THE HISTORICAL DEVELOPMENT OF CLINICAL THERAPEUTIC TRIALS

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DELIBERATE experiments designed to assess upon patients the value of therapeutic procedures are an essential feature of modern medicine. These clinical trials link laboratory results with medical practice and so provide a reliable basis for advance in treatment. They are seldom easy, are usually costly in time and effort, and sometimes are dangerous to patients. The danger may be to patients treated in the trial or to patients badly treated as a result of reliance upon an inadequate trial. The efficiency of these experiments is thus a matter of some importance.

A study of the problems tackled in the past, by what methods, and with what success, should yield lessons for the future. It may show some of the pitfalls and limitations of the clinical therapeutic experiment as well as its triumph in certain circumstances. The conditions for such success may be seen and, further, the best methods to use when those conditions are present.

THE ANCIENT WORLD

The methods of therapeutic investigation used by the ancient Egyptians are unknown. The outstanding lessons from records discovered are (1) the extreme antiquity of systematic medicine (a papyrus in the British Museum gives prescriptions believed to date from circa 2000 B.C.,[1] the time of the building of the great Pyramids), and (2) the high quality of treatment for certain lesions. While medical conditions were typically treated with a combination of ritual exhortations and fantastic mixtures of herbs and natural products,[2] surgical treatment and, in particular, minor surgery was at a much higher level. The Edwin Smith papyrus,[3,4] dating from circa 1600 B.C., refers to bandaging and stitching of wounds and, for instance, the treatment recommended for a dislocated jaw by reduction is that of modern surgery. We do not know how such methods of treatment were worked out, but it is interesting to note that the

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types of lesion so excellently treated were all of simple etiology, mostly accidental injuries, with mechanisms of production and treatment not dissimilar to those of structural engineering of which the ancient Egyptians were such masters. The success of the treatments would be unequivocal, so that therapy based on simple mechanical principles could readily be tested by trial and error. The simplicity of such surgical conditions can be contrasted with the complexity of etiology, diagnosis, and criteria of cure of medical conditions likely to have been prevalent in the Nile valley. Even with modern aids the differentiation of tropical fevers is not easy and one of the characteristic Egyptian diseases, schistosomiasis (possibly the A'a disease of the papyri) has only recently been the subject of satisfactory therapeutic trials.

The surviving records of Babylon and Assyria show a state of medical knowledge similar to that of ancient Egypt[5] and there is much evidence of interchange with Egyptian medicine. An elaborate pharmacopeia was used but much of the therapy was irrational or ritualistic. Exorcism of hostile powers was the declared aim of treatment but incantations were often combined with practical measures such as the use of poultices, purgatives, and enemas. No elaborate trial would be necessary to test the effects of these simple treatments and the persistence of the associated irrational ritual suggests a low level of scientific criticism. Not all the ritual, perhaps, should be so dismissed; it is known, for instance, from excavations that public hygiene was highly developed in Babylon and the frequent recommendation of purification by water or fire may indicate that lessons learned in hygiene were applied in therapeutics.

According to Herodotus[6] it was a custom of the Babylonians to exhibit their sick in a public place so that passers-by might advise suitable treatment based on their experience with similar cases. It seems unlikely that successful treatments would be fully validated on such a system and the records give no suggestion that orthodox medicine benefited by these public clinical trials.

Like that of other ancient civilizations the medicine of the Hebrews was closely allied to religion. Public hygiene, in which the Jews excelled, was administered by the priests and enforced by religious sanctions. The knowledge of preventive measures against infectious diseases was perhaps a product of life in tribal communities, large enough to have an administrative structure and small enough for each member to be known personally. The pressure of hard living conditions and the ever-present danger of communicable disease would favor the growth of a sound knowledge of hygiene. There is no evidence of any deliberate experiments and little is known of ancient Hebrew therapeutics as distinct from preventive medicine. It is possible that the lost book of the *Wisdom of Japheth* which emphasized the value of observation in medicine would have thrown light on methods of advance in treatment.[7]

GREECE AND ROME

Modern medicine is often said to have begun in Greece. The wealth of original observation and cautious deduction recorded in the Hippocratic books is one of the outstanding achievements of mankind. The study by the Coan school of the natural history of disease gave rich results in diagnosis and prognosis but there was less success in therapeutics. Surgical treatment, especially of minor complaints, reached a high standard as it had many centuries before among the Egyptians. In contrast, medical therapeutics were dominated by a priori theories. These theories, though less speculative than those of other schools, were oversimple derivations from a general philosophy of nature. Therapy was intended to assist the natural powers of healing by simple exercises and diets. These were rationally deduced from the postulates, but there is no suggestion that experimental trial and judgment by results were used. Thus the *Regimen of Acute Diseases*[8] urges physicians to inquire into the best treatments and goes on to give reasons in favor of barley gruel for fevers, but characteristically the gruel is recommended because it is smooth and soft and not because of its observed effects upon patients, nor is any comparison offered with alternative treatments.

Medicine in contrast to more theoretical subjects has the advantage of enforcing a continual testing of theory by practice. This was recognized by the writer of the *Precepts:* "One must attend in medical practice not primarily to plausible theories, but to experience combined with reason."[9] The natural sequel in therapeutics would seem to be the clinical trial which aims to test the day-to-day impressions and to substitute a deliberate advance for the accumulation of plausible theories. The Hippocratic writers with their confidence in general philosophy did not draw this conclusion. A study of the successors of the Hippocratic school emphasizes different aspects of this paradox between a stated reliance upon observation and an actual trust in a priori theory. The Dogmatists developed the theory of humors and qualities into a rigid formalism.[10] The Empirics, on the other hand, discounted theory and relied upon practical tests only. In this way knowledge of drugs was advanced and poisons and their antidotes, in particular, were widely studied. Attalos and other rulers tested the effect of poisons upon criminals by a kind of reversed clinical trial, and the famous antidote of Mithridates comes from this era. Extreme Empiricism with its undue emphasis on "cures" and its neglect of general principles of etiology and diagnosis led to extravagant polypharmacy and hindered therapeutic progress.

Roman medicine derived directly from that of Greece, and many of its leaders were of Greek origin. The arguments of the conflicting schools continued but the outstanding men favored an eclectic compromise. Celsus, after reviewing the history of classical medicine, states fairly the Empiric view of the development of therapeutics, ". . . careful men noted what generally answered the better, and then began to prescribe the same for their patients. Thus sprang up the Art of Medicine which from the frequent recovery of some and the death of others, distinguished between the pernicious and the salutary."[11] Celsus agrees that ". . . nothing adds more to a really rational treatment than experience" and concludes that ". . . the Art of Medicine ought to be rational but to draw instruction from evident causes, all obscure ones being rejected from the practice of the Art, although not from the practitioner's study." Like other early writings *De Medicina* cites little evidence to support the claims made for its treatments and though these include sound use of some drugs, in particular local application of astringents, many others are only "sympathetic" remedies and it seems unlikely that either the experience of "careful men" or consideration of "evident causes" could justify giving ox spleen for splenic enlargement or pole reed for injuries by splinters.

In the first century A.D. Dioscorides wrote the earliest scientific account of medical botany.[12] He recognized natural families of plants and classified their medicinal qualities. His work was the foundation of herbals for 16 centuries,[13] but he did not describe methods of testing therapeutic action. He recommended Mandragora wine for insomnia and as an analgesic draught which could be used in surgical operations. Dioscorides was himself a military surgeon and had, presumably, opportunities for trying such analgesic properties. Some other important pharmacologically active plants, for example, digitalis and Atropa, are not mentioned and others, such as Salix, are recommended for a multitude of complaints often not including what is now known to be their most valuable action. It would be unreasonable to expect an exhaustive account in a pioneer work but the absence of these important parts of materia medica may explain some of the impotence of medicine in medieval times when Dioscorides was followed slavishly.

The advances in surgical technique in Roman times were probably related to experience with gladiatorial and military injuries.[13] Galen himself served as physician to the gladiators and became one of the great founders of scientific medicine. His experimental approach was well shown in physiology but, although he tried to deduce therapeutics rationally from knowledge of disease and understanding of remedies, inadequate testing permitted general theories such as that of treatment by contraries to override practical results upon patients.

THE MIDDLE AGES

After the fall of the Roman Empire the scientific trend in European medicine was arrested. The newly developing Moslem culture took up and preserved the classical and early Christian medical teaching. The doctrines of Islam favored conservatism in therapeutics and, in particular, the objection to touching the human body delayed advances in anatomy and surgery.[13] The authority of Galen was, in general, accepted and his teachings were often mixed with astrology. Arab merchants dominated the spice and drug trade so it is not surprising that there were numerous pharmacologic experiments.[14] Rhazes (860-932) was outstanding in this field and Avicenna (980-1037) in his encyclopedic *Canon* gives some interesting rules for the testing of drugs. He suggests that in the trial of a remedy it should be used in its natural state upon uncomplicated disease, that two opposed cases be observed, and that study be made of the time of action and of the reproducibility of the effects. He further stated: "The experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man."[15] These rules imply a very modern approach but there seems to be no record of their detailed application. It is possible, however, that documents not yet translated may throw more light on this.

In Europe the supernaturalism of medicine of the monastic period was countered in the eleventh and twelfth centuries by the School of Salerno. Here a simple rational therapy was based on direct study of disease. The famous *Regimen sanitatis* gives sensible advice on hygiene and diet and considerable detail on blood letting but no suggestion of methods of testing remedies.[16] Roger of Palermo in his *Practica* (circa 1170) recommended seaweed for goiter and mercury salves for skin diseases, and one can only surmise that some kind of simple trial had shown their usefulness.[13]

Latin translations of Arabic scholars such as Avicenna became available in the thirteenth century and, at the same time, the Roman Church which dominated intellectual life was rejuvenated by the Franciscan movement. An outstanding exponent of this medieval renaissance was the Franciscan Roger Bacon (1214-1292). In his *De erroribus medicorum*[17] he points out inconsistencies in current medical teaching but excuses some of the defects "for it is exceedingly difficult and dangerous to perform operations on the human body, wherefore it is more difficult to work in that science than in any other. So that physicians are always to be excused since needs must be that they have deficiencies. For the operative and practical sciences which do their work on insensate bodies can multiply their experiments till they get rid of deficiency and errors, but a physician cannot do this because of the nobility of the material in which he works; for that body demands that no error be made in operating upon it, and so experience (the experimental method) is difficult in medicine. Wherefore physicians are to be excused for their defects more than are workers in the sciences." Bacon favored appeal to experience and mathematical demonstration but does not appear himself to have applied these principles to therapeutics since his own recipes given at the end of *De erroribus* are on traditional lines.

In the fourteenth and fifteenth centuries the attempt was made rather to reconcile Aristotelian dialectics with Arabian medicine than to continue the lead of the thirteenth century theorists by advancing knowledge by experiment. This failure was in keeping with the medieval intellectual atmosphere and its emphasis on faith, authority, and philosophical idealism,[18] but quite apart from the intellectual controversies the practitioners of many crafts continued to make sound observations and steady progress. The use of water power was greatly developed, methods of agriculture improved, and, with the introduction of the modern type of ship's rudder, long sea journeys became possible.[19] Similar progress presumably occurred in therapeutics. Something of this is suggested by Henri de Mondeville (1260-1320) who defended cleanliness in the management of wounds against the "coction" and "laudable pus" of the Arabian commentators on Galen.[20] His claim that "wounds dry much better before suppuration than after it" implies direct observation and appeal to experience rather than to authority.

THE RENAISSANCE

It is not appropriate to discuss here the various aspects of the revival of learning which, beginning in Italy in the fifteenth and sixteenth centuries laid the foundation of modern science. The renewed study of Latin texts by Petrarch

(1300-1374) and his successors, of Greek originals by Boccaccio (1313-1375) and others, the invention of gunpowder (circa 1330) and of printing (1440-1450), the fall of Constantinople (1453), the discovery of America (1492), and Magellan's circumnavigation of the world (1519-1522) all played a part in this enormous development of theory and practice. Two contrasting threads of this story are important in the history of clinical trials. In common with all other branches of thought, medicine was affected by the revival of Classical Humanism. Early medical Humanists such as Leonicenus (1428-1524) and Linacre (1460-1524) provided new and accurate translations of Hippocrates and Galen; they and their followers were thus in an excellent position to attack contemporary medical teaching based on indirect annotations of the classics, but their criticism of the new empirical medicine could be just as stringent. This empiricism was a continuation of the mixed science and magic of the alchemists. Paracelsus (1493-1541), its great exponent, was a pupil of Leonicenus and from him acquired a lifelong respect for Hippocrates, but his public burning (1528) of the works of Galen and Avicenna shows his violent opposition to current medical orthodoxy. He wrote and spoke in the language of the common people and from them collected information on folk medicine. Being also an expert alchemist he made experiments in the use of metals in therapy. No details are available of his methods of trial, but he says, "experience has shown that Mercury is the sovereign and only remedy for the cure of all ulcers tainted with the great pox,"[21] and again, "practice should not be based on speculative theory; theory should be derived from practice. Experience is the judge; if a thing stands the test of experience it should be accepted; if it does not stand the test it should be rejected."[22] The implied scientific approach was not always sustained. Paracelsus also originated one of the earliest sympathetic remedies. The response of the Humanists to these new ideas was decidedly hostile. One of them, Fernel (1497-1558), also an admirer of Hippocrates, attacked the use of mercury not because it was ineffective but because of its empirical origin. Fernel based his own therapeutics on the doctrine of contraries and favored guaiac for syphilis.[23]

Meanwhile Leonardo da Vinci (1451-1519) had developed the theory and practice of the modern scientific experiment. He saw the importance of mathematical demonstration and said, "I shall test by experiment before I proceed further, because my intention is to consult experience first and then with reasoning show why such experience is bound to operate in such a way. And this is the true rule by which those who analyse the effects of nature must proceed; and although Nature begins with the cause and ends with the experience, we must follow the opposite course, namely . . . begin with the experience and by means of it investigate the cause."[24] Although there are claims to the contrary, it seems doubtful that Leonardo appreciated the full scope of scientific method. His experimental approach continued to be that of the craftsman and engineer—the testing of materials and of ad hoc hypotheses rather than part of an inductive system.[25] Although the testing of drugs by clinical trials falls well within the scope of his type of experimentation Leonardo did not apply these methods to therapeutics and was scornful of doctors, probably with justification. The few recipes he gives in the *Notebooks* are of traditional type.[26] Ambroïse Paré (1510-

1590) the greatest figure in Renaissance surgery, popularized the revolutionary anatomic teaching of Vesalius (1514-1564) and also made one of the earliest reported clinical trials, albeit an unintentional one. In 1537 while serving with the Mareschal de Montegni he was responsible for the treatment of the wounded after the capture of the castle of Villaine. They were so numerous that, he says, "at length my oil lacked and I was constrained to apply in its place a digestive made of yolks of eggs, oil of roses, and turpentine. That night I could not sleep at my ease, fearing that by lack of cauterization I would find the wounded upon which I had not used the said oil dead from the poison. I raised myself early to visit them, when beyond my hope I found those to whom I had applied the digestive medicament feeling but little pain, their wounds neither swollen nor inflamed, and having slept through the night. The others to whom I had applied the boiling oil were feverish with much pain and swelling about their wounds. Then I determined never again to burn thus so cruelly the poor wounded by arquebuses."[27] The other recorded instance of Paré's use of such methods of trial is perhaps less fortunate. One of his later masters, Charles IX had a bezoar stone supposed to be a universal antidote. Paré criticized this claim and suggested it be tried on a convict. A prisoner agreed and instead of being hanged was given poison and the bezoar stone. He died after about 7 hours and Paré did an autopsy which confirmed that death was due to corrosive sublimate. Similar tests of antidotes upon criminals were made by other rulers about this time, and in view of the commonness of poisoning such ruthlessness was perhaps understandable.

During the sixteenth century there was an increasing interest in natural history, stimulated by the numerous voyages of discovery. There was a corresponding development of systematic botany and the work of Fuchs (1501-1566) and Valerius Cordus (1515-1544) provided first-hand descriptions and classification of plants.[28] This resulted in improvements in materia medica and the earliest pharmacopeias date from this time. There were also several treatises on purges and presumably some kind of testing of pharmacologic properties was performed, aimed at symptomatic rather than curative therapy.

THE SEVENTEENTH CENTURY

The seventeenth century saw great growth of the application of scientific method, but medicine was less affected by this than were physics, chemistry, and biology, and there was little development of therapeutic trials. As in the preceding periods practical men did note and learn from comparative observations. For example in the first expedition to India by the newly formed East India Company in 1600, there were four ships; on one of them only, that of General James Lancaster, was lemon juice provided and this ship was almost free from scurvy whereas the others were badly affected during the slow voyage. The Company was sufficiently far-sighted to supply all its ships with lemon juice for subsequent voyages.[29] This lead was not taken up by medical men for other diseases; in fact, it was not until the next century that a corroborative trial of this same treatment for scurvy was made.

Francis Bacon (1561-1626) the great protagonist of the inductive method in science, devoted a section of his *De augmentis scientiarum* to medicine. He discussed the dangers of crude empiricism to which doctors were driven by the demand for "cures" and said of therapeutics, ". . . this part of phisic which treats of authentic and positive remedies, we note as deficient; but the business of supplying it is to be undertaken with great judgment, and as by a committee of physicians chose for that purpose."[30] How this "committee" was to proceed Bacon did not specify.

The outstanding contribution to physiology made by Harvey's *De motu cordis* (1628)[31] inspired others to attempt overfacile simplifications of medicine based on general principles analogous to those discovered in physics by Newton. A similar result was produced by Boyle's brilliant chemical discoveries which led in the later iatrochemical school to speculations which were often far removed from sound scientific principles.[32] There was failure to apply the applauded scientific methods to test hypotheses; instead reliance was still placed in a priori reasoning. Boyle (1627-1691) was himself very skeptical of current medicine though very interested in drugs and diseases. He made numerous suggestions for imitating medicinal waters and cheapening drugs and in *The Usefulness of Natural Philosophy* he says, "Another way by which the naturalist . . . may help to lessen the changeableness of cures is by showing there hath not yet been sufficient proof of their having any medicinal virtues at all. . . ."[33] Boyle also recommended experiments on animals and with Wren he performed the early blood transfusions. In 1657 they succeeded in transfusing animal blood into a human subject as is recorded by Pepys, but this was hardly intended as therapy and when extended as such by Denis in France it was soon discredited.[34]

An outstanding new therapeutic agent introduced to Europe about this time was Cinchona bark. The precise circumstances of its discovery are still disputed but it is clear that it had been used for many years previously by the Peruvian Indians before it came to the attention of Spanish colonizers about 1630. Its success in the treatment of fevers must have impressed the Jesuit missionaries for they brought the bark to Europe in 1632. It had a hostile reception by orthodox medicine. This was partly due to suspicion of the Jesuits but a further objection was that its acceptance meant an overthrow of Galenical theory. As Ramazzini later observed, cinchona did for medicine what gunpowder had done for war.[13] No careful trials of the value of this drug seem to have been made and there is even doubt as to the nature of some of the bark used since, apart from fraudulent preparations, there seems to have been confusion between cinchona with its antimalarial action and quinaquina, the source of Peruvian balsam.[35] Jesuits' bark, discounted by doctors, became the property of quacks. One of these, Talbor (1641-1681), achieved great fame with his remedy for fevers and became Physician to Charles II.[36] Sydenham (1624-1689) broke away from orthodoxy and, although a nihilist in many fields of therapy, used and recommended Peruvian bark for intermittent fevers. His methods of trial are unfortunately not known, but his skepticism of the newly developing sciences of anatomy and physiology[37] make it unlikely that his techniques were derived from the contemporary scientific trends of the Royal Society. His reliance upon clinical experience contrasts with Boyle's confidence in experiment. The marriage of these two approaches to produce a satisfactory clinical trial did not occur in the seventeenth century, although it appears that Locke (1632-1704), a friend of both Boyle and Sydenham, had something of this sort in mind in his projected work *Ars medica* on the philosophy of medicine.[38] Therapeutics, instead, was at the mercy of fashion and quackery. The status of antimony provides an example; it had first been publicized at the beginning of the century by extravagant claims made in *The Triumphal Chariot of Antimony*. This book was probably written by Thold but was attributed to a fifteenth century monk, "Basil Valentine." By the middle of the century antimony had fallen into disrepute, but in 1657 it was used in treating an illness of Louis XIV. The king recovered and antimony again became popular for the treatment of fevers.[39]

By contrast, surgical treatment made more steady progress. Wiseman (1622-1676), the outstanding English surgeon of the century, accepted as self-evident the virtues of bleeding, purging, vomiting, sweating, and salivation but nevertheless he made acute observations on simple therapeutic advances. He vividly describes successful treatment of edema of the legs with laced stockings, the recurrence of the trouble when treatment was interrupted, and the further improvement on re-placing the appliance.[40] This kind of simple trial with limited mechanical aim has frequently contributed to practical surgical techniques.

THE EIGHTEENTH CENTURY

In the eighteenth century the new advances in scientific knowledge and method began to be applied to therapeutics. This was achieved often in the face of opposition from the orthodox theorists who still tried to impose a priori systems upon medical treatment. It is not surprising therefore to find that the advances were made sporadically by persons of independent mind often working in the provinces away from the fashionable systematists. In default of a scientific background new treatments were borrowed from folk medicine but the need of adequate trials of their effects was increasingly realized.

Inoculation as a preventative of smallpox was introduced from Constantinople by Maitland (1668-1748) and Lady Mary Wortley-Montague. They persuaded King George I to permit a trial upon six Newgate convicts in 1721.[41] All survived the operation and were released; one, in whom the inoculation failed, was found to have had smallpox before; another was exposed to infection after the treatment and was found to be immune. The results were thought to be conclusively in favor of inoculation and it became widely practiced. The trial has since been criticized because it was uncertain which of the subjects had previously suffered from the disease and the trial would seem to have tested the safety of the procedure rather than its effectiveness.[42] Subsequent experience soon showed that inoculation could have a considerable mortality and that complete protection could not be assured. These variable results were obtained with different modifications of technique which the early trial could not have been expected to test, but the numbers treated and the precision of the trial were inadequate to give a fair picture of the effects of the operation.

Other treatments continued to be proposed on very slender evidence. Dover published his *Ancient Physician's Legacy to His Country* in 1733,[43] claiming extravagant cures of gout, dropsy, and diabetes, and in the same year Bradley published a rejoinder accusing Dover of quackery[44]; neither performed careful trials of the recommended treatments. Cures for the stone were in great demand and a Mrs. Stephens was given a Parliamentary grant of £5,000 for her secret remedy. The very able experimental physiologist Stephen Hales (1677-1761) was on the committee which examined the claims for the treatment. Patients supposedly cured were questioned and the grant was supported. Hales may have had some misgivings since he later experimented with the mixture and decided that only the "soap lees and lime of eggshells" which it contained among many other ingredients could have had any solvent effect upon calculi[45]; he does not seem to have considered the necessity of careful trials upon patients. Heberden (1710-1801) was critical of many traditional treatments and in his *Antithriaka* (1745) he dealt the final blow to the spurious antidote of Mithridates famous in various forms for 2,000 years.[46] He based his attack on the variable constitution and the inconsistencies and unreasonableness of the supposed properties of theriac rather than upon a demonstration of its ineffectiveness. Another popular remedy was publicized in 1744 by Bishop Berkeley in *Siris: A Chain of Philosophical Reflexions and Inquiries Concerning the Virtues of Tar Water.*[47] From anecdotal evidence of tar water curing smallpox and scurvy he goes on to quote his own use of it in the Irish epidemics; the transition is then made through chemistry and physics to philosophy and theology. Although no comparative results are given to substantiate the claims, tar water became so popular that a special warehouse was opened in London for its distribution.[48] Hales also examined this remedy and cautiously attributed discrepancies in its effects to variations in method of preparation.[49]

At this time an investigation of quite a different quality was made by a ship's surgeon, James Lind (1716-1794). Appalled by the ravages of scurvy in Anson's recent circumnavigation of the world when three-quarters of the men died from the disease, Lind planned a comparative trial of the most promising scurvy "cures." On May 20, 1747, he says, "I took twelve patients in the scurvy, on board the Salisbury at sea. The cases were as similar as I could have them . . . they lay together in one place . . . and had one diet common to them all." To two of them was given a quart of cider a day, to two an elixir of vitriol, to two vinegar, to two oranges and lemons, and to the remaining two "an electuary recommended by an hospital surgeon." "The most sudden and visible good effects were perceived from the use of the oranges and lemons, one of those who had taken them being at the end of six days fit for duty. . . . The other . . . was appointed nurse to the rest of the sick."[50] Apart from the cider, which seemed to do a little good, the other remedies were ineffective. In spite of this apparently conclusive demonstration Lind himself continued to cling to other theories; in discussing the treatment of scurvy later in the book he recommends fruit and vegetables but he gives priority to "pure dry air" and says again "hence the first step . . . is change of air." Others seemed no less doubtful and there were several suggestions for cheap alternatives supposedly equal to fruit. A conclusive trial of fruit as an antiscorbutic is sometimes attributed to Captain Cook who used it on his second voyage in 1772; but this cannot be sustained since many different prophylactics were used, among them beerwort, of which Cook wrote to Sir John Pringle that it was "one of the best anti-scorbutic sea-medicines yet found out."[51] The British Navy did not supply lemon juice to its ships until 1795.

A close association existed at this time between general science, exploration, and medical research. Pringle was one of the founders of preventive medicine and, when awarding Cook the Royal Society's Medal, praised him as much for his achievement in preventing scurvy as for his geographic discoveries. Sir Joseph Banks, who succeeded Pringle as President of the Royal Society, had himself accompanied Cook on his first voyage around the world and became a great supporter of scientific work; among his many correspondents were John Hunter and Edward Jenner. Another feature of the intellectual life of the eighteenth century was the rise of medical and scientific societies where the members met to discuss a wide range of subjects. The Lunar Society in Birmingham included the leaders in science, engineering, and medicine of that rapidly growing industrial area. Contact was maintained with continental and American workers, and in this atmosphere of scientific triumphs it is not surprising that along with genuine advances less authentic ones were introduced. Many experiments were made on static electricity, and electric shock treatment became popular under the name of "Franklinism." How little this name was justified is shown by Franklin's letter to Pringle in 1757 describing his tests of electricity upon paralyzed patients who came to request it. The letter recounts the temporary improvement which Franklin cautiously suggests may have been due to the exercise of the journey in coming for treatment or the "spirits given by the hope of success."[52]

Similar evidence of popular and even medical credulity was shown by the success of Perkin's tractors. These were metallic rods which were supposed by some electrical influence to cure a great variety of diseases. The treatment was recommended by several distinguished doctors, including Nathan Smith, the founder of Yale Medical School, and an "Institute of Perkinism" was founded in London.[39] Haygarth (1740-1827) of Bath submitted the method to a devastating clinical trial described in his book *Of the Imagination as a Cause and as a Cure of Disorders of the Body*.[53] On 5 patients he used imitation "tractors" made of wood and all but one of the patients were relieved. The following day he repeated the treatment using instead a pair of genuine tractors and obtained identical results. Haygarth aptly quotes Lind's comment on the fictitious scurvy remedies used at the siege of Breda, "an important lesson in physic is here to be learnt, viz., the wonderful and powerful influence of the passions of the mind upon the state and disorders of the body. This is too often overlooked in the cure of diseases. . . ."

Several new medical schools were founded in the eighteenth century, and another important development was in hospital construction. This, after having "approached perfection in the fifteenth century,"[13] had been seriously neglected in the sixteenth and seventeenth. The number of hospitals actually diminished as a result of the disbanding of religious houses during the Reformation, and little was done to replace the loss in spite of increasing populations. In the eighteenth century the position began to be corrected by the founding of new hospitals both in London and in the growing provinicial cities. William Withering (1741-1799) became Physician to the Birmingham General Hospital at its foundation in 1778. Here were more patients upon which to continue his trials of the preparations of digitalis first brought to his notice as a constituent of a folk remedy for dropsy. In his *Account of the Foxglove*[54] he gives his experience of the drug in 163 cases. There is a masterly description of his establishment of correct dosage. At first, he thought it necessary "to bring on and continue vomiting," then he persisted until nausea was caused, later he aimed at either diuresis, sickness, or purging, but having noticed slowing of the pulse in some cases his final method was not to repeat the drug too quickly and to continue "until it either acts on the kidneys, the stomach, the pulse, or the bowels." Withering's achievements in deciding the types of patients who would benefit from digitalis are equally remarkable when it is remembered that virtually nothing was then known of the pathology of different kinds of edema. After describing patients apparently with hypertension and malignant ascites as showing little improvement he says, "on the contrary if the pulse be feeble or intermitting, the countenance pale, the lips livid, the skin cold, the swollen belly soft and fluctuating, or the anasarcous limbs readily pitting under the pressure of the finger, we may expect the diuretic effects to follow in a kindly manner." In assessing the value of this treatment, Withering relied upon close observation of his patients and used all the appropriate clinical methods then available; he compared the results with the same patients' previous condition and sometimes with their relapses on discontinuing the drug. This technique is particularly appropriate for such a problem.

The originality of Withering's discovery was disputed by his fellow member of the Lunar Society, Erasmus Darwin,[55] but Darwin's sporadic use of the drug in apparently excessive dosage bears no comparison with the other's systematic study of a long series of patients.[56] Another acquaintance of Withering's was Thomas Fowler who had succeeded him at Stafford Hospital (founded 1772). Here Fowler made his study of arsenic solutions in the treatment of a variety of diseases. In his *Medical Reports of the Effects of Arsenic*,[57] he gives a good account of toxic effects and claims that arsenic is a possible substitute for Peruvian bark in the treatment of ague, and he quotes 247 cases of this disease treated by his method. He claims to have cured two-thirds of these patients, but it appears that his methods of observation were unequal to the difficult task of assessing a remedy for such a notoriously intermittent and relapsing disease, which even with the modern advantages of microscopic diagnosis has only recently been the subject of satisfactory clinical trials.

The history of surgery in this period is dominated by the work of John Hunter (1728-1793), and it was he who established modern surgery on a scientific basis. There is an incident in his early days as a military surgeon during the Belle Isle campaign (1760-1761) which is reminiscent of the experience of Paré two centuries earlier. It was current practice to search for and if possible remove the missiles from gunshot wounds. Hunter describes 5 cases in which this was not done and explains that the "neglect rather arose from accident than design." The patients were Frenchmen who had hidden since being wounded and, with only superficial dressings, they all recovered. Hunter modified his treatment of gunshot wounds accordingly and writes, "This practice has arisen from experience, for it was found that balls when obliged to be left, seldom or ever did any harm when at rest and when not in a vital part."[58] As with Paré and the cauterization of wounds, the necessities of military surgery forced this unintentional trial upon Hunter. Being outstanding men, they both drew the correct lessons from these experiences.

At the end of the eighteenth century Jenner published his famous studies on vaccination.[59] This again was a procedure derived from folk medicine and had been suggested by the belief among country people that infection with cowpox prevented subsequent attack by smallpox. Jenner's original account cites 14 persons who, having had cowpox, did not take smallpox when inoculated subsequently. In a further 10 patients, artificial infection with cowpox is described, and 4 of these did not take smallpox when inoculated. A reasonable prima facie case was thus provided in favor of vaccination but the trial was not so conclusive as has sometimes been claimed. The method was the uncertain one of arm-to-arm infection, the people in whom protection was demonstrated were few; this protection was against artificial inoculation and not the naturally occurring disease, and no account was taken of the possibility of natural or previously acquired immunity. George Pearson in 1798 published another smaller trial in which he made a detailed study of the results of inoculating 5 persons with smallpox, of whom 3 previously had had cowpox and 2 had not. The results confirmed the protection given by cowpox but Pearson was guarded in his conclusions and recommended "well-directed observation in a thousand cases of inoculated cowpox."[60] Studies of this magnitude were soon available since smallpox and inoculation hospitals provided ample material,[61] but the conditions of observation and the techniques whereby mixed infections of cowpox and smallpox were transmitted prevented the drawing of clear and consistent conclusions. A smaller trial, the counterpart of Pearson's, was made by Waterhouse, the first doctor to use the method in America.[62] He vaccinated 19 boys; 12 of these he afterward inoculated with smallpox, as he did 2 others who had not been vaccinated. Only these latter 2 took the smallpox infection.

A study of the relative merits of different treatments for syphilis was made by John Pearson. He dedicated his book to Thomas Fowler and in it compared the claims and his experience of various herbal and chemical remedies "to ascertain whether any other substance than Mercury be a true and certain antidote."[63] As surgeon to the London Lock Hospital he had a wide knowledge of the disease and he tried out, apparently not very systematically, any likely remedies. He gives the details of studies on 31 patients in support of his opinion that guaiac, China root, sarsparilla, and other treatments recommended as alternatives were only of value when used in addition to mercury. As to mercury itself, he states that its effectiveness was demonstrated in "not less than twenty thousand cases" of which he had personal experience. He was not blind to its disadvantages and looked forward to further discoveries since "it were highly desirable to acquire a medicine equally potent as an antivenereal, and not possessing certain active properties peculiar to that mineral." This study, based on simple clinical assessment of results, seems to have been highly successful, particularly so since there was at that time little understanding of the pathology of the disease nor were there accurate tests of cure and, as Pearson was aware, symptoms due to syphilis were frequently confused with those of excessive treatment with mercury.

THE NINETEENTH CENTURY

Early in the nineteenth century a further emphasis began to be placed on the need for a careful statistical approach in the evaluation of remedies. This was chiefly directed to criticism of extravagant claims. Cobbett, for instance, in his pamphlet *The Rush Light*[64] threw doubt upon Rush's evidence for the value of bleeding and purging in yellow fever, and was one of the first to appeal for the application of statistics to such problems.[32] Theoretical statistics was also advancing rapidly; the *Théorie Analitique de la probabilité* appeared in 1810 and in it Laplace, after reviewing the application of statistical methods in many fields, says, "La même analyse peut-être étendue aux divers résultats de la Médicine."[65] This approach was developed by P. C. A. Louis (1787-1872) chiefly to establish the diagnostic features and the natural history of diseases such as typhoid fever and phthysis.[66] In his *Essay on Clinical Instruction*,[67] he lays down admirable rules for the use of his "Numerical Method" in the assessment of therapy. "As to different methods of treatment, if it is possible for us to assure ourselves of the superiority of one or other among them in any disease whatever, having regard to the different circumstances of age, sex, and temperament, of strength and weakness, it is doubtless to be done by enquiring if under these circumstances a greater number of individuals have been cured by one means than another. Here again it is necessary to count. And it is, in great part at least, because hitherto this method has been not at all, or rarely employed, that the science of therapeutics is still so uncertain; that when the application of the means placed in our hands is useful we do not know the bounds of this utility." Louis goes on to detail some of the necessary precautions, "in order that the calculation may lead to useful or true results it is not sufficient to take account of the modifying powers of the individual; it is also necessary to know with precision at what period of the disease the treatment has been commenced; and especially we ought to know the natural progress of the disease, in all its degrees, when it is abandoned to itself, and whether the subjects have or have not committed errors of regimen; with other particulars." The method was not likely to be easy. "The only reproach which can be made to the Numerical Method . . . is that it offers real difficulties in its execution. For, on the one hand, it neither can, nor ought to be applied to any other than exact observations, and these are not common; and on the other hand, this method requires much more labour and time than the most distinguished members of our profession can dedicate to it. But what signifies this reproach, except that the research of truth requires much labour, and is beset with difficulty." The most famous example of Louis's use of this method is in his *Recherches sur les effets de la saignée.*"[68] He studied the effects of bleeding upon 78 cases of pneumonia, 33 cases of erysipelas, and 23 cases of inflammation of the throat; he found no appreciable difference in mortality or in duration or type of symptoms or signs between patients bled and those not bled or between patients bled at different stages of the disease. This result, which was contrary to orthodox teaching of the time, caused an uproar among French physicians, but it dealt a fatal blow to the "depletive" treatment then in vogue.

A quite different approach to research in therapeutics was also developed in the early nineteenth century. This was based on tests in animals and its great exponent was Magendie (1783-1855). Similar methods had been used sporadically for many years but now many new chemical substances were being prepared and many alkaloids identified, particularly by French scientists. Magendie and his co-workers tested these substances upon animals to investigate their toxicities and pharmacologic actions. In this way halogen compounds, strychnine, emetine, quinine, morphine, and other drugs were introduced to medicine. Magendie, in his preface to the *Formulaire* states, "la manière d'agir des médicamens et les poisons est la même sur l'homme et sur les animaux"[69] and, with confidence in this belief, trials upon man were limited to confirmatory tests, upon healthy persons, of the pharmacologic actions observed in animals. Such an approach is highly appropriate for drugs used to obtain a physiologic response or for symptomatic treatment but it is inadequate for the assessment of curative value. Pharmacologic investigation is a valuable and perhaps essential prerequisite for a clinical trial but it cannot be a satisfactory substitute.

The rapidly increasing knowledge of chemistry, physiology, and pharmacology made the need for good clinical trials increasingly evident. Several attempts were made to clarify the requirements of a satisfactory trial. An American physician, Elisha Bartlett (1804-1855), in *An Essay on the Philosophy of Medical Science*, which he dedicated to P. C. A. Louis, said that in therapeutic investigations cases which are to be compared must have equal disturbing factors of location, social class, and the like; they should be susceptible of a clear and positive diagnosis; there must be no selection of cases; and the method of treatment must be clearly defined. The certainty of results, he said, will be "in proportion to the fixed and uniform character of the compared facts and to the greatness of their numbers." Bartlett was well aware of the dangers of unbalanced use of the method. Countering the accusation that it tended to therapeutic nihilism, he points out that certain orthodox procedures though they had received no formal trial had been "established by a series of observations of such vast extent as to compensate in a good degree for the absence of the other conditions." It is interesting to note that in this category along with quinine for intermittent fever, opium for colic, and calomel for syphilis he includes bleeding for acute pleurisy, although he warns that "even in these cases it is only by a faithful adherence to the rules and methods which have been described that the exact value of the several remedies can be ascertained." Bartlett dealt also with the danger of losing sight of the individual in the statistical group, "No acquaintance, however perfect, with the laws of pathology and therapeutics, can ever remove, or in any degree diminish, the necessity of a thorough and discriminating study and knowledge of the single instances which unite to make up the materials of the law."[70]

The influence of Louis was particularly important in the development of scientific medicine in America[71]; one of his admirers, Oliver Wendell Holmes (1809-1894), in a lecture given in 1860, analyzed the errors which led to over-medication. He cited incapacity for sound observation, inability to weigh evidence, the counting of only favorable cases, the "post hoc ergo propter hoc" fallacy, and failure to learn from experience. Holmes further laid part of the blame on the public which "insists on being poisoned."[72]

Clinical trials on the lines of Louis's suggestions were made in Great Britain by Bennett in Edinburgh and Sutton in London. Bennett in 1865 reported his experience, over 20 years, with 129 cases of pneumonia treated on "restorative" principles. He analyzed his patients carefully in respect to sex, age, severity, mortality, and duration of illness and was able to compare his results favorably with those of other series treated by more heroic methods. He also showed that his treatment gave good results in the hands of others and concluded that bleeding and the use of tartar emetic should be abandoned.[73] Also in 1865 Sutton published a trial made upon patients with rheumatic fever under the care of Sir William Gull. At the time, claims were made for a multitude of treatments for this condition and the trial consisted of the careful observation of 20 patients receiving only mint water. The results demonstrated the great natural variation in the disease and the marked tendency to spontaneous curve. Sutton concludes, "A perusal of the above cases tends to show that the best treatment for Rheumatic fever has still to be determined, and will also convince the reader . . . that it is absolutely necessary to understand the natural progress of the disease before any conclusion can be arrived at concerning the operation of remedies. The cases show that too much importance has been attached to the use of medicines, especially in those acute cases where the tendency to a natural cure is the greatest."[74]

Parallel with these developments in medicine, surgery was making enormous strides since the introduction of general anesthetics (1842-1847). The precise priorities of the discoveries are still disputed but it is clear that all the early trials of anesthetics by Long, Wells, Morton, and Simpson were made on very few patients.[75] The unconsciousness of the patient and his subsequent recovery were sufficiently evident not to demand formal control cases nor large series. As it happened, none of the early agents had marked long-term ill effects nor was individual variation of great importance, so the small numbers and short period of study of the early trials did not lead to serious error on these scores. Research into the best methods of administration was made by Snow (1813-1858), who in 1858 published *On Chloroform and Other Anaesthetics*.[76] Here he summarized a wealth of observations both experimental and clinical which could only have been made by someone who, like Snow, combined a scientific approach with the great experience in one field made possible by specialism.

The other great development of nineteenth century surgery was in antiseptic and aseptic methods. Lister (1827-1912) introduced his new techniques initially as rational procedures to avoid sepsis and supported his arguments by the evidence of a few carefully followed cases. In 1870 he published his statistics for amputation operations and compared 35 cases before the use of antiseptics with 40 cases treated by the new method. He showed a mortality of 43 per cent in the former and 15 per cent in the latter but was diffident about drawing conclusions saying, "These numbers are, no doubt, too small for a satisfactory statistical comparison. . . ."[77] Our comment now might be that the numbers are not at fault for the chi square test shows them to be highly significant; what is more open to question is the adequacy of the comparison with previous experience since so many relevant features such as selection of cases for operation must also have changed. Had it been possible, a careful comparative trial of rival methods at this stage might have prevented the bitter and profitless controversy which raged for many years on the subject of the importance and technique of prevention of infection at operation.

The increasing knowledge of bacteriology led to many new applications of immunity to therapeutics. The earliest trial was of Pasteur's vaccine for the prophylaxis of anthrax in animals. The experiment of 1881 is vividly described by the *Times* correspondent[78]: 60 sheep were used; 25 were inoculated and infected, 25 were infected only, and 10 were neither inoculated nor infected. Care was taken that the infecting virus was given in equal doses, the skeptical Colin shaking the phial himself and the injections being alternated between protected and unprotected animals at the suggestion of other critical observers.[79] The results could hardly have been more conclusive; of the infected animals all the uninoculated died and all the inoculated survived. The discovery was immediately hailed as a triumph and applied practically.

Pasteur's method for immunization against rabies was more difficult to validate conclusively. It was recognized that the disease was fatal once a person was infected, and Pasteur was able to show that his vaccines gave recovery in patients believed to have been infected. The claim for the effectiveness of the injections was doubtless reasonable, but it has subsequently been very difficult to appraise modifications of Pasteur's technique since treatment cannot morally be withheld though evidence of genuine infection is often scanty.[80]

Increasing knowledge of metabolism and nutrition was followed by corresponding advances in therapy. One of the earliest dietetic trials was made by Takaki in the Japanese Navy. Study of official records showed him that until 1883 beriberi accounted for one-half of the fatalities and much of the invaliding. After making a review of the possible causes in the same way as Lind did 150 years earlier, he decided that the food must be at fault. A more generous diet was introduced in 1884 and from then beriberi began to decline and was eliminated by 1886.[81] This was achieved in ignorance of vitamins and success was attributed rather to increased protein allowances.

In 1891, treatment of myxedema by thyroid extract was introduced by Murray.[82] Kocher had described the development of myxedema in man following extirpation of the thyroid gland and Horsley had produced similar results experimentally in monkeys. Murray had some diffidence in reporting a single successful case since "some cases do improve to a certain extent when untreated," but he considered that return of perspiration and menstruation after 4 years suggested real benefit. An efficient, although perhaps not conclusive, trial was here achieved by careful observation of the effects of a simple replacement therapy and its results were fully supported by subsequent experience.

The continued rapid growth of bacteriology at the end of the nineteenth century led to the preparation of a therapeutic serum for diphtheria. Behring, Boer, and Kossel[83] described the early trials of this, quoting 30 patients treated of whom 6 died, and comparing this result with the then usual mortality of about 50 per cent and with the previous year's experience at the same hospital when 21 of 32 patients died. The authors said that more cases would be required to prove the value of the new treatment. Statistically their figures are significant if the cases were comparable throughout.

The following year the rival French school published a study of 300 diphtheria patients treated by serum.[84] A mortality of 26 per cent was observed after various corrections for anomalous cases, and this was compared with a 51 per cent mortality during the previous 4 years at the same hospital and with a mortality of 60 per cent in concurrent cases at another hospital. The series were compared as far as possible in respect to type of illness and severity and it was shown that the patients treated with serum had a lower mortality in each group.

An attempt to eliminate the uncertainities of inadequately controlled trials of this treatment was made by Fibiger[85] in Denmark. He used the serum for alternate cases of diphtheria and analyzed the "treated" and "untreated" series for comparability in age, symptoms, and severity. He then compared the results, within age and severity groups, for mortality, extent of diphtheritic membrane, pyrexia, paralysis, and albuminuria. He was able to show that the mortality was less among the serum-treated, that the membrane disappeared sooner, and that pyrexia, albuminuria, and paralyses were unaltered. This excellently conducted trial was less valuable than it otherwise might have been because, although adequate numbers were studied, the disease at the time happened to be very mild—the over-all mortality in 488 cases studied was only 8 per cent.

Other studies of immunity at the end of the nineteenth century led to the introduction of prophylactic inoculation for typhoid fever. Wright[86] reported the comparative statistics of incidence of the disease in various units of the Army in India. Of more than 11,000 men about 3,000 had received inoculation; less than 1 per cent of these developed typhoid. Among the remaining 8,000 unprotected men the incidence was 2.5 per cent. The circumstances of this trial prevented randomization of the prophylaxis among the men and the possibility of differerences in susceptibility and exposure cannot therefore be excluded. A more evident difficulty arose from the necessary reliance upon many different observers to diagnose the disease and record its presence or absence. These observers were army doctors who would inevitably vary in skill and in interest in the trial. While the results clearly suggest a degree of protection achieved by the inoculation, they cannot be considered conclusive.

THE TWENTIETH CENTURY

The enormous development of organic chemistry, parallel with the previously mentioned growth of bacteriology, laid the foundation for chemotherapy, the greatest contribution of our age to medical treatment. At the turn of the century Ehrlich began his search for trypanocidal agents. His success with arsphenamine in vitro led to its trial first for syphilis in the rabbit, then for the human disease. From the animal experiments Ehrlich believed he had achieved his aim of a "magna therapia sterilans" and the early trials of arsphenamine were made on this assumption. Wechselmann[87] reported on 9 patients, each treated with a single dose of the new drug. In several, rapid clinical improvement occurred but failure in others was attributed to the use of too small a dose. Although the Wassermann test had been introduced 4 years earlier, it does not seem to have been used routinely in these early trials of "606." Relapses soon showed that persistent treatment was necessary, and, as further chemotherapeutic substances were developed, increasingly stringent tests of their effectiveness were used. Such criteria are listed by Moore and others[88] and include the rate of disappearance of surface organisms, of clinical healing of lesions, and of seroreversal; the proportion of clinical and serologic relapses; the occurrence of spinal fluid changes; and the number of resistant cases.

Meanwhile, several established drugs were subjected to renewed trial. Digitalis, which had been studied so profitably by Withering in the eighteenth century, was assessed in more modern terms by Mackenzie.[89] The general approach was almost unchanged; a wide range of carefully studied cases was reviewed in which standard preparations of the drug had been used along with the latest techniques of examination. The results confirmed and elaborated Withering's findings.

A trial of emetine by injection for the treatment of amebic infections was made by Rogers,[90] who published a favorable report based on 3 patients who were not able to take ipecachuana by mouth. All made quick recoveries on a low dosage. The small number of patients, the vagaries of the usual clinical course, and the absence of a long follow-up make this trial by itself unconvincing, but other workers soon confirmed the results.

World War I raised new problems of large scale prophylaxis and treatment in medicine and surgery. Routine tetanus antiserum for the wounded was introduced at the end of 1914. The incidence and severity of tetanus fell dramatically,[91] though it is conceivable that change of terrain or of surgical procedures may have contributed to this result. The evidence in favor of prophylactic antityphoid and anticholera inoculation and the value and limitations of the chi square method of testing such data were reviewed by Greenwood and Yule.[92] In the treatment of wound shock the use of gum-saline solutions was a major advance.[93] This was based on sound physiologic theory and its value was first demonstrated upon experimental shock in animals. Its freedom from immediate toxicity was also tested and its effects in the resuscitation of a series of patients were carefully observed;[94] the delayed effects upon the liver which have since caused gum-saline to be abandoned were overlooked.

The aftermath of the war provided both the stimulus and the opportunity for accurate clinical trials of the treatment of rickets. In Vienna the disease became very common in children's hospitals and was there believed to be of infective origin. The diet given in treatment was grossly deficient in vitamins. A team of British research workers was thus able to make a conclusive controlled trial of vitamin supplements and irradiation, with corrections for other factors such as season of year and exposure to sunlight.[95] An exceptional type of control was available for some of the observations. A child treated for scurvy and rickets was found to have a twin brother elsewhere in the hospital with whom progress could be compared. Photographs of the two show the enormous improvement following vitamin therapy.[96] Another problem repeatedly attacked was the assessment of prophylaxis against the common cold and other respiratory infections by immunization.[97,98] These trials, though having unspectacular results, developed controlled investigations upon large numbers of persons to a new stage. For instance in the second study the element of suggestion was minimized by treating all the subjects similarly so that only the research workers knew which had received the saline and which the vaccine injections. The first part of this trial included only volunteers, but in the second part, in order to increase the numbers of observations, nonvolunteers acted as controls. It is interesting that the two parts gave similar negative results so that in this particular example of a trial upon a fairly homogeneous student population the less stringent comparison between treated volunteers and control nonvolunteers seems to have been sufficient.

The two great therapeutic advances of the postwar decade were of a physiologic type. Banting and Best's introduction of insulin for the treatment of diabetes was initially based upon experiments on pancreatectomized dogs;[99] careful trial followed of the effects upon the blood sugar, glycosuria, ketonuria, and general condition of diabetic patients.[100] The other outstanding development was the demonstration of the value of liver treatment for pernicious anemia by Minot and Murphy.[101] These workers had previous wide experience with the disease and knew that they might expect spontaneous remissions in about one-third of cases. They gave the liver diet to 45 patients in relapse and found that all improved and remained cured so long as they continued treatment; 3 who stopped treatment suffered relapse. Hematologic studies showed that the first response was the rise in reticulocytes and that clinical improvement could be recognized a few days later. This trial shows how much can be achieved without formal control cases when a markedly successful treatment is tried upon a chronic condition and the results are cautiously interpreted.

The treatment of lobar pneumonia by sera was the subject of several extensive and careful trials. Cecil[102] treated several hundred cases in certain wards with serum and in others without. Typing of the pneumococci made precise comparisons possible and the mortality results showed an improvement with the serum in all but the Type III infections which were almost unchanged. Park, Bullowa, and Rosenblueth[103] made a similar trial treating alternate patients with serum. Typing was also used but the authors point out that randomization of cases within serologic types was not feasible since treatment must begin before a typing result is available. The conclusions were very similar to those of Cecil and were subsequently confirmed in other trials.

New assessments of drugs used for chronic cardiac disease were made by Sir Thomas Lewis and his school. Harris[104] made a study of the long-term results of quinidine treatment of auricular fibrillation. Lewis[105] gave a detailed clinical description of the effect of amyl nitrite upon 4 cases of angina pectoris. A complementary study of the same and alternative drugs was made by Wayne and Laplace[106] upon the functional capacity of patients with angina estimated by the amount of exercise required to precipitate pain. This group of trials had in common an emphasis upon precise diagnosis and careful clinical observation of relatively few patients. The diseases studied were of chronic and sustained type so that the treated patients themselves could be considered as controls. The careful accessory observations provided not only an estimate of the utility of the remedies but also new information on their mode of action.

The hypothesis, based on animal experiments, that vitamins had a prophylactic value against infection was tested by Green, Pinder, Davis, and Mellanby.[107] They studied the incidence of puerperal sepsis in 550 women when supplementary vitamins A and D were given to alternate admissions. The treated and control series were carefully analyzed for comparability in respect to parous state, age, and the like. The results showed a consistent improvement in those receiving the vitamins in all clinical severities of sepsis. The official standard of puerperal morbidity was felt to be inadequate since, in spite of the evident and statistically significant lowered incidence of sepsis, judged by the morbidity standard, there was no significant advantage.

The years since 1935 have possibly seen more clinical trials than occurred in the whole of previous medical history. It is evidently not feasible to review even briefly all these recent therapeutic studies. Instead a few examples only will be considered representing the fields of chemotherapy, substances used for their physiologic effects, and antibiotics.

Domagk's announcement in 1935[108] of successful treatment by Prontosil of experimental streptococcal infection in animals led to numerous trials of the sulphonamides for human disease. Colebrook and Kenny[109] and Colebrook and Purdie[110] showed that Prontosil and sulfanilamide were effective in puerperal sepsis. They observed a mortality rate of 8 per cent which they compared with the finding of 22 per cent for the previous years at the same hospital where the condition had long been studied. In 1937 Snodgrass and Anderson[111] showed in a controlled trial upon 312 patients that Prontosil shortened the durations of spread, of primary pyrexia, and of toxemia in erysipelas. Control groups received ultraviolet radiation therapy or scarlet fever antitoxin. Their comparability with the group receiving Prontosil was checked in respect to age and state and severity of the disease. The authors noted that mortality in this condition was too small for it to be a useful criterion of comparison. Evans and Gaisford[112] demonstrated the value of sulfapyridine for lobar pneumonia by a controlled trial in which 100 alternate patients received the drug while the other 100 had routine nonspecific therapy in the wards of colleagues. The comparability of the patients in sex and age distribution were tested. The case mortality of the sulfapyridine series was 8 per cent compared with 22 per cent in the controls. Further comparisons are offered with the results at other hospitals and previously at the same hospital which showed a mortality similar to that of the control series in the trial. Banks[113,114] showed that the mortality from meningococcal meningitis could be reduced spectacularly. He first used a variety of doses combined with serum treatment and in this series 16 per cent died; those receiving larger doses did better, so in a second series adequate amounts of sulfanilamide or sulfapyridine only were given and of 67 patients so treated only one died. The trial also provided valuable information on dosage, route of administration, and the resulting levels in blood and cerebrospinal fluid. No formal controls were arranged, comparisons being implied with the previously uniformly high mortality in this clearly defined disease and with the intermediate results in the first inadequately treated cases. A trial of sulfonamides by Wagle and others[115] during an epidemic of plague in Bihar is an interesting example of what can be achieved in difficult circumstances. Successive admissions to an emergency center were treated either with antiplague serum or iodine, a common Indian remedy, or sulfonamide. Treatment was commenced before completion of diagnosis by culture; negative cases were subsequently excluded. Other exclusions had to be made because some patients discharged themselves, but enough cases remained to show that sulfonamides reduced the mortality to less than half that of the iodine-treated controls. A similar advantage was also shown when the more severe septicemic cases were considered alone.

Another field of advance in chemotherapy has been that of the antimalarial drugs. Methods of study analogous to those of the sulfonamide trials have been used but there have been further special features. Therapeutic infections with malaria in the treatment of general paralysis provided a supply of known cases of standard type on which antimalarial therapy could be tested. The results of such studies were reported by the League of Nations Malaria Commission.[116,117] The definite course and symptomatology of the induced disease and the clear criteria of cure made it possible to give precise comparisons of the effects of different drugs and treatment routines. The ease with which the experimental disease could be produced made it possible also to use otherwise normal volunteers for trials either in hospitals where detailed responses could be studied or under various conditions of stress simulating active service conditions. The latter method was used in a large scale wartime trial on the chemotherapeutic suppression and prophylaxis of the disease in the southwest Pacific area.[118,119] The research team included entomologists to supply the infected mosquitoes, pathologists to study the effect of the drugs upon parasites and patients, and clinicians to look after the patients, supervise therapy, and study the clinical course of the disease. Infected treated volunteers were compared with infected untreated controls for occurrence of the disease, appearance of parasites in the blood, and capacity to infect other volunteers by subinoculation. Not only was the great value of mepacrine and later that of Paludrine clearly established, but new ancillary information on the life cycle of the malarial parasite was obtained; further, this and the prewar trials at last firmly assessed the antimalarial status of quinine after it has been in clinical use for 300 years.

In addition to the spectacular developments of chemotherapy for infection there has been progress in the use of substances acting upon the disordered physiology of disease. Transfusion of burned patients with plasma is an example. Black[120] made a careful study of the biochemical and blood volume changes produced by such treatment in a small series of patients. The findings before, during, and after the transfusion were compared and further comparisons were made between patients receiving different quantities of plasma for different severities of burning. A therapy with a less definite rationale but which presumably acts upon the physiology of the circulation is the treatment of migraine with ergotamine tartrate. Lennox and von Storch[121] reported a trial upon 120 patients in whom other treatment had failed. Given by various routes, the drug relieved consistently the attacks of 109 of these people; this was contrasted with the previous unsuccessful treatment of this chronically recurrent condition in the same patients. O'Sullivan[122] reported a similar trial; experience over several years had suggested to him the value of ergotamine, so he made a trial of it on 97 patients during 2 years. This showed abrupt termination of attacks in 89 of them and of 1,132 headaches 92 per cent were immediately relieved after the use of the drug. No data are given to indicate how many attacks would have subsided spontaneously nor in how many the psychologic effects of the therapy of this largely subjective disease may have played a part. Comparisons are available only with the previous general experience of the disease, the observer's previous experience of the disease when treated with other drugs, and the previous course in the same patients. The striking results give presumptive evidence of the value of ergotamine but cannot be considered conclusive.

The possible value of methionine for infective hepatitis was suggested by biochemical and histologic studies in animals. Wilson, Pollock, and Harris[123] studied 100 cases of this disease, giving alternate patients a dose of methionine in orangeade, while controls received the orangeade only. Treatment was otherwise similar and the two series were checked for comparability in respect to age, stage and severity of disease. Comparisons of the durations of anorexia, jaundice, liver enlargement, liver tenderness, and hospital treatment and of the incidence of relapses showed slight and insignificant advantages among the patients treated with methionine. Higgins and co-workers[124] made a similar trial upon a smaller series of alternate cases. They followed these patients very thoroughly and checked the quantities of extraneous methionine given in the diet. Their conclusions were similar to those of the other workers.

Penicillin, still the outstanding antibiotic, was first subjected to full clinical trial by Abraham and associates.[125] The scarcity of the material determined the selection of a few desperately ill patients, several of them children, so that maximum results could be obtained with small quantities. Dramatic improvement resulted although administration was stopped early and some relapses then occurred. Apart from trouble with pyrogenicity due to impurities, the low toxicity was established. When more penicillin became available the trial was extended on similar lines to more cases and systemic dosage was arranged to maintain inhibitory blood levels against the causal organisms.[126] The development of methods of detection and estimation of the drug greatly aided the precision of this trial and its conclusions have since been amply confirmed. No formal controls were used but the implied comparison of the clinical course of these patients under treatment with that before treatment and with the known prognosis is sufficiently convincing. Further confirmation was provided by the demonstration of the mode of action of the drug in that bactericidal levels could be shown in body fluids which corresponded to changed bacteriologic findings and clinical improvement. The effects of local application of penicillin in 15 patients with war wounds were investigated by Pulvertaft[127] who reported a great improvement in infections with gram-positive organisms but no effects upon gram-negative infections. The clinical effects of penicillin in the treatment of such wounds were studied in North Africa and in an extensive trial conducted in the 21 Army Group.[128] For this the cooperation of surgeons was enlisted to compare the effects of penicillin with those of the most favored alternative in the treatment of similar conditions of infection. The period of healing was used as criterion of success. It was soon found that allocation of cases was not impartial since surgeons did not feel justified in withholding penicillin from the more seriously injured. In spite of this adverse loading of the scales the penicillin group did demonstrably better. In retrospect this trial would appear to have been more successful than might have been anticipated with such indirect organization and multiple observers. Had penicillin been less effective the biased control might have caused an inconclusive result; since the effect was so great perhaps a smaller and more precise trial would have demonstrated it with greater efficiency. While supplies of penicillin were still short, a large-scale planned trial of its value in subacute bacterial endocarditis was begun.[129,130] Fourteen treatment centers were organized, and different treatment schedules allotted to different centers. No controls were arranged, since the universally bad prognosis of untreated cases provided sufficient comparison. All centers at first gave a total of 5 million units, but the length of the course was varied. This showed that a prolonged course gave the highest rate of cure for a given total dose, so in the second period all patients had a long course but the daily dosage was varied. By this method of successive approximation invaluable information was obtained on the treatment of this extremely serious disease. As it happened, the optimal dosage does not seem to have been "straddled" in either of the sections of the trial and work has continued on yet higher doses for longer periods. A less severe condition in which the relatively slight effect of penicillin makes precise controls imperative is that of finger pulp infections. Various series have been published in which the results with use of penicillin have been compared with those of preceding or subsequent cases. Conflicting conclusions were drawn but a carefully controlled trial clarified the problem.[131] Patients were first admitted to the experimental series and were then randomly allocated to the different treatment groups. Detailed clinical progress was recorded and a considerable advantage could be demonstrated in patients receiving systemic penicillin. As frequently happens in such studies other improvements in treatment were developed during the trial but each such improvement was applied equally to "treated" and control cases. Had concurrent controls not been used, the effect of these changes would have been confused with that of the treatment under trial. There would seem to be many opportunities for trials of this type where several factors in the therapy, such as incision, rest, and chemotherapy, are important but where the optimal balance cannot easily be determined.

CONCLUSIONS

Although the clinical trial is one aspect of scientific medicine, its status as a scientific experiment is modest. The full sequence of observation-theory-hypothesis-experiment-validation is not usually invoked. The "hypothesis" is usually very simple—that the test treatment is better than some other treatment. Procedurally this is equivalent to problems in technology, such as the building materials to be preferred for certain purposes or the most efficient driving mechanism for a piece of machinery. Such problems were being solved by a simple form of experimentation long before the modern scientific era. Their solution does not necessarily imply any appreciation of inductive reasoning such as was introduced by Francis Bacon and Galileo in their advancement of scientific method. It is therefore not surprising to find that the principles on which satisfactory trials could be based were already implied in classical writings,[9,11] described in detail by Avicenna,[15] and the peculiar difficulties of experiment in medicine recognized by Roger Bacon.[17] In spite of this there are very few records of tests of therapy until the last two centuries. Why this should be must remain speculative, but certain factors can be seen to be relevant:

1. *Reverence for Authority.*—Until modern times the current habit of mind was to deduce "facts" by argument from premises approved by tradition and authority without appeal to experimental validation. Even when observation ran counter to such "facts," as for instance in the case of Jesuits' bark, it was still felt that perhaps in some more mysterious way authority must still be right. Many of the leaders of scientific development, such as Roger Bacon, Leonardo da Vinci, and Harvey, continued to favor traditional therapy, and even pioneers of clinical trials often failed to rely upon their own findings. Having demonstrated the effect of fruit in the cure of scurvy, Lind recommended change of air as the first requirement of treatment; similarly after Louis had shown the futility of bleeding in a variety of conditions he still continued to advise it for the hemoptysis and pleurisy of phthisis. The emergence of the modern therapeutic trial is thus an aspect of the growth of reliance upon impartial observation as the foundation of scientific medicine.

2. *The Relationship of Doctor and Patient.*—Roger Bacon early called attention to this difficulty in the scientific approach to medicine. The patient needs to be cured, and there are important ethical considerations in an experimental therapy; the doctor tends to adopt an authoritarian attitude; the organization of careful comparative study is inconvenient in a busy practice.

3. *The Paucity of Records.*—The recording and publishing of scientific evidence is a relatively recent development. Printing was a prerequisite for large-scale dissemination of new findings and even after the development of printing it only gradually became a recognized and easy method of scientific communication.

4. *Lack of Facilities for Investigation.*—Until the eighteenth century, hospitals were inadequate and unsuitable for sustained studies. Techniques of accurate diagnosis and assessment of cure were lacking, and until hospitals had been organized as functioning units there were few opportunities for specialization so that sufficient numbers of cases of the same type could be studied by one person.

5. *Polypharmacy.*—From ancient times through the Middle Ages and even now in some places, polypharmacy pervades medical treatment. It implied exact information on the effect of the ingredients of a mixture and of their interaction when in combination. This information did not really exist, and the practice of polypharmacy helped to perpetuate this ignorance.

6. *Lack of Active Remedies.*—This must be a main reason for the absence of early clinical trials. Apart from a few agents such as mercury, quinine, opium, and purgatives, few really active materials were available until the nineteenth century, when with the development of organic chemistry and later biochemistry and bacteriology a multitude of new and active products stimulated the demand for reliable clinical trials. Parallel with the discovery of new remedies came a more critical appraisal of current treatment, and it is noteworthy that many of the early trials discredited the claims of charlatans or of traditional therapy.

The history of clinical trials gives an indication of the circumstances in which they can be successfully and easily performed, and conversely the sources of difficulty. The therapy should be simple and measurable so that it can be applied similarly on all occasions. The condition treated should be clearly definable and either of regular severity in different patients or of measurable severity so that similar cases can be grouped together. This can sometimes be achieved by experimental induction of the disease. A satisfactory comparison must be available between treated cases and cases otherwise similar but not receiving the treatment under test. This may be provided by a known uniform prognosis in untreated cases, by use of alternating control periods in chronic diseases, or by randomization of different cases into treated and untreated series. The criteria of success and failure should be clear and should be recognizable early. Preferably they should be chosen so that the control cases show a high proportion of "failure" since the trial may otherwise be prolonged or inconclusive. The trial will further increase in efficiency the more regular is the clinical material and the more constant and marked the effect of the therapy. A controlled trial offers an enormous increase of precision over other methods, but it is still imperative that the soundness of the comparison be critically examined. Results must be carefully interpreted so that conclusions drawn are within the limits of the logical structure of the trial and due regard to special experimental conditions should be paid when the findings are applied clinically.

A difference between trials in medicine and surgery has been noted: whereas surgery made great progress in ancient times, the development of medical therapy was delayed until recent years. Part of this discrepancy can be attributed to the differences in the respective clinical trials demanded. Much of surgery deals with lesions of simple etiology and diagnosis, and the application of simple mechanical principles often produces immediate spectacular results. Suturing of wounds and reduction of dislocations and fractures give evidence of success at once and leave little opportunity for elaborate theorizing. The fundamentals of such treatment had already been worked out in ancient Greece and Egypt. By contrast, few medical conditions could be understood until ancillary scientific methods had been developed. The aspects of medical diseases which could be appreciated, such as fever, dropsy, jaundice, or wasting, were of such varied etiology that any but the simplest treatment by rest or diet would have inconstant effects and even if active agents were available the results would seldom be immediately apparent. It is thus not surprising that superstition and scholastic theorizing thrived and few therapeutic advances were made.

It seems possible that the success of simple surgical trials in the past has led workers to believe that similar methods remain applicable to the complex procedures of modern surgery. In his criticism of the validation of gastrojejunostomy, Ryle[132] pointed out that trial and error methods have been repeatedly misleading and that, in the absence of controls, adequate follow-up of patients, and statistical analysis, such an operation cannot be fairly assessed. The effects of extensive surgery can be quite as complex as those of elaborate medical therapy. Not only must immediate operative mortality and the achievement of anatomic success be considered but also late effects of altered function and possibly secondary disease. Such a situation demands the same care in the planning of a satisfactory clinical trial as does the detailed assessment of a new and potentially dangerous antibiotic.

The unintentional "trials" of wound treatment made by Paré and Hunter were incidental to the usual routine of practice. In a comparable way some modern trials have been incidental to other studies. The observations of Anning[133] on the effects of calciferol upon chilblains provide an example. The occurrence of chilblains in patients receiving this treatment for other complaints was compared with their occurrence in patients not so treated. No difference was found between the groups. Studies on the pathogenicity of certain organisms can also be profitably combined with tests of antibacterial therapy; this has been done in trials of local antibiotics for burns.[134,135] This integration of therapeutic trials with other aspects of medicine is further shown in the diagnostic advances made in Withering's study of digitalis and the Vienna studies of rickets and in the new information on the life cycle of *Plasmodium vivax* which resulted from Fairley's trials of mepacrine and Paludrine. A thorough trial inevitably involves a close study of patients, often a large number of similar ones. It is therefore not surprising that other discoveries may be made even though they are not anticipated.

The present century has seen an intensification of therapeutic problems, not least by two World Wars, an increase of facilities for their study in hospital and laboratory accommodation and in research organizations. As well as the continued production of new remedies from bacteriology, there have been added contributions from organic chemistry such as the arsenicals and later the sulfonamides. More recently still, from bacteriology, the antibiotics have been introduced and some of them have been synthesized. There is increasing appreciation of the importance of adequate controls and in other fields new statistical methods have been developed, many of which still wait to be fully applied to clinical trials.

The stage is set for great therapeutic advances in which clinical trials must play an important part. This is not to say that all features of therapy should be subjected to trial; some are too minor for the effort and expense to be justifiable, others too complex to be feasible. A reasonable balance would seem to be the establishment of crucial principles by careful clinical trials followed by practical application of the conclusions, modified where necessary in the light of scientific and clinical knowledge. At a later stage an assessment of results may be possible which will check whether or not the modifications are justifiable. Further exploratory tests can be made as new treatments become available or inconsistencies appear in results, and in due course a new full-scale trial will be required. In this way therapeutics should advance by a series of steps, careful trials providing at each stage a firm basis for exploratory hypotheses and experiments which can assist in determining the next advance.

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