nervous integration, the whole basic structure of the science of endocrinology may be said to have been completed. A vast field of research of course still lay ahead and even now has by no means been exhausted. In the intervening decades, the details of the physiology and the inter-relation of the ductless glands has been largely elucidated, their active principles

have been extracted and isolated in pure form and in many cases have been successfully synthesised and added to our therapeutic armament.

In this survey of the evolution of modern treatment, our study has been largely restricted to the purely medical, or applied pharmacological aspect of therapeutics, since this is the branch of the subject which may be said to have evolved from materia medica. As a result of this, many therapeutic triumphs have perforce remained unsung. Chief among these is perhaps the discovery in 1845 and 1847 of the anaesthetic properties of ether and chloroform respectively, together with the development by Lord Lister of the techniques of antiseptic surgery. These advances, however, are to be regarded as constituting the stepping stones to the staggering achievements of modern surgery rather than as therapeutic agents in themselves. Similarly the great triumphs achieved at the turn of the century in the fight against tropical disease belong for the most part to the realm of preventive medicine and public health rather than to the science of therapeutics *per se* and hence although mention has been made of the history of cinchona bark and of the pioneer work in the treatment of trypanosomiasis, no detailed review of the advances in this field has been attempted. Radiotherapy too, following rapidly on the discovery of x-rays by Röntgen in 1895 and of radium by Pierre and Marie Curie in 1898, constitutes a very specialised type of therapy rather divorced from the pharmacological aspects of therapeutics, and has accordingly been omitted from the main discussion.



Summary and Conclusion

In the preceding pages, an attempt has been made to trace the slow evolution of therapeutics from the empirical discoveries of the folk medicine of earlier centuries until it suddenly blossomed forth into the exciting new scientific discipline of applied pharmacology in the second half of the nineteenth century. Within 50 years of this new development, all the main branches of therapeutics, as we now know them, had been established on a relatively sure foundation.

It has been pointed out that these epoch making advances may be regarded as the logical culmination and crowning glory of the advance of medical knowledge generally, and especially with regard to our understanding of disease aetiology, in the absence of which a rational system of treatment is impossible. Moreover, the application of the experimental method in assessing the value of any given drug, and the great advances in the isolation of the active principles of old remedies, coupled with the concept of biological standardisation, contributed immeasurably to the scientific progress of treatment.

An account has been given of the main fields of progress which evolved, often as entirely new branches of physiological and pharmacological science towards the end of the 19th century, so that by the First World War almost the whole of therapeutics had achieved a firm scientific basis from which was to arise the awe-inspiring cavalcade of therapeutic thunderbolts which in the past 50 years have transformed the face of medicine; insulin in 1922, sulphonamides in 1934, penicillin discovered by Fleming in 1928 and introduced into medical practice in the early 1940's, cyanocobalamin synthesised in 1948 and, about

the same time, the appearance of the three great antituberculous drugs, the nation-wide active immunisation against diphtheria during the Second World War, a campaign resulting in the virtual eradication of this scourge, while more recently, B.C.G. and polio vaccination, the ever increasing range of widespectrum antibiotics and the dramatic group of cytotoxic drugs have continued the march of progress.

In gazing on this therapeutic vista, we can only marvel, and give thanks for the tremendous line of dedicated and illustrious scientists and clinicians who have made these advances possible.

References

Dale, Sir H. (1956-1960)

"The Collected Papers of Paul Ehrlich"

Vols 1-3 Pergamon Press, London 1956-1960.

Guthrie, D. (1958)

"A History of Medicine".

Thomas Nelson & Sons, Edinburgh.

Haggard, H.W. (1929)

"Devils, drugs and doctors: the story of the science of healing from medicine man to doctor". Heinemann, London.

Haggis, A.W. (1941)

"Fundamental Errors in the Early History of Cinchona".

Bull. Hist. Med. vol. x.p. 417

Holmes, O.W. (1860)

Quoted by Haggard (1929)

Martí-Ibáñez, F (1958)

"Centaur. Essays on the history of Medical Ideas."

M.D. Publications/Inc. New York.

Thomson, Sir A. (1959)

"The Three Revolutions in Medicine".

(Linacre Lecture). B.M.J. 2: 130-134.