Drug Discovery
A History

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The quest for the elixir of life by the mediaeval alchemists may not have resulted in success, but the last one hundred years have witnessed the introduction of a number of drugs that have literally saved countless millions of lives. Society at large is indebted to the men and women in the laboratories and clinics of the pharmaceutical industry, research institutes, hospitals and universities whose commitment to science has brought about what in an earlier era would simply have been called miracles. This book is dedicated to these men and women.
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Preface

The contents of this book range from the faltering attempts of our ancient ancestors to discover herbal remedies to the present quest of scientists to develop safe, efficacious medicines. This will enable readers to understand both why efficacious drugs were not developed until the twentieth century and why progress has been so rapid over the past fifty years.

The book consists of three parts. The first part progresses from the possible use of medicinal herbs by Neanderthals on to the endeavours of ancient civilisations in Mesopotamia, Egypt, Greece and Rome. A subsequent consideration of the impact of Greek medicine on the Arab world and then renaissance Europe is followed by an examination of the heritage of the alchemists whose attempts to transmute base metals into gold provided the chemical techniques that allowed purified metallic compounds to be introduced into medicine. After reviewing how the influence of the enlightenment on drug discovery was impeded by the introduction of unsubstantiated medical systems that were popular from the seventeenth to nineteenth centuries, this part of the book concludes with an account of the twentieth century development of life-saving organic compounds incorporating various metals.

The second part of the book examines the commonest source of drug prototypes from which other medicines are derived – the natural world. Prototypes from vegetable, animal and microbial sources are described in separate chapters, as are the medicinal compounds prepared from them. The problem of relying on nature as a source of drug prototypes is confronted.

Modern drug discovery has consisted of a series of thematic developments that began with the isolation of pure alkaloids and glycosides from plants in the early years of the nineteenth century. One hundred years later, a parallel development witnessed the isolation of pure hormones from mammalian sources. The chapters throughout the book are organised so as to heighten awareness of such thematic developments, but this is particularly relevant in the second part of the book.

The third part considers those synthetic compounds that have served as drug prototypes, followed by a consideration of compounds derived from them. The role of serendipity in providing synthetic prototypes is also investigated. The book ends with a cautionary note concerning the future of drug discovery.

The specialist reader will find that the book contains an extensive list of bibliographic references relating to the discovery of drugs, but the book has been written for the general reader. No particular expertise in chemistry is assumed, but chemical structures have been interspersed with the text to enable those familiar with the subject to obtain a deeper understanding. Their presence should also enable others to begin to appreciate why chemistry has appealed to so many great minds. The chemical structures are presented in such a way as to allow even those with little experience of the subject to understand how prototypes and compounds obtained from them were manipulated in order to provide novel compounds with unprecedented healing properties.

Walter Sneader
December 2004
Foreword

One of the best presents I ever had was a copy of Dr Sneader’s 1985 book *Drug Discovery: The Evolution of Modern Medicines*. It was a great introduction to the fascinating world of the way in which many medicines have been discovered, a world of which I had gained only snippets from books on clinical pharmacology. And now Dr Sneader has produced not just an updated version of that book but a completely new work which comprehensively spans the whole subject from the earliest times to the present.

Dr Sneader is exceptionally well qualified to write such a book having trained in both pharmacy and medicinal chemistry. His distinguished academic career at the University of Strathclyde, Glasgow, where he is the Head of the School of Pharmacy, includes the writing of two other acclaimed books, *Drug Development from Laboratory to Clinic* and *Drug Prototypes and Their Exploitation*.

The author takes us right back to the pre-historic period, but he does so critically and with caution as to how to interpret earlier evidence, for example as to when opium poppy was first used. Critical evaluation is a hallmark of Dr Sneader’s writing. I like the way that the book has been divided into three major sections, dealing first with previous history, then with drugs developed from natural compounds and finally with synthetic drugs. Phytochemicals are of especial interest and we know that over 30 modern medicines owe their origin to plants in one way or another. Sometimes a folk remedy has stood by itself, but more often it has been scientific investigation that has either found a new use for the plant substance, or has developed a synthetic compound from it. Here as elsewhere one is continually impressed by the details that the author gives as to who were the actual people making the discoveries. Likewise Dr Sneader has a plethora of fascinating stories, for example the one that recounts how the discovery of coal gas for illuminating the home led to the use of antiseptic treatment by Joseph Lister. In another he relates how the Nazis suppressed the fact that aspirin was developed by a Jewish chemist.

Natural remedies or their derivatives are of great importance but so are purely synthetic drugs, sometimes sneered at by the ignorant as “chemical medicine”, not realising that chemical molecules are the same whether produced by nature or by a pharmaceutical company. The beta blockers owed everything to Sir James Black’s ideas and nothing to the natural world.

Dr Sneader deals with synthetic drugs in one complete section of the book and here as elsewhere our understanding is greatly helped by the chemical formulae he carefully places within the text. This is where his expertise in chemistry is so useful.

A good chapter is the one on screening. Companies are doing mass screening of natural compounds in the hope of finding an interesting looking molecule, and furthermore by combinatorial chemistry they are creating huge numbers of totally new compounds. The author notes that there are 17 million compounds on the chemical register, but will screening find a new treatment for say psoriasis?

It is a pleasure to give a whole hearted commendation to a really fine account of a very important subject, written and written clearly by someone who has a deep understanding of it. There are many references to the literature and the index is excellent.

Arthur Hollman, MD FRCP FLS
Emeritus Consulting Cardiologist, University College Hospital, London
Formerly Chairman of the Advisory Committee of the Chelsea Physic Garden
The quest to discover healing drugs has always been influenced by prevailing social and cultural factors, one of the most important being the ability to communicate what has been learned to others. The success of modern drug research has in no small measure been dependent upon the rapid and universal publication of scientific results. Before the appearance of writing about five thousand years ago, accumulated knowledge and wisdom could only be passed on by word of mouth from generation to generation, or be preserved in epics and poems recited by bards who memorised their content. In some instances, these verses were eventually committed to writing.

According to some, ancient paintings on the walls of caves may hold clues to the early use of drugs that had a pronounced effect on the mind. However, it is only the written accounts that communicate something of the reasoning that led our ancestors to seek out remedies for treating disease, such as those compiled by the inhabitants of Ancient Egypt, Mesopotamia and particularly Greece.

How our earliest ancestors selected drugs is a matter for speculation. Clues may be found by considering the behaviour of contemporary primitive peoples and the nature of their folk medicines. This, in conjunction with the written record, suggests that most societies initially adopted a straightforward empirical approach to treatment of the minor ailments of everyday life, selecting healing herbs by a process of trial and error. Those living in hot, sandy desert conditions sought out soothing balms and lotions to apply to their dry skin and eyes, while others whose diet was deficient in fibre sought herbs to relieve their constipation. The ache following the eating of contaminated foods was relieved by swallowing other herbs that irritated the wall of the stomach to induce vomiting, while the bleeding of minor cuts or the pain of burns was dealt with by rubbing with leaves or barks rich in astringent tannins.

Serious illness was a different matter. Unable to explain how it was possible to be fit and healthy one moment yet be writhing in agony or even dying a moment later, our ancestors turned to magic and the supernatural. The art of healing became inextricably interwoven with magic and religion. Disease was then seen as a manifestation of the power of demonic characters to enter the body, presumably through one of its orifices. Attempts were made to expel these demons through their supposed route of entry by administering drugs that could produce vomiting, purgation, urination or sneezing. An alternative was to administer foul-tasting or obnoxious substances such as dung or dead flies. Sympathetic magic was also employed, whereby properties associated with plants, animals or other objects were deemed to be transferable to the sick. A patient might then have been treated with a skin newly sloughed from a reptile because the act of sloughing was considered to be a process of life renewal. Whether expurgating demons or transferring life-endowing properties, the objective was to treat the demon-possessed patient rather than a specific disease. Therein lies the origins of holistic medicine.

Witch doctors, sorcerers, shamans and medicine men preceded their administration of herbs by elaborate rituals involving fervent dancing, weird utterances, grotesque facial expressions, use of charms and other devices – all likely to have a powerful effect on the mind of the sick.
person and thereby enhance any benefit to be derived from the treatment. Even when belief in magic was undermined by the arrival of both pantheistic and monotheistic religions, the remedies themselves hardly changed. Treatment was instead administered in conjunction with appropriate benedictions rather than the incantations previously uttered in the hope of driving out the demons. The successes seen in those few patients who recovered despite the ministrations of their attendants were probably produced by the incantations and benedictions rather than the medicaments themselves, for these were invariably naturally occurring substances of which few could produce any effect other than purgation. Failure was explained away by asserting that the medicament had not been properly prepared or administered.

Once a truly effective remedy has been recognised, the quest for alternatives usually dissipates or, in our modern era, becomes limited to a few commercially viable alternatives. It is a telling point that the natural products employed in the past, and still favoured in some quarters, were frequently recommended for a wide variety of disparate medical conditions, a feature that is suggestive of a lack of any clearly defined effect. This is not to say that none of the ancient remedies had any beneficial action; the few that did were the exception rather than the rule.

When the philosophically inclined Greeks arrived on the scene, supernatural beliefs were rejected in favour of rational concepts. The quest to find drugs became based on the belief that they had to correct an imbalance in body humours thought to be the cause of disease. This was to have a major impact on the selection of plants for use as drugs.

The writings of the second century physician Galen so convincingly presented the accumulated knowledge of Greek medicine that they dominated medical thinking until the seventeenth century or later. During the Dark Ages, however, medical knowledge became fossilised in much of Europe. The asceticism of the Christian Church fostered the attitude that treating the sick was in the hands of the Almighty alone. Eventually, it was recognised that the soul had still to be cared for and consequently some monasteries became hospitals. These acquired surviving medical manuscripts which monks laboriously copied by hand. Herbal gardens were also established to supply medicines, yet new treatments were not introduced, or if they were then it was in the hands of local folk healers who did not record their observations for posterity.

The Christian influence did not extend to the Arab world. There, ancient texts were translated and given a new lease of life, especially in ninth century Baghdad. Arab physicians took delight in the legacy from their Greek counterparts and compiled treatises that elaborated at length on this and their own contributions to therapeutics. It was from the Arab world that Europe was to rediscover its own medical heritage three centuries later, when the first European medical school was established in the southern Italian port of Salerno. Its influence and that of its successors quickly developed, largely because the Church took steps to prevent the practice of medicine in its monasteries out of concern that it was in danger of becoming their prime activity.

The secularisation of medicine in Europe helped its practitioners to question the authoritarianism that had crippled it for so long. Another factor in this was the introduction of the printing press in the second half of the fifteenth century, which gradually made available the old Greek herbals and the Arab additions to them. By this time the Renaissance was well under way and there were those prepared to challenge the authoritarian views of Galen and his devotee ibn Sina. Prominent among them was the maverick physician Paracelsus. His writings were complex and at times obscure, but they attracted a band of followers who were to change drug therapy. Among them were chemists who strove to isolate active principles from medicinal preparations rather than attempt to transmute base metals into gold as the alchemists had aspired. Initially, they met with some success when using traditional alchemical techniques such as distillation or sublimation to refine metallic compounds. However, when plants were exposed to these techniques, the heat treatment involved destroyed any active principles. All that could be obtained were odiferous waters and a few volatile oils.
ISOLATION OF ACTIVE PRINCIPLES

For any drug to produce a real as opposed to an imagined response, it must at the very least interact at the molecular level with either a component of the body or an infectious microorganism. A drug may also interact elsewhere to produce an undesirable effect. As natural products such as plants contain a complex and variable mixture of chemicals, the risk of unwanted side effects occurring is always high. The simplest way to minimise this is to isolate the component that produces the desired response. While this may be obvious today, it was not the reason behind the successful isolation of active principles in the second decade of the nineteenth century. The sole motivation for this was the need to identify adulterated plant products by determining the amount of active principles in them. Only after this could be done was it recognised that the amounts of these principles varied both quantitatively and qualitatively throughout the life cycle of the plant, being influenced by changing climatic conditions. The time of harvesting, adequacy of the drying process, and nature and duration of storage further influenced the composition of these chemicals.

The inability to identify and quantitatively analyse the active substances in herbal medicines before the nineteenth century means that there is uncertainty surrounding the nature of all herbal remedies used before this period. It may also explain why there was no effective challenge to the beliefs of the ancient healers other than when mineral drugs were recommended, which was from the tenth century onwards. Unlike herbs, these could be purified and analysed due to their ability to withstand high temperatures. They could also survive exposure to strong acid or alkali to form salts that could be refined by crystallisation.

The uncertainty about the identity and quality of ancient herbal remedies meant that they could never be properly assessed in the clinic. Added to that was the total failure of reports about their medicinal applications to even consider, let alone apply, the various factors that we now know must be taken into account when evaluating any drug in the clinic, irrespective of its origin. Thus the ancient and mediaeval medical literature that we have inherited reveals no awareness of that classic example of mind over matter, the placebo effect. Nor does it take into account how patients were selected or how the nature of their ailment was assessed prior to treatment. Indeed, that would have been fraught with difficulty for those whose diagnostic skill was restricted to assessing which of the four bodily humours was present in excess or was deficient. In addition, there was never any attempt to eliminate bias on the part of the attendant physician. As to any consideration of the dose, or frequency and duration of the treatment, little was ever written. Side effects of medication were sometimes even considered to be evidence of their efficacy and at other times a sign of their failure. As for defining what could be considered as a successful outcome, again little was ever written. All of this means that claims made for traditional remedies in the past have no validity.

It is not a matter of commenting unfairly on what was done in the past by applying our modern understanding of the subject. The reality is that out of the myriad of plants and minerals found on this planet, remarkably few possess the ability to relieve disease when rigorously evaluated by the criteria of modern, evidence-based medicine which sets high standards for the conduct of clinical trials. Few minerals are able to penetrate across biological membrane barriers within the body, and if they do they are often highly toxic. As for the chemicals in plants, their very role as irritant or toxic materials that provide a defence against foraging predators is singularly inauspicious with regard to healing the sick. Plants did not evolve for the purpose of producing medicines! There are an estimated 320 000 plant species currently growing in this planet, with perhaps as many as 25 000 of these having been utilised in various systems of folk medicine. Many active principles were extracted over the last two centuries, yet only 120 or so are currently in use around the world. For any single country, the number is much lower; in the United Kingdom fewer than 40 are in regular use in mainstream medicine.
Pharmacologically active compounds from plants became available at the beginning of the
nineteenth century through the technique of solvent extraction. Access to pure alkaloids and
glycosides meant that patients received exactly what the prescriber intended, rather than a
product of highly variable composition, even if it was not adulterated. Furthermore, the ability
of alkaloids to form water-soluble salts meant that parenteral medication became a reality in
the middle of the nineteenth century when the hypodermic syringe was developed.

As more alkaloids and other pure products were isolated, it became obvious that most of
these were highly toxic when administered to patients. This is hardly surprising in view of their
role as poisons to protect the plants from foraging predators. While the ancient materia
medica has certainly been the source of a variety of valuable pharmacologically active
principles, there has been a tendency to underestimate their toxicity. Plant-derived substances
have a role to play, though they tend to be among the most toxic drugs in the therapeutic
armamentarium. It is noteworthy that the herbs promoted by the retailers of herbal nostrums
are supplied in formulations containing low doses for precisely that reason. Homeopathy
developed in the early nineteenth century by taking this approach to the extreme by diluting
toxic plant products to such an extent that patients ingested no active drug at all.

The influence of plant products on drug research has been disproportionate to their
therapeutic value. During the twentieth century, both academic and commercial researchers
spent time in seeking out novel preparations employed by native tribes or users of folk
medicines. The paucity of useful outcomes from this is hardly surprising, for the rationale of
treating the sick with such products is inherently unsound since in most cases the products
were chosen on account of a perceived property such as taste, smell, colour or shape.
Alternatively, plants were selected because of a dramatic effect like purgation, emesis,
sneezing, increased urination, salivation, sweating, stupefaction, hallucination or mood
alteration. Truly effective modern drugs such as antibiotics, antivirals, statins, hormone
derivatives, and the like, are often devoid of any perceptible effect that is related to their
action. If research into plant products is to be more successful in the future, rigorous criteria
for their selection for investigation will need to be developed.

SYNTHETIC DRUGS

The initial enthusiasm for the use of alkaloids and other active substances from plants in the
first half of the nineteenth century was followed by a period of therapeutic nihilism during
which many medical practitioners came to doubt the value of drug therapy. That was,
however, to change with the rapid development of synthetic organic chemistry to meet the
demands of the emergent synthetic dyestuffs industry in the wake of the serendipitous
discovery of mauveine by William Perkin in 1856. This meant that for the first time in history
it was not necessary to rely on nature to provide new drugs. This did not mean that natural
products were no longer important. On the contrary, these have remained the progenitors of
many drugs developed since then, but the universal success of the synthetic hypnotic chloral
hydrate in 1868 and then sodium salicylate seven years later resulted in the emergence of the
industrial production of synthetic drugs. At first these were discovered in universities, but by
the end of the nineteenth century the leading pharmaceutical companies were developing new
drugs in their own laboratories. A significant event at this time was the arrival on the scene of
industrial pharmacologists and chemists specialising in drug discovery.

Initially, chemists simply made minor changes to the chemical structures of natural products
by altering functional groups that had been identified. Some of these were converted to esters
or ethers, while others were alkylated, hydrolysed, oxidised or reduced. By the end of the
nineteenth century, the chemical structures of alkaloids were beginning to be determined. This
meant that analogues could be designed in which only essential parts of the molecule were
retained. In the second half of the twentieth century, the process of analogue design became
highly sophisticated as medicinal chemists wrestled with structural manipulations that both affected transportation of drugs to their intended sites of action and also ensured optimal docking on arrival there. In pursuing their manipulations chemists occasionally stumbled upon molecules that exhibited wholly unexpected activities, thereby extending the available range of pharmacophores. All this activity resulted in many hundreds of valuable new therapeutic agents that generated fortunes for their industrial exploiters. Patients, too, benefited and by the end of the twentieth century drug therapy had become the major mode of bringing succour to the sick. There still remained a strong dependence upon naturally occurring molecules as sources of inspiration for the design of new drugs, thanks to the discovery of mammalian hormones and also antibiotics.

**DRUG PROTOTYPES**

It was not until demonology, astrology and humoral imbalances had been thoroughly discredited that drug research could make progress. Yet until the late nineteenth century its scope had been limited to testing and evaluating readily available natural products. Once organic chemistry had finally developed sufficiently for a limitless range of new drugs to be synthesised, researchers began to modify the chemical structures of natural alkaloids in the hope of finding better products, or attempted to synthesise substitutes for them in order to overcome shortages and high costs of production.

Many of the successes of drug research have involved the preparation of analogues of natural products or synthetic compounds possessing some form of exploitable pharmacological or chemotherapeutic activity. It is helpful to describe the first pure compound to have been discovered in any series of chemically or developmentally related therapeutic agents as a drug prototype. In certain cases, there has been no perceived need to develop a prototype further. Such prototypes continue to serve as medicinal compounds in their own right, but others have been rendered obsolete by the analogues derived from them. In some instances, both the prototype and its analogue even compete in the market-place. In a recent study, nearly 250 drug prototypes were described, from which 1200 medicinal compounds were derived.3

Until the middle of the twentieth century, most drug prototypes were derived from plants. For a period thereafter, the major sources of these were micro-organisms that yielded antibiotics. Throughout the century, however, prototypes were being isolated from biochemical sources and this eventually became the principal route for discovering novel drug prototypes. Spurred by major advances in physiology, biochemistry, microbiology and pathology, chemists were at last provided with the full scope to apply their newly acquired skills. Hormones and antibiotics alike were then altered to limit undesired effects and to permit their administration as medicines that could survive in the human body long enough to exert a useful action. Indeed, the twentieth century was the first in which drug therapy contributed more to the progress of medicine than did any other single factor.

The start of the twentieth century had been marked by the isolation of the first pure hormone, epinephrine (adrenaline), yet analogues of it were not developed until after the introduction of the alkaloid ephedrine in 1926, when it was recognised that it was a chemical analogue of epinephrine with some advantages when used therapeutically. By that time, thyroxine, insulin and acetylcholine had also been isolated, followed by the corticosteroids and sex hormones in the 1930s. This formed the basis for some of the greatest achievements of medicinal chemists in the twentieth century when they later prepared analogues of epinephrine and cortisone in which undesirable effects on the body were largely overcome while leaving desired effects unaltered or even enhanced. This successful exploitation of hormones in drug research had much to do with their natural role, which is to regulate physiological function, not to disrupt it. With plant poisons it is the converse, since their role is to protect plants
against foraging predators. However, the hormones had presented problems when they were selected to serve as drugs. Not only did they often occur in only trace amounts, making isolation difficult, but they were also often chemically unstable. Additionally, when employed as drugs, they lacked sufficient specificity of action, and it required considerable effort by medicinal chemists to develop them into selective therapeutic agents.

During the year 2004, the 25 millionth compound was listed in the registry of the Chemical Abstracts Service. The availability of so many compounds prepared for a wide variety of purposes other than drug therapy has provided opportunities for serendipitous discoveries of unexpected pharmacological activity. In addition, the screening of ever expanding collections of synthetic compounds prepared by drug companies for earlier projects has provided another potential source of novel prototypes.

The first major break with reliance upon natural products as drug prototypes was inspired by the development of synthetic dyes. This was the introduction in 1904 by Paul Ehrlich of the antitrypanosomal agent known as Trypan Red. Developed as a result of screening over one hundred dyes in a quest to find one that would bind to and kill the trypanosomes that caused the tropical disease known as sleeping sickness, Trypan Red proved toxic to the optic nerve and was reserved for veterinary use. Five years later, Ehrlich evaluated arsphenamine, an organic arsenical drug that cured syphilis. It was an analogue of Atoxyl®, a highly toxic compound used for treating sleeping sickness and originally introduced as an anticancer drug in the unsubstantiated belief that it would be less toxic than arsenic trioxide as it was an organic compound. Further dyes and arsenicals were developed from those introduced by Ehrlich, leading to effective chemotherapy against sleeping sickness, malaria and a variety of bacterial diseases.

By the middle of the twentieth century the majority of drug prototypes were no longer gleaned from the plant kingdom. Biochemists had come to grips with delicate molecules harboured within cells and vesicles or circulating in body fluids. The animal organism had now become the single greatest provider of drug prototypes. It has retained that role, rivalled only by prototypes obtained from fungi and other microbes. In the 1940s a therapeutic revolution occurred when the first antibiotics were introduced. However, the vast majority of the antibiotics that have been discovered are, like the products from plants, too toxic for therapeutic application. This toxicity is a reflection of their role in the battle for survival of their host organisms in the natural world.

The range of drug prototypes now includes hormones, cellular metabolites and other substances found in the human body, as well as vitamins and antibiotics. Chemists have used their skills to create new drugs by synthesising analogues of those that exhibited desirable characteristics such as greater safety or efficacy, enhanced stability, improved selectivity or duration of action, superior absorption and distribution characteristics, and so forth. In the closing years of the twentieth century, attempts to generate novel prototypes from which new medicines could be developed moved in a new direction with the introduction of combinatorial chemistry. This permitted the automated synthesis of vast numbers of molecular variants that were fed into high-throughput screening systems in the hope of finding active compounds. While the variants can be analogues of compounds with known activity, the possibility of now screening compounds with no resemblance to anything found in nature may further lessen the dependence upon nature as a source of drug prototypes.

ANALOGUES OF DRUG PROTOTYPES

All drugs exhibit unwanted side effects in at least some individuals. For that reason alone, attempts will always be made to find alternatives so long as it is economically viable to do so. Another reason is the need for commercial companies to hold patents on their products. As these have only a limited lifespan, companies will protect their own interests by seeking
successor products to patent. Whatever the motivation, the simplest and most frequent way of finding an alternative to an existing drug is to synthesise chemical analogues and test these.

Analogues of existing drugs could only be made once pure compounds had been isolated. Some of the first to be made were analogues of morphine, quinine, atropine and cocaine. In these particular cases, the correct chemical structure of the prototype had not yet been determined when its analogues were synthesised. Chemists merely replaced or modified functional groups believed to be present. At first, simple derivatives were made by esterification, hydrolysis, oxidation and reduction. Analogue formation became more sophisticated once the chemical structures of these and other compounds were correctly established and when recognition of the importance of the physical properties of the drug became widespread, especially in the second half of the twentieth century.

Structural modification was used to change lipophilicity in order to control the ability of drug molecules to penetrate biological membranes by passive diffusion; e.g. alkyl side chains were lengthened or shortened to make compounds less or more polar and thus increase or decrease the likelihood of penetrating into the brain. This was followed by a growing awareness of the relevance of constraints placed on organic molecules through the degree of ionic dissociation, which could render potential drugs useless if the charged molecular species was that mainly present in the body. Careful placing of chemical substituents was found to alter radically the tendency of molecules to ionise, thereby enhancing their pharmacological activity.

Apart from altering the physicochemical properties of drugs to develop novel analogues, chemists have also manipulated the molecular shape or electronic distribution within drugs with a view to modifying molecular interactions at their site of action. Unfortunately, such change has frequently proved to be incompatible with the desired physical properties that affect the distribution and metabolism of drugs within the body. This is the principal reason why the vast number of analogues fail to behave in a satisfactory manner.

It is exceedingly difficult to develop new drugs that are both safe and effective. It may take years of intensive research before structural alterations to a prototype or an existing drug will provide a compound that can satisfy the stringent safety requirements universally applied to all new pharmaceutical products. Even when that much is achieved, sometimes all that is obtained is a novel compound that is no more than a commercial success. Such products have been much maligned for their failure to confer any therapeutic advantage over their predecessors. Nonetheless, there have been several instances in which drugs that appeared to be unnecessary variants of an existing product have been found from long-term studies to be safer, more efficacious or sufficiently different in their mode of action as to constitute important therapeutic developments. This factor alone could justify the marketing of almost any variant that is at least as safe and efficacious as the existing product, but the cost of bringing a new drug to the market is now so high that companies are reluctant to invest in any drug that does not have some significant advantage over its rivals. In the past, this restraint was not so powerful and consequently there are still redundant drugs on the market.

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In 1975, Ralph Solecki of Columbia University described excavations at the Shanidar Cave in the Zagros Mountains of northern Iraq, where he had unearthed 60 thousand year old Neanderthal bones laid out in the foetal position. Alongside were clusters of pollen grains from 28 species of flowers. As seven of these were recognised to be medicinal herbs, it was suggested that this could explain their presence. Solecki dismissed the possibility that the Persian jird, *Meriones persicus*, a rodent that stores seeds and flowers, may have contaminated the site by its burrowing. A later investigation by Jeffrey Sommer of the University of Michigan revealed that the types of pollen grains in the Shanidar grave were also found in jird burrows. While this does not prove contamination had occurred, it does mean that further investigation is required before firm conclusions about the Shanidar Cave can be drawn. Moreover, the presence of a few plants that are reputed to possess medicinal properties does not in itself mean they were used for such purposes. They could simply have been food, especially as ancient medicines often originated as components of the diet that were deemed to have beneficial effects on health.

There is indirect evidence of drug use in the Neolithic period, which began around 11 thousand years ago. Among remains of plants found in the Spirit Cave in the north-west of Thailand were seeds of the mildly psychoactive betel nut (*Areca catechu*), placed there between 7000 and 5500 BC. The earliest direct evidence for human consumption of betel nut comes from the Duyong Cave in the Philippines, where a skeleton from 2680 BC was found buried beside shells containing lime. This is reminiscent of the practice still seen in India, of wrapping the nut in betel leaf (*Piper betel*), adding lime (thus liberating the readily absorbable free base of arecoline), then chewing. As with modern users of betel nut, the teeth of the Duyong Cave skeleton were blackened.

Warming of the Fertile Crescent in the Middle East after the end of the last Ice Age permitted agricultural development. A transition from hunting and gathering to settling in villages developed over a six thousand year period, spreading to Europe, the Indus Valley and onwards, with parallel developments occurring in Central America and Northern China. Following upon the domestication of the horse by the fourth millennium BC, our ancestors acquired the ability to travel great distances with alacrity, a freedom the slow-moving ox had denied them. The consequences of this were profound. Trade developed, cities were established and conquest ensued, all of which created a need for law and order that in turn stimulated the development of writing in Mesopotamia and Egypt. With improved communications and the interchange of ideas, knowledge of herbs that could be used as spices, to treat disease or to offer some other beneficial action was no longer confined to isolated communities, and trading began in those products that could be preserved.

**ROCK ART**

Even before the appearance of writing there was another form of communication that has preserved information about the lifestyle of our prehistoric ancestors. This was rock art,
consisting of paintings and inscriptions on rocks either exposed to the elements or protected inside caves. In 1958, the American anthropologist Thomas Campbell drew attention to intriguing parallels between aspects of the ancient American Indian cult of the mescal bean (*Sophora secundiflora*) and drawings on the walls of caves near the confluence of the Pecos River and the Rio Grande in the south-west of Texas. The drawings depicted dancers with bows and arrows, hunting and deer. Campbell also noted that mescal beans had repeatedly been found in nearby caves over the preceding 25 years and in one case had been radiocarbon-dated as originating in the period 7500 BC to AD 200. In another cave were remains of peyote, a mescaline-containing cactus (*Lophophora williamsii*), and Mexican buckeye (*Ungnadia speciosa*), both known to be psychoactive.7,8 

The Pecos River cave drawings are now believed to be only four thousand years old, but that has not deterred the publication of reports5 about prehistoric cave drawings involving psychoactive drugs since the appearance of the paper by Campbell.6 There are many who dismiss such claims as being highly speculative and it should be pointed out that cave art with similar content to that of the Pecos River drawings has been discovered in parts of the world where there have been no findings of mescal beans or other psychoactive materials. Just as controversial are reports of cave paintings that are said to depict shamanic healing rituals in which the medicine man entered a trance-like state that may have been induced by either hyperventilation, ritual music and dancing, or drugs.9 It has, for example, been proposed that central Saharan Desert cave paintings from the period 7000–5000 BC represent the ritual use of hallucinogenic mushrooms since they portray scenes of harvesting, adoration, dancing and the offering of mushrooms.10

**DRUGS THAT ACT ON THE MIND**

The historical record of drugs consumed by our Neolithic ancestors could have been unduly influenced by those that exhibited an effect on the mind, such as mescal bean, peyotl, betel, the poppy, alcohol, coca, cannabis, tobacco, soma and pituri.11,12 The social and recreational use of these drugs is associated with artefacts, in much the same way as nicotine and alcohol are today involved with pipes and liquor glasses respectively. Drugs employed for medicinal purposes, by contrast, do not leave enduring evidence of their consumption, particularly if they were also considered to be foods rather than medicines – as is still the case today among North American Indians who cultivate certain plants for consumption as food, yet also employ them for therapeutic purposes.13 It is hardly surprising therefore that archaeologists have found more evidence of drugs used for social and recreational purposes than those selected as medicinal substances. It is noteworthy that when written records appeared in the third millennium BC onwards, psychoactive drugs did not appear to be dominant.

Not only has it been suggested that the original use of drugs was in religious rituals14 but it has even been claimed that early religious practices arose from the cultic use of psychoactive drugs.15 This may be controversial, but the role of wine in religious practice in ancient times is beyond dispute if we consider the Greek Dionysian festivities, the Roman Bacchanalia and the importance of wine in Judaism and Christianity.

**Alcohol**

The most widely consumed drug is, of course, alcohol. It is not surprising that alcoholic beverages were among the earliest of drugs to have been discovered since their effects must have been readily perceived within a short period of administration. This remained a basic necessity for drug discovery until the isolation and testing of active ingredients from plants in the nineteenth century. When toxic effects also occurred with little delay, the drug was considered to be a poison. However, if these were not manifest until a considerable time had
elapsed, there was little likelihood they would be connected with the drug. This remains a problem for those who consume herbal remedies, but it also applies to modern synthetic drugs. In recent years, thousands of people were prescribed drugs such as thalidomide, benoxaprofen, practolol and others without anyone being aware of the damage these caused because of the delay before it happened. It was left to astute physicians to detect the link between these drugs and their toxic effects.

Alcohol appears to have first been consumed in the form of wine. Evidence of wine being available over seven thousand years ago has been obtained from chemical analysis of yellow residues found in six vessels sunk in the floor of a mud brick building of the Neolithic Hajji Firuz Tepe village unearthed in the Zagros Mountains of western Iran. The capacity of each vessel was nine litres, indicating that organised production had taken place. Infrared, high-performance liquid chromatographic and chemical analysis of the yellow residue indicated that it consisted largely of calcium tartrate together with resin from the terebinth tree. The calcium tartrate could only have come from grape juice as there is no other common natural source. The juice would have fermented into wine on storage, while the resin served as a preservative to prevent despoliation by bacteria that convert wine to vinegar.17 Excavations further south in the Zagros Mountains uncovered a military centre known as Godin Tepe, where earthenware jars from 3500 to 3000 BC were found. Again, deposits of calcium tartrate were present.18 By this time wine and beer were being prepared throughout the Aegean.19 Silver and gold drinking vessels unearthed by Heinrich Schliemann when he was excavating the second city of Troy reveal the significance attached to the consumption of wine around 2500 BC.20

It is not clear whether the production of beer preceded that of wine. A 4000 BC seal depicting two people drinking beer with a straw (characteristically used to filter out the mash floating in the beer) was discovered in the 1930s during excavations of the Tepe Gawra site near the ancient city of Nineveh in north-east Iraq, and beer is frequently featured in Sumerian drawings and text of the third millennium BC.21

Opium

Alcohol may have been the most frequently consumed drug in history, but the most effective medicinal drug available before the dawn of the twentieth century was opium obtained from the poppy, *Papaver somniferum* L. – one of the oldest cultivated species known. Claims that opium was used in the Neolithic period should be viewed with extreme caution. They are based on the finding of seeds of the closely related *P. somniferum* subsp. *setigerum* in Germany at the Danubian settlements, the location of the first central European farms around 4400–4000 BC. Much greater quantities of poppy seeds have been found in northern France and farming settlements on the shores of lakes in Switzerland and surrounding areas, which date back to 3700–3625 BC. Both *P. somniferum* and its subspecies *setigerum* produce morphine and related narcotic compounds, though the former generates greater amounts. However, the seeds of both plants contain insufficient amounts of active alkaloids to produce any narcotic effect. The greatest concentration of active alkaloids is to be found in the latex exuded from the unripe capsule, which is dried to prepare opium. The seeds from the Neolithic period were probably used for the production of oil, as they certainly were in later times.

Evidence of what appeared to be early opium use came from the Cueva de los Murciélagos (Cave of the Bats), situated 50 metres above a ravine near Granada in Spain. In 1868 Góngora y Martínez reported that he had found poppy capsules in esparto grass bags in this ancient burial site. The capsules were radiocarbon-dated in 1975 as having originated about 4200 BC, but this was later revised to around 2500 BC. It thus appears that there is no reliable evidence for the use of opium prior to the appearance of writing.
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Pre-Hellenic Civilisations

Writing developed in Mesopotamia and Egypt six thousand years ago in the form of crude pictographs representing everyday objects, but gradually these were modified to represent ideas and ultimately sounds. Considerable progress was made in the nineteenth century in transcribing the wedge-shaped cuneiform text introduced by the Sumerians around 3100 BC, as well as the hieroglyphics of the Egyptians. Consequently, there now exists substantial knowledge of the lifestyle of these civilisations, including how they used and administered drugs. However, progress in identifying individual drugs has been more difficult.

A major source of information about drugs used in Mesopotamia is provided by the 660 tablets of clay recovered in the 1920s from the library of the palace in Nineveh of the last king of Assyria, Asshurbanipal (669–626 BC). Most of them appear to have been written around 1700 BC. They were among 20 thousand tablets unwittingly preserved by being baked when invaders set the palace on fire. The tablets were deciphered by R. Campbell Thompson, who established that many were copies of much older texts, with some of the drugs possessing Sumerian names from the third millennium BC.1

Thompson painstakingly sought to identify each plant mentioned in the tablets, both from the general context in which its name appeared and by reference to other cuneiform texts. He then adduced philological evidence from other languages before comparing his conclusions with the findings of other scholars, taking fully into account the ancient, mediaeval and modern usage of drugs in the Middle East. His work remains important, despite valid criticism that there were many errors in his identification of the 115 or so drugs.2 A number of his findings were revised in a posthumous publication,3 but his mistaken belief that the wild poppy, *Papaver rhoeas* L., produced narcotic substances persisted and has continued to mislead those who are unaware that morphine is not formed in this species. This has resulted in the widespread belief that opium was used 5000 years ago in Sumer. The situation has been further confounded by the suggestion that a third millennium BC ideogram on a clay tablet from the holy city of Nippur depicted *HUL GIL*, the plant of joy, this allegedly being the opium poppy. That opinion was originally expressed in a personal communication from a professor at Yale.4 There is no evidence to support it.5

The herbs cited in his posthumous publication that Campbell Thompson claimed to have identified include aloes, ammi (toothpick plant), anemone, anise, asafoetida, balm of Gilead, beetroot, black cumin, black hellebore, bitter or black nightshade, cannabis, carob, cassia, castor oil, cedar, chamomile, chasteberry, citron, coccynth, cornflower, cress, cumin, danel ryegrass, date palm, elder, fennel, fig, frankincense, galbanum, garlic, ginger, heliotrope, henbane, hound’s tongue, laurel, leek, liquorice, mandrake, meadow saffron, mint, mustard, myrrh, myrtle, nettle, oak, Pellitory, pine, pomegranate, poppy, rocket, rosemary, Syrian rue, saffron, squirting cucumber, styrax, sweet flag, sycamore fig, tamarisk, thistle, thorns, thyme, turmeric, white hellebore, winter cherry, willow and wormwood. Caution must be exercised in accepting his conclusions, though many of these plants are used to this day in herbal medicine – albeit with little more evidence of their efficacy than was available to the inhabitants of Mesopotamia. It is interesting to note that the medical texts distinguished between different
parts of the plant. This indicates an early awareness that this was an important aspect of using herbal medicines.

Many of the plants mentioned by Thompson had multiple uses – a feature of all ancient systems of medicine since they held that all ailments were different manifestations of the state of disease. Thus any remedy that was believed to expel the demons from the body or ameliorate an imbalance of humours would inevitably have a broad spectrum of application. This did not change until the emergence of pathology as an independent medical science. As for the actual uses mentioned by Thompson, they are diverse and include treatment of a wide range of gastrointestinal, urinogenital, pulmonary and abdominal problems, as well as external afflictions such as scorpion stings, bruising and blistering, irritation of the eyes, ears, mouth, feet and so forth.

In addition to the cuneiform tablets from Nineveh, there are many others, including 420 translated by Franz Köcher. From these sources we learn that there were two types of healers, namely sorcerers who belonged to the clergy, and physicians. The former, known as the ashipu, believed that disease was caused by demons and employed magic, incantations, charms and exorcism to expel them, while the latter, the asu, followed a therapeutic tradition of using animal, vegetable and mineral remedies in a pragmatic manner. There was often interaction between these groups, but it is clear that an independent therapeutic tradition had developed in Ancient Mesopotamia. This was an old tradition that originated in the prehistoric world and it appears likely that it passed to the Egyptians.

There may be problems with the identity of the drugs cited in ancient tablets, yet they can provide valuable information about how drugs were prepared and administered. Samuel Kramer wrote about a four thousand year old clay tablet excavated at Nippur that may be the oldest pharmaceutical text known. He and chemist Martin Levey translated the tablet and found it contained more than a dozen prescriptions with ingredients from animal, vegetable and mineral sources, but there was no indication of their uses. Of the minerals, both salt (sodium chloride) and saltpetre (potassium nitrate) were preferred, while from the animal kingdom milk, snakeskin and tortoise shell were favoured. However, most of the medicaments were of vegetable origin, a situation that persisted until modern times. Amongst these were said to be cassia, myrtle, asafeotida and thyme. There was no mention of the quantities to be incorporated, but all parts and secretions of the plants were used for making the prescriptions. In some cases, several plants were treated with wine and then mixed with cedar or similar oil to prepare soothing salves. The liquid formulations were obtained by decoction of plants in boiled water, followed by addition of alkali or salts that may have enhanced the extraction process. For prescriptions administered by mouth, the pulverized ingredients were taken up in beer. Sometimes the ingredients were specially treated, such as the burning of soda-rich plants to free the alkali ash from vegetable matter. There was even a degree of chemical interaction, as in two prescriptions where fats were combined with alkali to form a soap. The cleansing and antibacterial action of this when applied directly to infected wounds was probably of more benefit than the odoriferous ingredients of other prescriptions in the clay tablet.

EGYPT

The most useful record about drugs used in Ancient Egypt is a document purchased in Thebes in 1872 by the Egyptologist Georg Ebers. Generally known as the Ebers Papyrus and dating back to around 1550 BC, this lists more than 800 prescriptions then in vogue, including most of the drugs cited in Thompson’s interpretation of the medical tablets recovered from Nineveh. This would be due to the trade routes between Egypt and Mesopotamia, resulting in cultural exchange. Both sources include elements dating back to the third or fourth millennium BC. In the Ebers Papyrus, there is once again a problem with the identification of specific herbs, but there are many prescriptions incorporating culinary materials such as dates,
figs, grapes, pomegranates, roasted barley, wheat, honey, sweet beer, wine and milk. Spices abound, including absinth, cassia, caraway, coriander, cumin, fennel, gentian, juniper, peppermint and thyme. Fats are also present, albeit from unusual sources such as cats, crocodiles, geese, hippopotamuses, lions, oxen and serpents. Among the oils are cedar wood, linseed, turpentine and other essential oils. There are also locally obtained minerals such as common salt, natron, alum, red and yellow ochres (iron oxides), as well as salts of lead, copper, mercury and antimony. Many of the prescriptions are for skin and eye complaints, as in the tablets from Nineveh, while remedies for gastrointestinal complaints are also common. Once again, the former doubtlessly reflects the hot, sandy environment and presumably the latter is related to the unwholesome diet of those days.

The prescribing of soothing balms for skin problems and purgatives for what appears to be constipation indicates that there was a strong empirical element in both the Mesopotamian and Egyptian systems of medicine, while the preponderance of spices and culinary herbs supports the view that drugs were initially considered to be foods that had some beneficial value. However, what lay behind the selection of the herbs?

Many plants contain substances that will irritate one part or another of the gastrointestinal canal, from the mouth to the rectum. The response to these substances, and consequently their application, will depend on which region is irritated, varying from salivation, or emesis, to purgation. If the elements of magic, superstition or religion are involved rather than pragmatism, the scope for innovation is immense. It does not, however, augur well for efficacy, and therein lies the problem for those who look to herbal remedies as a source of new drugs. It is conceivable that some might be, but much effort will be wasted examining worthless nostrums in the vague hope that something of value will be found.

Whereas in Mesopotamia the treatment of the sick was in the hands of two distinct classes of healers, the priestly ashipu and the therapeutic asu, most physicians in Egypt were priests. Imhotep, the earliest physician known to historians, lived during the Third Dynasty of the Old Kingdom around 2650 BC and was High Priest of Heliopolis. At that time, elements of religion and magic were closely intertwined with drug use, incantations routinely being uttered prior to administration in order to confer the healing property upon it. Without such a spell being cast, the drugs would in most cases have been ineffective. Modern knowledge of the placebo effect, whereby psychological elements influence the response to therapy, suggests that this greatly contributed to any success of the Egyptian priest–physicians. Although there were some herbs that did have real properties, such as the ability of castor oil to produce purgation, the likelihood of recognising such effective remedies would have been diminished as the outcome of their administration was difficult to distinguish from the many worthless herbs that were introduced.

Medicine acquired such a high status in Egypt that its physicians were sought out by leaders of surrounding nations. There was considerable specialisation in the treatment of different parts of the body, further increasing the demand for physicians. Although there were some who were not priests, they lacked the influence of the priest–physicians. All, nevertheless, were ever ready to administer a wide range of herbs. Regrettably, it was not the tradition of the asu of Mesopotamia that was passed to all subsequent generations by the Ancient Egyptian priest–physicians, but rather a heritage of mainly worthless remedies. Most of these are still being sold in our modern shopping malls as ‘herbal’ or ‘natural’ medicines.

Finally, it should be noted that claims that traces of morphine had been found in the tomb of the Egyptian chief royal architect Kha, who died in 1405 BC, have been disproved by modern chemical analysis.

**INDIA**

Recent scholarship has established that not only were there trade links between Mesopotamia and Egypt at the beginning of the second millennium BC but that the Silk Road to China was
also being established. Due to the immense distances involved, no single individual was able to travel from the West to the Far East. Although goods were exchanged, the transfer of knowledge and culture was therefore erratic and unreliable. Consequently, there are both similarities and differences in the ancient medical systems of the East and the West.

There are many who believe that the four Vedas that constitute the Brahmanic basis of Hinduism could have been compiled by the second millennium BC and that some of the mantras in them trace their origins back a further one or two thousand years. A recent challenge to established concepts of Indian history could further complicate the dating of the compilation of the Vedas.

Each of the Vedas covers the role of ritual in a different sphere of life. The last, the Atharvaveda, is held by believers to have originally contained the basis of Ayurvedic medicine, which was rearranged and revised perhaps around 800 BC in Samhitas (treatises) by the physician Charaka and the surgeon Sushruta. Charms for expelling demons are to be found in their works and there is a god of medicine, Dhanvantari. The Charaka Samhita may not have been written in its present form until the first century AD. It refers to over 300 vegetable drugs, the remainder being from animal and mineral sources. The current version of the Sushruta Samhita might date to the seventh century AD. Although a text on surgery, it mentioned nearly 400 vegetable drugs. The number of plant medicines cited in these two works is greater than that of any other ancient people who left a record of such matters. However, it does not rest there, for in sutra 26 the Charaka Samhita asserts that there is nothing in the world that cannot be used as a medicine, so long as an appropriate use can be found for it!

Ayurveda considers man to be born in a state of humoral balance that is gradually lost through changes in diet, lifestyle and environment. The humours are wind, bile and phlegm. In some traditions there is a fourth humour, blood. To restore a healthy balance in those who are sick requires not merely the use of appropriate drugs but also dietary change, controlled breathing and spiritual meditation. There is an obvious similarity to the Greek system of humoral medicine insofar as both are holistic in aiming to restore a healthy balance of humours. In both there is liberal use of emetics, purgatives, enemas, sneezing powders and the like, not to expel demons but rather to eliminate excess of undesired humours. This would hardly be surprising if the writings upon which Ayurveda is based were compiled hundreds of years after the Hippocratic Corpus of the fifth century BC, but if the concept of the humours originated before 2000 BC, a major revision of medical history would be necessary. The matter has not yet been settled, but from the perspective of the history of drug discovery, the debate is of limited concern since humoral medicine was nothing other than an impediment to the discovery of efficacious drugs.

As with several other ancient medical systems, that of India has been associated with the use of a psychoactive drug. In this instance it is soma, a substance featured in the oldest of the Vedas, the Rig Veda. Many suggestions as to its identity have been made, including the celebrated claim by Gordon Wasson that it was a psychedelic mushroom, Amanita muscaria. More recently, it has been suggested that soma consisted of a mixture of herbs including Syrian rye, Peganum harmala, the substance originally proposed to be soma in 1794. This new claim, however, depends on the assertion that soma was introduced into Northern India by Aryan invaders. However, the proponents of the antiquity of vedic medicine strongly deny such an invasion ever occurred. From this, the reader may conclude that unravelling the history of early drug use in India is no simple matter. A thorough investigation of the subject is required.

CHINA

During the Han Dynasty in China (206 BC–AD 220) there was a proclivity to fabricate history in order to elevate the reputation of the state. Mythical figures were said to have rescued the
world from chaos, such as the inventors of fire, writing and agriculture. The latter was supposed to be a peasant who became the Emperor Shen Nung in the third millennium BC and it was claimed that valuable information about the use of drugs could be gleaned by scouring the pages of his herbal, *Pen Ts’ao Ching* (*Classic of Materia Medica*), in which he described how he tested more than 300 herbs upon himself. Acceptance of this story has persisted in China where Shen Nung is revered as the Father of Medicine, but in fact this herbal was written during the last years of the Han Dynasty and then modified in the sixth and seventh centuries. By this time, it would have been influenced through contacts with India and the Hellenic world and so diminished in value as a guide to the early use of drugs.

The concept attributed to Shen Nung that herbs have properties of inducing warmth or coolness will strike a chord with anyone familiar with the writings of Aristotle (384–322 BC). In the absence of reliable evidence to the contrary, the concept must be considered as coming from Aristotle. Another text that is just as prominent in Chinese medicine is the *Huang Di Neijing* (*The Yellow Emperor’s Classic of Internal Medicine*), written around the same time as *Pen Ts’ao Ching* but supposedly authored by a fifth millennium BC ruler.18 This introduced the concepts of yin and yan, the forces that must be balanced for the maintenance of good health. Yin is a negative or passive force, while yan is positive or active.

The best known of the Chinese herbals is *Pen Ts’ao Kang Mu*, which was compiled during the Ming Dynasty by Li Shih-Chen (1518–1593). Featuring nearly 2000 herbs, as well as minerals and animal products, it summarised all that was known about Chinese medicine at that time. Since then, the number of herbs used has increased to around 5000.

**Cannabis**

Although native to Asia, it is generally accepted that *Cannabis sativa* L. was first cultivated in China around 4500 BC when its seeds served as a grain crop. Soon after, its decaying stems became the source of hemp fibre for making clothes, ropes and fishing nets. However, reports of early hemp use in China are open to question either because of inadequate identification of fibre remains or because they relate to impressions on pottery and other objects. These are assumed to have been made by hemp since other fibres, except the much finer silk, are not found in the region. Such cord impressions have been seen on material from 4000 to 3000 BC unearthed in Taiwan and also on similarly dated pots found in Henan Province, eastern China, at an archaeological site of the Yang-Shao culture, the first civilisation to manufacture pottery. Outside China, clay shards showing impressions of what are thought to be *Cannabis* seeds from around 3000 BC were discovered during excavations at a Linearbandkeramik Culture site north of the Black Sea. There are also reports of hemp fibres from objects recovered at Adoueute in the south of France (2000 BC), Gordium in Turkey (800 BC) and St Andrews in Scotland (800 BC).19 While these and many other findings indicate that hemp fibre was of importance as long ago as the third millennium BC, they do not constitute reliable evidence that *Cannabis* was being used as a drug. The frequently repeated assertion that it was then being used in China as a medicine or a euphoriant is based on the mistaken belief that *Pen Ts’ao Ching* was written in the third millennium BC by Shen Nung.

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