THE STATE CONTROL OF MEDICINES: THE FIRST 3000 YEARS

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Introduction

Sir William Osler said:

'Man has an inborn craving for medicine. Heroic dosing for several generations has given his tissues a thirst for drugs. The desire to take medicine is one feature which distinguishes man, the animal, from his fellow creatures.' (Bean, 1950.)

Certainly the alacrity with which he doses himself with substances that in other circumstances would be regarded as poisonous serves to distinguish him from the lower orders.

The human race has been taking medicines since history began and throughout all this time there is some evidence of control by governmental or other regulatory bodies. Early regulations were usually on quality and supply on rather the closed shop principle. It was not until quite modern times that humanitarian thought demanded the protection of the general public with regard to efficacy and safety. There were notable exceptions to these general comments all the way through history and attention will be drawn to these later. It is important to realize that every control measure presupposes a standard against which a performance may be assessed. It also implies that this control measure must be issued by a political unit (sometimes in the widest sense) backed by the requisite political authority and capable of both a police and judicial function.

In these days of rapid communication, large populations and ubiquitous bureaucracy, the early geographical constraints on the development of workable controls must not be forgotten. With regard to England, it may just have been possible in London and some other larger towns to separate dispensing and prescribing practice, but not so in the country where by and large anyone engaged in the healing art would normally be forced by circumstances both to prescribe and dispense though he may call himself physician, surgeon or apothecary.

It was not until modern times that the physician became so divorced from the actual preparation of his own medicines. For those he prepared himself, may be with herbs gathered personally, he would have direct knowledge of their formulation. His other medicines would have been made by an apothecary

known to him and probably to his special direction. There were exceptions to this, of course, but it was not until the rise in the 19th century of the pharmaceutical industry and the rapid increase in the number of potent drugs that the need was so emphasized for universally applicable standards.

Self-medication is another important strand of drug control and until quite recently drugs were generally available and the modern idea of 'prescription only' medicines was unknown. It is also impossible to put effective restrictions on the use of such drugs as are readily available in the field, the kitchen and garden, when every man could be his own doctor.

The quality of the preparation of a drug in its marketed form is also a property that is often taken for granted but, as will be shown, has historically received more attention than its other attributes. In all cases it is necessary to ensure that the components are as stated and to introduce therefore the concept of adulteration. This is defined by Stieb (1966) as:

'any practice which through intent or neglect results in a variation of strength and/or purity from the professed standards'.

The fight against adulteration has been a continuing one since the earliest times and will be discussed later.

These controls on safety, quality, efficacy and supply of a drug often proceeded along quite separate pathways for many centuries until in Britain they were brought together in the Medicines Act of 1968.

Control in ancient times

It has already been said that it would be a mistake to think that consideration of quality, safety and efficacy of a drug is entirely of recent origin. Homer was certainly aware of the toxic nature of some herbs and, in a tacit acknowledgment of the debt that Greek medicine owed Egypt, comments in *The Odyssey* that:

'... there the earth, the giver of grain, bears greatest store of drugs, many that are healing

when mixed, and many that are baneful; there every man is a physician, wise above human kind; for they are of the race of Paeëon'. (*Odyssey*, iv. 228.)'

The ancient Egyptians did indeed have a very flourishing medical profession which was rigidly controlled and, in the 1st century BC., another Greek writer, Diodorus Siculus said of them:

'... the physicians draw their support from public funds and administer their treatments in accordance with a written law which was composed in ancient times by many famous physicians. If they follow the rules of this law as they read them in the sacred book and yet are unable to save their patient, they are absolved from any charge and go unpunished; but if they go contrary to the law's prescription in any respect, they must submit to a trial with death as the penalty, the lawgiver holding that few physicians would ever show themselves wiser than the mode of treatment which had been closely followed for a long period and had been originally prescribed by the ablest practitioners'. (*Library of History*, I, 82.)

These Egyptian controls appear to be not only on the quality of the preparation but also to reflect on efficacy and safety. Perhaps the sacred book might be thought of as the earliest data sheets. Other recognition that drugs are toxic is to be found in the Hippocratic Oath. In this oath which originated somewhat after the 5th century BC., the physician is enjoined against the giving of 'pharmacon oudeni'. This part of the oath has been translated as 'I will give no deadly drug' though some translators have taken this phrase to mean a poison. There is very little evidence on the existence in Greek times of any control of the apothecary himself but this is hinted at from an inscription dating from the 4th century BC and found on the Athenian Acropolis to commemorate that Evenor the Physician had been chosen inspector of drugs (Withington, 1894, p. 74).

Ancient drugs on the whole were not very harmful and probably not very effective either, though of course the art of the poisoner had been highly developed but this can hardly be called therapeutic. Even so there were continued warnings about the safety of medicines.

Celsus (fl. AD 30) in '*On medicine*' (Book V.1) says:

'... on the other hand Asclepiades dispensed with the use of these (medicaments) for the most part, not without reason; and since nearly all medicaments harm the stomach and contain bad juices, he transferred his treatment rather to the management of the actual diet ...'.

It must be admitted that Celsus at times liked

to back his horses both ways and in a paragraph (Book IV.7) discussing the treatment of 'angina' (quinsy) by what today might be considered reasonable local applications or surgery says:

'... I hear it commonly said that if a man eat a nestling swallow for a whole year he is not in danger from angina; and that when the disease attacks anyone it is beneficial to burn a nestling which has been preserved in salt and to crumble the powdered ash into hydromel which is administered as a draught. Since this remedy has considerable popular authority and cannot possibly be a danger, although I have not heard of it in medical authorities yet I thought it should be inserted here in my work. ...'

The resemblance is quite obvious to the arguments in favour of traditional products of the modern day British concept.

Control of drug quality was certainly the preoccupation of the early regulations and an early comment appears in the Old Testament (*Ecclesiastes* 10.1):

'Dead flies cause the ointment of the apothecary to send forth a stinking savour. ...'

Adulteration has been briefly referred to above and many ancient writers comment on the problems caused by sometimes fraudulent, sometimes accidental practices such as adding of bulk, removal of active constituents and concealment of defects of the various drug substances. The development of obligatory pharmacopoeial standards in the 16th century helped matters as the earlier pharmacopoeias often used as a guide lacked the force of legal authority. Solutions to the problem did not really emerge until the 19th century and the development of sophisticated tests. Previously the major means of detecting adulteration was by organoleptic (sense perception) tests and these are given in some detail by classical writers such as Theophrastus (370–287 BC) and Dioscorides (fl. 60 AD). The *Materia Medica* of Dioscorides was widely used throughout the Middle Ages and does give some examples of how to detect adulteration. These tests were mainly organoleptic but did involve some chemicophysical methods. Pliny the Elder (23–79 AD) also discussed adulteration with some comment on the social and economic reasons. Pliny was no admirer of the doctor or the druggist and comments tartly in his *Natural History* (XXXIV.25):

'... But of all these facts the doctors, if they will permit me to say so, are ignorant—they are governed by names; so detached they are from the process of making up drugs, which used to be the special business of the medical profession. Nowadays whenever they come on books of

prescriptions, wanting to make up some medicines out of them, which means to make trial of the ingredients in the prescriptions at the expense of their unhappy patients, they rely on the fashionable druggists' shops which spoil everything with fraudulent adulterations, and for a long time they have been buying plasters and eye-salves ready made; and thus is deteriorated rubbish of commodities and the fraud of the druggists' trade put on show.'

It would seem that criticisms of the doctor's lack of knowledge of the drugs he uses have changed little in nearly 2000 years.

Terra Sigillata

One interesting early example of what could be loosely called control of drug quality is that of 'terra sigillata'. This fine clay classically known from its occurrence on the Isle of Lesbos ('Lemnian Earth') was used from early Greek times for the treatment of wounds, dysenteries, ulcers, haemorrhages as well as being a constituent of some theriacs. It was made up into round cakes of about 0.5 oz weight which were stamped with designs alluding to its origin (hence 'sigillata') and presumably being thought to guarantee its authenticity.

Similar earths were known from a considerable number of places, each being given its own distinctive stamp and usage continued until fairly recently either in medicines or to make vessels of various types. The clay on Lemnos was dug out on only one day each year attended by much ceremony and in the presence of the principal inhabitants.

The particular day was originally associated with the worship of Diana (May 6th) but in Christian times was transferred to the Fete of Our Saviour (August 6th).

Medieval and early European controls

In medieval Muslim countries the manufacture of medicines was controlled quite rigorously. The office of the *hisba* was established in the early part of the 9th century to compel observance of the codes and regulations for the safeguarding of public morality and the faith and to prevent fraud, trickery and charlatanry. The functions of the *hisba* were soon expanded from its specifically religious character of the censorship of morals to embrace the whole conduct of social and economic life. Medicine did not escape and various regulations were made concerning physicians, ophthalmologists, surgeons, bone-setters, phlebotomists and syrup makers (who also prepared medicines). The official in charge, the *muhtasib*, was given specific instructions regarding the syrup makers:

'It is necessary that the *muhtasib* make them fearful, try them and warn them against imprisonment. He must caution them with punishment. Their syrups and drugs may be inspected at any time without warning after their shops are closed for the night. (Levey, 1963.)

It is interesting to note that the inspectors themselves were also trained as apothecaries and that the punishments involved were stringent and included heavy fines, the *bastinado* and the pillory (Hamarnah, 1964).

Adulteration was obviously a problem and in an attempt to rectify this, standards were officially laid down by means of a pharmacopoeia and tests described to detect adulteration of such drugs as henna, nard, mastix, saffron, sugar, pepper, musk, aloeswood, acacia, Chinese ginger and balsam oil.

The physician in charge of a case was also not forgotten and had to give the relatives of the patient a copy of any prescription. If the patient recovered the physician received his fee but, if the patient died, the relatives would take the copy of the prescription to the chief physician. If he decided that the treatment was appropriate the verdict was given:

'death occurred at the termination of his allotted span'.

If the verdict was of improper treatment, the relatives were told:

'demand blood money from the physician for your kin, for he killed him by his lack of art and his inadequacy.' (Levey, 1963.)

Salerno and Sicily

In some European countries this desire to control the quality of medicines was also expressed early in legislative form and was much influenced by the Islamic example. In 1140, Roger II, King of the Two Sicilies, promulgated the first known law in Europe for the regulation of medical practice:

'... whosoever will henceforth practise medicine, let him present himself to our officials and judges to be examined by them but if he presume of his own temerity, let him be imprisoned and all his goods sold by auction...' (Withington, 1894, p. 233.)

Roger's grandson, the German Emperor, Frederick II of the House of Hohenstaufen, also issued a sequence of laws between the years 1231-1241 to supervise the art of medicine and the practise of the apothecary in this southern Italian kingdom which, though it consisted of Naples and Sicily, the laws were also effective in North Italy, France and Germany.

The education of the doctor at the Medical School of Salerno near Naples was also closely controlled with an initial study of logic for 3 years followed by a 5 year course in medicine (which also included surgery) and an additional year of practice under the supervision of an experienced practitioner. At the end of this period the candidate was publicly examined by the 'Masters of Salerno'. Doctors were also forbidden to keep apothecaries shops or to enter into business relationships with apothecaries as it was recognized that pharmacy required skills separate from those of medicine. Apothecaries were strictly controlled and were obligated to prepare drugs reliably and of proper quality; this was probably the first European suggestion of the official pharmacopoeial standards to come. The number and siting of their pharmacies was also controlled and a fixed scale of charges and profits imposed. Inspectors of the apothecaries were appointed and it is of interest to note that growers of plants meant for medical purposes were also regulated. The sale of poisons was simply and effectively controlled:

'... whosoever shall have or sell any poison or noxious drug not useful or necessary to his art, let him be hanged.' (Withington, 1894p. 234.)

Similar rules were issued soon afterwards in other countries and there is, for example, an apothecary's oath issued in Basle between the years 1271-1322 by the Burgomaster, Council and Guildmasters. As in Salerno, doctors were not allowed to be apothecaries or to own an apothecary's shop. Any apothecary had also to convince the Council of his skill and to take an oath to provide the physician with drugs of the proper quality (Mez-Mangold, 1971).

The preparation of theriac

Another example of the civic control of drug quality in the Middle Ages was the preparation of theriac. There were many kinds of theriac which was a multi-ingredient antidote to the bites of venomous creatures such as snakes, scorpions, spiders, bees, mad dogs and the like. Composed mainly of herbs, some theriacs also had animal ingredients such as viper flesh and a very few contained minerals.

There is no doubt that the municipal authorities of the time were concerned to ensure the proper compounding and usage of appropriate ingredients in their theriac so the efficacy was beyond question, it having become an article of considerable commercial value.

Watson, in his monograph 'Theriac and Mithridatum' (1966), gives a very clear idea of how,

in a number of countries, the municipal authorities took a leading part in collaboration with the physicians and apothecaries in the manufacture of theriac. This occurred as early as 1258 in Venice and gradually became a civic occasion as was shown by the diary of John Evelyn for 23rd March 1646:

'The making and extraordinary ceremonie whereof I had ben curious to observe for tis extremely pompous and worth seeing.' (Beer, 1955.)

Similar controls were imposed in the Low Countries, Germany and France, but in England the manufacture of theriac was not marked by such ceremonies. Even so, the Royal College of Physicians in the reign of Elizabeth I and especially later when the London Pharmacopoeia was issued, closely supervised the making of theriac. As late as 1722 it was publicly prepared by the Society of Apothecaries and sold in pots stamped with their seal at their laboratory in Water Lane.

The early period of drug control in Britain

Legislation in Britain about drug control was at first specifically concerned with the quality of the drug but only to establish the identity of the substance and its freedom from contamination.

The effect of formulation on the availability of the drug to the body is a very modern concept and played no part at this time. The professional bodies such as the physicians and the apothecaries were also very jealous of their position and sought to maintain their monopoly and the story of the development of drug control is often one of antagonism between such groups rather than a desire for the public good.

The earliest written code of quality control in Britain seems to be the Ordinances of the Gild of Pepperers of Soper Lane in 1316. The Pepperers in the 12th century took over the distribution of imported drugs and spicery (which includes spices, sugar, confections and fruit). They were not always easy to distinguish from the Spicers who themselves became intermingled with or perhaps succeeded by the Grocers. The Ordinances of 1316 possibly included the apothecaries and the spicers and forbade the mixing of wares of different quality and price, the adulteration of bales of goods or falsifying their weight by wetting (Riley, 1868).

For the next several hundred years the story is a confused one containing the roots of the later separation of the apothecaries as a craft guild and their emergence first as compounders of medicine and then a division into those who ultimately became general medical practitioners and those who together with the emergent chemists and druggists founded the

Pharmaceutical Society and became the pharmacists as we know them today.

The Apothecaries were originally part of the Guild of Grocers and unsuccessfully petitioned Elizabeth I in 1588 for a monopoly of selling and compounding of drugs. It was not until 1607, however, that James I was to grant a Charter to the Grocers which recognized the Apothecaries as a separate section. Ten years later in 1617 James gave the Apothecaries a Charter to separate them from the Grocers as 'The Worshipful Society of the Art and Mystery of Apothecaries'.

The story over this period and for much later is that of a long fight with the physicians and as early as 1423 the 'Commonalty of Physicians and Surgeons of London' appointed two apothecaries to inspect the shops of their colleagues and bring any who offended in the quality of their wares before the Mayor and Aldermen (Trease, 1964).

The College of Physicians was founded in 1518 by Henry VIII and a few years later in 1540 one of the earliest English statutes on the control of drugs was passed (32 Hen VIII c. 40 For Physicians and their privileges) which empowered the Physicians to appoint four inspectors of 'Apothecary wares, Drugs and Stuffs'. Section 2 of the Act gave the Physicians the right to search apothecaries shops for faulty wares with the assistance of the 'Wardens of the said mystery of Apothecaries within the said City'. If the search showed drugs that were 'defective, corrupted and not meet nor convenient to be ministered in any medicines for the health of man's body the searchers were to call for the Warden of the Apothecaries and the defective wares were to be burnt or otherwise destroyed (Goodall, 1684).

This Act of Henry was obviously incorrect in defining the apothecaries as a separate body and was corrected later in the reign of Mary by an Act of 1553 (1 Mary sess 2. c. 9) in which it was enacted 'for the better execution of the searche and view of Poticarye Wares, Drugges and Compositions according to the tenour of a Statute made in the Two and Thirtieth yeare of the Reigne of the said late King Henry th' eight That it shall be lawfull for the Wardeins of the Grocers or one of them to go with the sayd Physitions in their view and searche'.

It is revealing that whereas the penalty for refusing to have wares examined was 100s in Henry's day (of which he took half), by Mary's day this had been raised to £10. The wording of the Act was also changed slightly in that under Henry, the Wardens were to be called for but under Mary they had to go.

Henry was also determined that the 1540 Statute would be obeyed and an errant apothecary punished and not allowed to make excuses:

'... in the Kings Court ... no wager of law, essoin [excuse] or protection shall be alloweth ...'.

The first recorded visit took place on 25th January 1542 and the last visitation of apothecaries shops by the Censors, accompanied by a Warden of the Society of Apothecaries took place 2nd November 1858 (Cooke, 1972). The inspecting Physicians would take one district at a time covering perhaps as many as 20 shops in one visit and aiming to repeat the visit every 4 months or so. The right of the Royal College of Physicians to perform this visitation was withdrawn at the time of the Food and Drugs Act in 1875. The Society of Apothecaries also carried out their own inspections independently from those of the Royal College of Physicians which they were entitled to do under the Charter of 1617.

The Physicians, therefore, had control of the inspection of the shops of the Apothecaries for adulteration and similar abuses. They also waged a constant war against those apothecaries who prescribed for the public rather than just obeying the prescription dictates of the physicians.

A group of physicians and apothecaries meeting together in 1614 agreed the draft for a Charter for the incorporation of the apothecaries (Wall, Cameron & Underwood, 1963, pp. 13-14) and this was approved by the College. The apothecaries agreed not to supply cathartics, vomits or sudorifics without the knowledge of a physician; or opiates, hypnotics or abortifacients without a prescription; and also not to supply poisons (especially mercury sublimate, prepared arsenic or orpiment) without a signed prescription which was to be kept or unless the purchaser signed in a book against the date and the quantity supplied. These apothecaries also agreed not to prepare general epidemics (e.g. mithridate or theriac) except in a public dispensation supervised by the College and Private Court. A book called the 'London Antidotary' was to be prepared by the College for the guidance of apothecaries who were to stock their shops only with compound medicines prepared strictly in accordance with the Antidotary. These requirements were subsequently dropped and the draft headings substantially revised.

The Charter of 1617 did not confine the Apothecaries to an 'Antidotary' or to the prescriptions of the collegiate physicians nor were any express restrictions placed on the supply of poisonous or dangerous drugs. Some scandal was caused at the time when it became known that Francis Bacon, the Lord Chancellor, had been given £200 by the Grocers, £40-50 and a lump of ambergris by the Apothecaries remaining with the Grocers and £100 by the separated Apothecaries.

In June 1632, however, the Physicians were instrumental in obtaining an Order in Council which was to be added to the Freeman's Oath of the Apothecaries (Wall *et al.*, 1963, pp. 46-47, 262-264). This Order approved a regulation forbidding

apothecaries to sell or prescribe any poisonous substance or drug '... to the body of any man, woman or child' save on the written prescription of a physician or upon a note in writing from the purchaser.

The Apothecaries hotly disputed this Order and there is no record of any action being taken on it. They asked the Physicians to tell them of specific abuses and that they would then co-operate in reforming them. The Apothecaries said that others such as druggists, grocers, chandlers, could sell poisons quite freely and many craftsmen used them daily. The Apothecaries further said that to restrict them to providing poisons solely at the request of the physicians would take away their livelihood and interfere with the liberty of the subject to have free use of all medicines.

The development of the pharmacopoeia

Another technique to control the quality of drugs is the issue of a pharmacopoeia (Greek 'pharmakon', a drug, 'poia', making).

These authoritative lists of drugs, their preparation and uses have been known since the earliest times. Some of these were considered necessary reading and, for example, Basel apothecaries of the 15th century had to have certain formularies available. None of these was considered the final authority and an errant apothecary could always 'play the authority'. In 1498 the Florentine guild of physicians and pharmacists (*L'arte dei medici e speziali*) issued a formulary, the *New Compound Dispensatory* (*Nuovo receptario composto dal famosissimo Chollegio degli eximii Doctori della Arte et Medicina della inclita cipta di Firenze*). This was the official and obligatory guide for the apothecaries of Florence and is generally regarded as the first official pharmacopoeia in Europe in the modern sense, i.e., of a specific political unit.

Other cities soon followed in the publication of obligatory formularies, Barcelona in 1535 (*Concordia Pharmacolorum Barcinonesium*), Nuernberg 1546 (*Dispensatorium Valerii Cordis*). Similar compilations were also issued in Mantua in 1559, Augsburg 1564, Cologne 1565, Bologna 1574, Bergamo 1580 and Rome 1583.

Britain was somewhat slower and it was not until Elizabethan times that it became obvious that there was a need for such a pharmacopoeia or formulary. This was first considered by the College of Physicians in 1585. Work, however, proceeded very slowly and the *Pharmacopoeia Londinensis* was not published until 1618. There were two issues; one on May 7th and the first 'official' edition of December 7th. This latter was by no means a reprint of the earlier one and was substantially enlarged and changed. It is worth

noting that this pharmacopoeia was to apply not only to London but throughout England as well. This made it effective over a much larger political unit than the previous European 'city' pharmacopoeias.

It is of interest to consider the following extracts from the preface which is titled for the interest of the 'candido lector' or the friendly reader. The whole of the pharmacopoeia was in Latin and the following translation is taken from a facsimile edition published in 1944 (*Pharmacopoeia Londinensis*, 1618):

'... In order to cure the first requirement is to secure the most wholesome medicine. ...'

The preface then discusses the confusion caused by the vast number of books available each with different methods for making medicines and resolves:

'... we propose to stabilize this fluctuating state of pharmacy... accordingly, we do not only instruct but we impose and enforce one and only one law and one method of compounding, from which we would allow no deviation whatsoever, not even that of a finger's breadth, so to speak ...'

The preface then criticizes the ethical standards of some of the medicine sellers of the day:

'... our book will counteract, namely the very noxious fraud or deceit of those people who are allowed to sell the most filthy concoctions... for the sake of profit and instigated by sordid avarice....'

It was obvious that in those days the proposed punishments for offenders were considerably more severe than those used today:

'... such criminal murderers [i.e., the people mentioned above] must be subdued by this our censor office—if need be by the lash or even by the fork'.

The preface goes on to talk about the arbitrary nature of some of the instructions given by previous authorities and resolve to stop this:

'For the future we have removed all such power of arbitrary decision on the part of the compounder... we have adopted uniform measures and have determined upon a certain dose which the pharmacist shall neither increase nor decrease.'

It was also made very clear as to the audience the new *Pharmacopoeia* was addressing:

'Finally, in most of the older, as well as the more recent antidotaria, the uses and medical attributes of each remedy have been described. From this quiver, the itinerant drug peddlers and the quacks, being as ignorant as they are unscrupulous, equip themselves for their medical practice and seizing

our weapons, are responsible for the death of the sick, to the great detriment of the state. We, therefore, do not add anything about the efficacy of the medicines. We write this book only for the learned, for the disciples of Apollo and for the welfare, not the information of the common people.'

James was also very certain that he wanted the new Pharmacopoeia to be used and issued a Proclamation on the 26th April 1618 which made it quite clear to the Apothecaries as to what was expected of them:

'Apothecaries within this our Realme of England or the dominions thereof . . . do not compound or make any medicine, or medicinale receipt or prescription . . . by any other bookes or Dispensatories whatsoever but after the onely manner and forme that hereby is, or shall be directed, prescribed and set downe by the said book and according to the weights and measures that are or shall be therein limited and not otherwise &c upon paine of our high displeasure, and to incurre such penalties and punishment as may be inflicted upon offenders herein for their contempt or neglect of this our royall commandement.'

The *First London Pharmacopoeia* was superseded by the *Second London Pharmacopoeia* in 1650 and further Pharmacopoeias were issued at intervals until the last, the tenth, was published in 1851. A similar pharmacopoeia was issued at Edinburgh in 1699 and at Dublin in 1807. In 1858 the Medical Act created the General Medical Council, one of whose duties was to compile an official Pharmacopoeia for the whole of the United Kingdom to supersede the three current ones of London, Edinburgh and Dublin and the first *British Pharmacopoeia* was published in 1864. The current edition is the twelfth (1973) and under the Medicines Act (1968) is now published by the Health Ministers on the recommendations of the Medicines Commission.

It is not the intention here to discuss further in detail the development of the *British Pharmacopoeia* but it should be noted that save for a brief period between 1872 and 1875 the *Pharmacopoeia* never achieved status as describing legal enforceable standards. Nevertheless it was always the presumptive standard for the Courts and loomed large in the relentless battle against the adulteration of drugs that started in the early 19th century. Drug adulteration has a long recorded history and the control of the quality of medicines by various professional bodies in medieval and later times has already been mentioned.

Jacob Bell, one of the founders of the Pharmaceutical Society of Great Britain, was well aware of the need to control the quality of drugs for he wrote in 1841:

'In reviewing the history of pharmacy in all ages we find that fraud has always prevailed to a remarkable extent in this kind of traffic (i.e., variations in the quality of drugs and the sophistications to which they are liable) which circumstances may chiefly be attributed to the facility of eluding detection by the imperfect acquaintance possessed by the public of the nature and properties of drugs only increases the responsibility of the druggist and demands the utmost vigilance. The detection of adulterations is therefore one of the most onerous duties of the pharmaceutical chemist and it is one which requires, beside chemical knowledge, a practical acquaintance with the sensible properties of all substances used in medicine.' (Bell, 1841.)

Nevertheless adulteration was an unsolved problem when Frederick Accum drew attention to it with his 'Treatise on Adulteration' in 1820. The development of chemical, physical and microscopic testing provided new weapons and in 1860 the Adulteration Act became law in Britain to apply, however, only to food and drink. It was extended in 1872 to drugs and by incorporating the Pharmacy Act of 1868 provided brief legal recognition of the *British Pharmacopoeia*. The Pharmacy Act made it an offence to compound any medicine in the *Pharmacopoeia* save according to the 'official' standards and such medicines had to be of the nature, substance and quality demanded. The 1875 Sale of Food and Drugs Act did not recognize the *Pharmacopoeia* which therefore ceased to be a legal standard (though still a presumptive one) in cases of adulteration.

Professional organizations were also formed who were greatly concerned with the detection and prevention of adulteration. One of the earliest was the Pharmaceutical Society of Great Britain founded in 1841. The Society of Public Analysts was founded in 1874.

Another important factor bearing on the development of drug standards was the rise during the 19th century of the pharmaceutical industry. Previously medicines had been prepared by the local apothecary often with locally gathered materials. The early industry gradually took over the task of preparing galenicals and was forced therefore to assume the responsibility of providing drugs of a sufficient standard of quality and efficacy to satisfy the pharmacist and the prescribing doctor that they were suitable.

There was also a rapid increase in the number of drugs available both due to chemical innovation and to exploration and discovery world-wide. The preparation and standardization of such drugs as morphine, quinine, atropine and synthetic chemicals such as carbolic acid, salicylic acid or phenacetin was certainly not a suitable task for the small pharmacist

and became even less so as the therapeutic explosion continued into the 20th century and to the present day. The development of pharmacology in the latter half of the 19th century provided a very necessary accompaniment for the testing and standardization of the new therapeutic armoury.

The 18th—early 20th centuries—the pre-thalidomide era

It is pertinent here to comment briefly on self-medication. Safety of a drug is relative and probably would be better considered together with the efficacy of the drug for the particular disease in question. There is no such thing as an absolutely safe drug and as Sir Derrick Dunlop once commented 'Unfortunately there are no therapeutic roses without their thorns'.

Put simply, a balance must be struck between the severity of the condition, the efficacy of the drug and its toxicity. This has led today to the concept that certain drugs are suitable to be used by the general public without medical supervision, whereas other drugs and some conditions must remain in the province of professional expertise. This has not always been so and until quite recently drugs have been generally available. It was obviously impossible to restrict the use of drugs obtainable by any knowledgeable person in field, garden or kitchen. The exotic herbs, elaborate compounds, mineral drugs and medicines from different places have not been accessible to all and professionalism with its closed shop principles has always tended to keep its tools and privileges in its own hands. Nevertheless, from ancient times, the ordinary person had far less recourse to the physician than today. The reasons were multiple and included expense and non-availability, beside an inherent desire to treat oneself and family. As Cesare Ripa observed in his 'Iconologia' of 1593 (translation in Schouten, 1967, p. 93):

'The Ancients considered it ignominious for anyone past the age of forty to call in a doctor, since by that time he should know what was good for him and avoid what was bad, thus curing himself by choosing the one and abjuring the other ...'

Every man his own physician has its earliest quote in Herodotus who, writing in the 5th century BC, said of the ancient Babylonians (incorrectly as it happens for there was an organized medical profession):

'having no use for physicians, they carry the sick into the market-place; then those who have been afflicted themselves by the same ill as the sick man's, or seen others in like case, come near and advise him about his disease and comfort him,

telling him by what means they have themselves recovered or seen others so recover. None may pass by the sick man without speaking and asking what is his sickness.' (Herodotus, I. 197.)

The Romans scorned to soil themselves with the practise of medicine but some acquaintance with the art was a prerequisite of every educated person and paterfamilias. It was probably for this reason that the '*On medicine*' of Celsus, quoted earlier, was written about AD 30.

In Britain, as time passed, the activities of the Royal College of Physicians and the Society of Apothecaries were bringing about better standards of medical and pharmaceutical practice but little had been done to protect the public from the dangers inherent in self-medication, from the patent (i.e., secret) medicines, or from the ministrations of the unqualified practitioner. As early as 1542 a statute was passed, often called the Quack's Charter, which having castigated the surgeons for:

'... minding onely their owne luces and nothing the profit or ease of the diseased. ...'

stated:

'... it shall be lawful to every person, being the Kings subject, having knowledge and experience of the nature of herbs, roots and waters or the operation of the same ... to practise, use and minister in and to any outward sore, uncome, wound, apostemation, outward swelling or disease, any herb or herbs, ointments, baths, pultes and emplaisters according to their cunning, experience and knowledge in any of the diseases, sores and maladies aforesaid and all other like to the same or drinks for the Stone and Strangury or Agues. ...' (Goodall, 1684.)

This was, of course, in direct opposition to the establishment views of the time and opened the door to unlicensed healers of many sorts.

In spite of the curbs placed on the Apothecaries by the machinations of the Physicians, little was done for many years to control these quacks. It is not proposed here to give a detailed account of quackery though it does form a significant commentary on the credulity of man through the ages. It is difficult to define 'quackery' and many of the unorthodox methods of healing at the time were sponsored by medical men. *The Concise Oxford Dictionary* (third edition 1976) does offer the definition that a quack is an ignorant pretender to skill especially in medicine or surgery; one who offers wonderful remedies or devices, a charlatan. It is this aspect of deliberate fraud that presented such a striking picture in the Britain of the 17th and 18th centuries. It was a characteristic of the quack that he advertised himself

and his cures in extravagant terms by handbills or in the public press.

The Medical and Physical Journal, one of the earliest to supply regular information on new work in medicine and pharmacy, chemistry and natural history, suggested in its first volume in 1799:

'... we would submit to the legislature the propriety of erecting a public board composed of the most eminent physicians for the examination, analyzation and approbation of every medicine before an advertisement should be admitted into any newspaper or any other periodical publication and before it should be vended in any manner whatsoever...' (Anonymous, 1799.)

This plea for legislation had no effect whatsoever and little progress was made until the next century.

The story of the control of the safety, efficacy and quality of medicines, however, now begins to develop the roots of the present day situation. Measures began to be taken also to control the supply of drugs and other poisonous substances and to ensure that this was to responsible and well-informed people. This control of supply does not perhaps fall into the mainstream of the present considerations bearing as it does on the development of the modern retail pharmacist.

Nevertheless it will be of interest to survey briefly the scene before returning to the major topics. Some control over the sale of dangerous and poisonous substances had indeed been taken as far back as the Gin Acts of the 18th century which recognized that Government had some responsibility to prevent the adulteration and abuse of what is in effect a drug. In 1819 a Bill was presented to Parliament entitled 'A Bill for establishing regulations for the sale of poisonous drugs and for better preventing the mischiefs arising from inattention of persons vending the same'. This Bill was supported by the 'Associated Apothecaries' (a body separate from the Society of Apothecaries) but was strongly opposed at a meeting in June 1819 of the Chemists and Druggists who said that the Bill was '... likely to embarrass the dispensing of medicines and not calculated to effect the object intended...' (Bell & Redwood, 1880, pp. 69-70). This opposition succeeded and the Bill was withdrawn. Nevertheless the meeting thought fit to give guidance to all chemists and druggists to minimize fatalities arising from the almost unlimited sale of poisons. These recommendations could not be mandatory but included the use of printed labels with the name of the substance and the word 'Poison'. Sale, moreover, should be only to responsible persons. Nevertheless it was recognized that some control over the sale of poisonous substances was long overdue as was shown by the Arsenic Act of 1851. Arsenic was then widely available as a rat

poison, seed dressing, treating sheep and various industrial processes, and poisoning from it had begun to worry the authorities. This Act controlled the retail sale of arsenic and required the details to be recorded in a register.

The modern concept of an authorized seller of poisons was still not then in being and there was no legal definition of a chemist or druggist. The first professional register of these was established by the Pharmacy Act of 1852 and it was the Pharmacy Act of 1868 which was the first to make a serious attempt to control the labelling and selling of poisons. Poisons were divided into two schedules and the seller was obliged to label them as 'poison' and with the name and address of the seller who had to be a registered chemist and druggist or pharmacist. These regulations were very similar to those introduced voluntarily by the chemists and druggists nearly 50 years earlier. The Poisons and Pharmacy Act of 1908 further amended the 1868 Act but there was still no restriction on the sale of poisons or dangerous drugs to prescription by a medical practitioner only and these substances could be sold to anyone known to the pharmacist. Not until World War One and the Defence of the Realm (Consolidation) Regulations of 1917 was the supply of certain drugs such as barbitone, cocaine and morphine limited to those for whom a physician had prescribed them.

In 1920 the Dangerous Drugs Act was the first of a long series of Acts which over the years have controlled the supply and prescription of dangerous and narcotic drugs which are today consolidated in the Misuse of Drugs Act 1971. This control was aided by the recognition of the pharmacist as a self-governing profession under the Pharmacies and Poisons Act 1933 in which the Pharmaceutical Society of Great Britain was entrusted with enforcement.

The British Medical Association and 'Secret Remedies'

Proprietary medicines obtainable by the public had not been forgotten. An expose of 'secret remedies' was made by the British Medical Association which were analysed as far as possible and estimates given of the cost of the basic ingredients together with the claims (Secret Remedies 1909, More Secret Remedies 1912).

The British Medical Association commented in the preface to 'Secret Remedies' '... Care has been taken to reproduce the claims and the exuberant boasts of the vendors and the contrast between them and the list of banal ingredients which follow must strike every reader. This juxtaposition of analytical facts and advertising fancies is instructive and sometimes entertaining, the fancy is so free and fact so simple....'

'Secret Remedies' also hit at the stamp duties collected and the necessity of displaying the Inland Revenue Stamp on the package which, as the British Medical Association cynically observed '... advertisement phrases ... tended to suggest that the Inland Revenue stamp upon their packages implied some sort of Governmental guarantee of the efficacy of the remedy ...' ('Secret Remedies,' p. 184.) They comment drily that '... the Inland Revenue authorities do not as a rule display any anxiety with regard to the welfare of the public in the matter of the sale of nostrums ...'

Select Committee on Patent Medicines 1914

Nevertheless, someone else *did* care and in 1914 there was published the report from the Select Committee on Patent Medicines. It is worth listing several of the recommendations of this Committee, some of which had to wait until the Medicines Act of 1968 and some of which were never taken up. (Report from the Select Committee on Patent Medicines, 1914.)

Recommendations

56(1). That the administration of the law governing the advertisement and sale of patent, secret and proprietary medicines and appliances be co-ordinated and combined under the authority of one Department of State.

56(5). That there be established at the Department concerned a register of manufacturers, proprietors and importers of patent, secret and proprietary remedies. ...

56(6). That an exact and complete statement of the ingredients ... and a full statement of the therapeutic claims made ... be furnished to this Department ...

56(7). That a special Court or Commission be constituted with power to permit or prohibit ... the sale and advertisement of any patent, secret or proprietary remedy. ...

56(12). That inspectors be placed at the disposal of the Department. ...

58(2). That the advertisement and sale (except the sale by a doctor's order of medicines purporting to cure the following diseases be prohibited: cancer, consumption, lupus, deafness, diabetes, paralysis, fits, epilepsy, locomotor ataxy, Bright's disease, rupture.

58(3 and 4). That all advertisements ... diseases arising from sexual intercourse or referring to sexual weakness ... abortifacient ... be prohibited.

The Therapeutic Substances Act 1925

The anti-syphilitic drug arsphenamine ('Salvarsan') had been discovered in Germany in 1907 and was

imported into Britain until the outbreak of World War I when the Board of Trade issued licences to certain British manufacturers to make it. Each batch had to be submitted to the Medical Research Council for approval before marketing. The problem was that although synthetic, and hence the chemical identity of the product was known, highly toxic impurities could only be detected by biological testing.

It began to be realized also that the increasing use of potent biological substances and the extension of immunization were raising new questions of proper standardization of such preparations and of the competence of manufacturers. The only law at this time concerned with the purity or quality of drugs was the Food and Drugs Act of 1875 and this had a very limited application.

Control of biological substances was difficult to contain within a pharmacopoeial monograph for it demanded the use of biological standardization as the purity and the potency of these substances could not be measured by chemical means. The Therapeutic Substances Act (TSA) aimed to regulate the manufacture and sale of such substances and to provide standards to which they must conform, to regulate their labelling and to a certain extent their sale. The principal substances to which the Act applied were vaccines, sera, toxins, antitoxins, antigens, arsphenamine and related substances, insulin, pituitary hormone and surgical sutures. It provided for a licensing system with the Minister of Health as the Licensing Authority for England and Wales, the Department of Health for Scotland and the Minister of Home Affairs for Northern Ireland. The TSA also recognized that the competence of the employees of the manufacturer and the conditions under which they worked were equally important as the tests applied to the end products. Factory inspections and in-process control therefore played a large part in supervision by the Licensing Authority. Records of sale also had to be kept by the manufacturer and the container had to identify both the manufacturer and the batch.

This Act began modern concepts of safety. Further regulations issued between 1925 and 1956 brought more substances under control and kept standards under review and many of these became internationally recognized. The whole TSA was revised and consolidated in 1956 but has now been superseded by the Medicines Act (1968).

Little attention was still paid to the efficacy of drugs and treatment. The Venereal Disease Act of 1917 and the Cancer Act of 1939 prevented the public advertisement and promotion of drugs for these conditions to prevent sufferers from inadequate or unsuitable treatment and from fraudulent claims. It was necessary to wait until the Medicines Act was in force before further consideration was given to efficacy (but see Therapeutic Substances Act), but it

may be noted here that this was a foretaste of control of advertisement and promotional literature for medicines.

The thalidomide episode and its consequences

Until the passing of the Medicines Act in 1968 no legislation was in force to assess the safety of a drug (with the exceptions already noted under the TSA).

This does not mean to say that attempts had not been made to do this and as far back as 1880, a BMA working party investigating sudden deaths occurring in chloroform anaesthesia had suggested the establishment of an independent body to assess drug safety. Chloroform was first used as an anaesthetic in 1847 and as its use increased it was found that occasionally people died unexpectedly during the induction of anaesthesia. In 1877 the British Medical Association appointed a committee to investigate this and the final report was published in 1880 (McKendrick, Coates & Newman, 1880). They found that chloroform not only depressed the respiration but had a deleterious effect upon the heart in very small doses and could cause a cardiac arrest. This was the first major collaborative investigation of an adverse reaction to a drug ever carried out.

Other collaborative investigations into adverse effects were carried out in later years and in 1922 a Medical Research Committee working party (the predecessor of the present day Medical Research Council) looked into epidemics of jaundice and hepatic necrosis following the use of organic arsenicals to treat syphilis in soldiers returning from World War I.

The story of thalidomide is too well known to bear much repetition here but, as it is the foundation stone on which the Medicines Act was built, it is relevant to summarize what happened.

Thalidomide first went on sale in 1956 in West Germany and enjoyed good sales both there and in other countries as a sleeping aid and as a treatment of vomiting in early pregnancy because of its prompt action, lack of hangover and apparent safety. In 1961 reports began to be made of a remarkable rise in West Germany since 1959 in the incidence of a peculiar malformation of the extremities of the newborn. This condition was characterized by the defective long bones of the limbs which had normal to rudimentary hands or feet. Owing to its external resemblance to a seal's flipper, it was given the name of phocomelia. This condition had previously been very rare in West Germany but whereas no cases had been reported in the ten years between 1949–1959, there were 477 cases in 1961 alone.

It took several years for it to become clear epidemiologically that thalidomide was the cause of these abnormalities but by this time some thousands

of babies had been born world-wide suffering from severe skeletal deformities caused by the drug.

Although it had been known for many years that chemical substances could act as teratogens in lower animals and in mammals, the medical world as a whole seemed to have paid little attention to the possibilities of danger to the developing human fetus. Certainly drug companies did not deem it necessary that new drugs should be tested for their hazards to the human embryo before marketing. Warnings against the use of drugs in pregnancy were, however, already being raised about this time, but these were largely ignored.

Until 1968, therefore, and the passing of the Medicines Act, no statute in the United Kingdom required the pre-marketing approval of medicines on the grounds of their safety. Kenneth Robinson observed in a parliamentary debate on 8th May 1963:

'I come to my last main topic which is the control and safety of drugs. This is of course a subject which was thrust to the fore both in this House and in the public press a year or so ago as a result of the thalidomide tragedy. The House and the public suddenly woke up to the fact that any drug manufacturer could market any product, however inadequately tested, however dangerous, without having to satisfy any independent body as to its efficacy and safety and the public was almost uniquely unprotected in this respect.'

Most reputable manufacturers did actually carry out tests and trials on their new drugs but were not legally required to do so. After the thalidomide tragedy, on the advice of a sub-committee under Lord Cohen of Birkenhead, a Committee on Safety of Drugs was established by the Health Ministers as a temporary measure until legislation could be enacted. This was an entirely voluntary arrangement under the chairmanship of Sir Derrick Dunlop and was official only in the sense that the Health Ministers provided the finance, accommodation and the secretariat. Despite the complete absence of legal sanctions (albeit not the only way of applying pressure) the Association of the British Pharmaceutical Industry (ABPI) and the Proprietary Association of Great Britain (PAGB) promised that their members would not perform a clinical trial or market a new drug against the advice of the Committee. This advice was solely on the safety aspects and did not consider efficacy.

The CSD therefore had three main functions: to scrutinize new drugs before clinical trial and before marketing and the surveillance of each drug after marketing so that adverse reactions could be monitored, documented and warnings issued. To aid them in this function, they had three sub-committees—on toxicity and clinical trials, on

chemistry and pharmacy and on adverse reactions to drugs.

The Committee itself did not undertake testing of drugs but evaluated the manufacturers' submissions and other available evidence.

The Medicines Act (1968)

This Act will not be discussed in detail but it does represent the drawing together of the three strands of safety, quality and efficacy (to which should be added a fourth of supply) and their control in Britain by statutory means. It is therefore appropriate that a brief summary be given of the salient points of the Act.

The Medicines Act was based mainly on the White Paper 'Forthcoming Legislation on the Safety, Quality and Description of Drugs and Medicines 1967'. It came into force on 1st September 1971 and even yet is not fully implemented. Successive statutory instruments and amendments have made it much more comprehensive today than it was on its introduction.

The working of the Medicines Act seem very complicated at first sight but if a few essential points are remembered, the rest soon falls into place. The Act provides for a Licensing System applicable to the marketing, manufacture, importation, distribution and clinical testing of medicinal products for both human and veterinary use. Licences are issued by a Licensing Authority which consists of the Health and Agriculture Ministers of the UK though in practice

the licensing of human medicines is carried out on their behalf by the Department of Health and Social Security and for veterinary products by the Ministry of Agriculture, Fisheries and Food. The Licensing Authority is advised by various expert committees and is required to take into account the safety, efficacy and quality of medicinal products.

These expert committees include the Committee on Safety of Medicines, the Committee on the Review of Medicines, the Committee on Dental and Surgical Materials and the Veterinary Products Committee.

The Medicines Act also established the Medicines Commission whose function is to give advice to the Ministers on any general matter relating to the Act. It also has under its direction the British Pharmacopoeia Commission which is now responsible for producing the *British Pharmacopoeia*.

The responsibility of the Licensing Authority is a continuing one and control of a drug not only includes scrutiny before clinical trial and before giving permission to market but during the whole of its clinical usage. This involves monitoring for adverse reactions, control of promotion and advertising, and inspection of manufacturing facilities.

The Medicines Act therefore forms the most comprehensive control of drug development, manufacture and sale to date in Britain and it is tempting to ask 'what next follows'. This is undoubtedly the extension of similar controls by the European Economic Community to all member states and the development of a uniform and agreed system of the control of drug safety, quality and efficacy.

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