at a point of time when there is still much contractile energy available in the muscle if effective motor impulses were provided. There is reason to regard the process of fatigue in the ischaemic limb as similar in most respects to what occurs with the intact circulation, though more rapid and acute.

Static Fatigue.

The onset of failure in this form of fatigue is of central origin, since when the continuous voluntary effort can no longer sustain the weight and prevent the shortening of the muscle from being overcome, the muscle can still respond strongly to direct electrical excitation. In this respect there is a general resemblance to the fatigue induced by a moderately slow (40 to 80 per minute) voluntary series of contractions. But in some other respects the two forms differ strikingly—for example, in relation to the influence of ischaemia.

The length of the period during which voluntary effort is effective in maintaining static contraction is very little affected by an ischaemic condition of the limb; indeed, the curves obtained in the normal and in the ischaemic states may be almost superimposable—in notable contrast to the rapid development of failure in voluntary serial contractions in ischaemia. Again, a period of static contraction has an improving effect (on contraction force), less than that of a period of rest, when interposed in the course of a series of voluntary contractions showing the progressive development of fatigue. There are indications which point to static fatigue with intact circulation as being essentially due to fatigue in the central nervous system, not dependent in any important degree on afferent impulses from the contracted muscle so far as evidence is available.

THE PINEAL GLAND.*

PROFESSOR HERRING (St. Andrews) showed a series of lantern slides illustrative of the histology of the pineal region of the mammalian brain. It was pointed out that the pineal body was not the remnant of the parietal eye found in some of the lower animals. The pineal body was a separate structure which was developed behind the parapineal organ or parietal eye. In man and most mammals the pineal body was bound up with the habenular and posterior commissures, but in the rat the pineal body lay on the surface of the brain between cerebrum and cerebellum. In this animal it was an isolated and highly vascular body which was suggestive of an organ of internal secretion. The pineal body of the cat was innervated only by fine nerve fibres, which entered it with the blood vessels. The mammalian pineal body contained a material which produced contraction of the melanophores of the tadpole, but its function was as yet unknown. Attention was drawn to the subcommissural organ of most mammals, which Dendy regarded as a receptor brought into action by changes in tension of the fibre of Reissner. The organ was well developed in most mammals, but was rudimentary in man.

PROTEIN METABOLISM IN CYSTINURIA.*

PROFESSOR D. MURRAY LYON and Mr. W. ROBSON, D.Sc. (Edinburgh), in a joint contribution, stated that various aspects of protein metabolism in a case of cystinuria had been studied. Cystine added to the diet to the extent of 20 grams over a period of four days was found to be quantitatively oxidized to inorganic sulphate. Likewise other amino acids were found to follow the normal paths of metabolism and to lead to increased urea excretion. Addition of sodium bicarbonate caused an increased output of cystine, practically the whole of it being in solution in the urine and only a small part in the urinary sediment. Disodium phosphate had no appreciable effect in producing the alkalinity necessary to hold in solution the cystine excreted. Changing the diet to one containing more protein gave rise to an increased excretion of cystine. The position of the "inborn error" was discussed.

* Brief abstracts of communications to the Section of Physiology and Biochemistry at the Annual Meeting of the British Medical Association, Edinburgh, 1927.

MODES IN WHICH DRUGS HAVE BEEN INTRODUCED TO USE.*

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THE early history of the introduction of remedies is closely interwoven with the origins of primitive religions and, while reserving judgement on the theory that some animals have a crude idea of "first aid," it is highly probable that, since man's continuous effort has been to overcome the obstructions of Nature to his welfare and progress, his selfish instincts must have led him to seek means of defence against his personal injuries and diseases even before he evolved a communal religion.

The customs of primitive tribes show that the etiologies of diseases and misfortunes were first ascribed to malevolent human agencies, then to the interference of demons, and, progressively as religious beliefs developed, to infringement of a taboo, to neglect of ancestral spirits, and, finally, to an offended deity.

Among the least cultured peoples treatment commenced as a magical rite or exorcism, associated with the external application or internal administration of some medium; this medium or "drug" was essentially an amulet aiding the protection of the individual or the expulsion of the demon; in Polynesia, for example, the medicine given was "considered more as a medium by which the god would act than as possessing any power itself to arrest the disease."²

When these primitive rituals had as objective the benefit of the individual they became the basis of primitive therapy, but when they had as purport the protection of the community from pestilence, famine, or other calamity, they became the foundations of religious belief or of public hygiene in the tribe.

As diseases became differentiated so the number of etiological demons multiplied; thus, there were evolved specialist medicine men and an expanding list of exorcising remedies of specific purport; in other communities exorcism or propitiation of several demons or deities was attempted by repetition of the magical rite or by numerical grouping of the remedies or the times of their administration. A typical instance of this phase is recorded by Rivers at Eddystone Island, where epilepsy is treated by stroking the patient with four leaves and calling on "four ancient women" of the tribe, the treatment being performed on the last four days of the waning moon and repeated after four months.³ This case shows the primitive use of herbs purely as amulets, associated with the numerical arrangement of the rite and the herbs to influence four etiological factors, and indicates a primitive belief in the influence of the satellite on epilepsy.

Early Vedic literature provides confirmatory evidence of these views; thus, in the Atharva-Veda (circa 1000-700 B.C.), treatment is uniformly magical in type and curative agencies are amulets; the exorcisms may be directed against a human sorcerer or demons, or an offended deity is propitiated.⁴ The remedies were chosen on religious or mythical grounds; thus, butea and the soma plant were of great holiness; lead,⁴ catechu, colocynth, cannabis, and mustard had potent demon-dispelling powers; while curcuma was used for jaundice because of its yellow colour—a type of sympathetic magic.⁵ Liquorice was a charm to secure the love of women, and ricinus was a component of a battle charm.⁴ In Zoroastrianism also drugs were utilized chiefly as charms to expel demons.⁶

Although there is some evidence, both from the primitive tribes in the Philippines and in America and also from the classical period, that drugs were tested upon animals and sometimes upon man, the evidence from primitive medicine regarding the evolution of drugs is against experimental therapeutics and in favour of the opinion that they were originally used for driving out the demons of disease from the body; hence we find in primitive therapy a preponderance of remedial measures having effects as purgatives,

* Read in the Section of the History of Medicine at the Annual Meeting of the British Medical Association, Edinburgh, 1927.

emetics, anthelmintics, etc., and of physical means such as bleeding, cupping, counter-irritation, and massage. Comparative philology also supports this contention by affording proof that in many languages the root which implied "magic" or "incantation" produced stems to which were applied the transferred meanings of medicine—remedy, poison, or physician.⁷

As, however, diseases became clinically defined, experience proved the empirical advantage of certain herbs or formulae. Two probabilities now arose: (1) the use of the drug might be continued while its magical rite was discarded, or (2) the symbolical ritual might be preserved—especially through folk medicine—and the remedy become obscured by admixture with others. This transitional phase is illustrated in Assyro-Babylonian tablets.

Our knowledge of Egyptian civilization affords proof that even in the first to third dynastic periods it was possessed of cosmetic pomades and paints, but the earliest medical treatises—the papyri of Ebers, Hearst, Smith, London, etc.—are all from a period approximating 1500 B.C., which may be regarded as a climax of Egyptian therapeutics. The Egyptians had, on the evidence of the Ebers Papyrus at least, largely discarded the incantation, but this papyrus contains many prescriptions consisting of four remedies which are to be given on four occasions. The numerical grouping is evidently an endeavour to propitiate the four sons of Horus, who guarded the four corners of Heaven and who presided over specific organs of the body;⁸ here we have an origin of the doctrine of physical and physiological fours.⁹ The Ebers Papyrus was a temple formulary which it was sacrilegious to amend, but the priest-physician might record against prescriptions of proved value the words "Good to use"; it shows, therefore, a break away from theurgy and an attempt to establish empiricism. The formulae are difficult to analyse, partly because of unidentified ingredients and partly because the active ingredient is rarely placed first, but, assuming that some of the formulae gave a measure of effective result, there is reasonable ground for believing that we owe to the Egyptians an elementary pharmacology of the following remedies:

Emetics.—Copper salts, squill.

Purgatives.—Figs, dates, raisins, aloes, ricinus seeds, sea-salt, artemisia.

Carminatives.—Caraway, coriander, juniper, myrrh, mentha (? pulegium), fennel, dill, onion.

Astringents for Diarrhoea.—Lead salts, egg-albumen, gruel.

Worms.—*Ascaris*: Pomegranate root bark, artemisia, ricinus seeds, sea-salt, copper subacetate. *Taenia*: Ricinus seeds, artemisia, mentha, lead salts, sea-salt.

Acute Disease (?hookworm).—Turpentine resin, artemisia, mentha.

Meal and linseed were used to make poultices, and to these were added herbs containing volatile oils which would act as counter-irritants; for wounds, poultices containing sea-salt, onions or aromatic herbs, and wine are advised; while conjunctivitis was treated by salves containing metallic astringents—for example, salts of lead or copper. Juniper and sea-salt occur frequently amongst diuretic prescriptions. Other drugs, of which the purpose is obscure, are opium poppy capsules—possibly also the juice—hyoscyamus, hemlock, zinc oxide, and iron sulphate.¹⁰

There is no doubt that the knowledge of Egypt filtered through to contiguous nations, and Assyro-Babylonian tablets dating from about 600 B.C., when the Assyrian physician had not succeeded in divorcing medicine from magic, contain recipes which may be grouped into two types—older forms redolent of exorcisms, and newer forms which are simply prescriptions. Assyrian remedies which have not been clearly established in the Ebers Papyrus are sulphur for itch, attar of roses, bitumen, almond oil, galbanum, alum, liquorice, and anise.¹¹

In Brahminical therapy a great improvement occurred between Vedic times and the Charaka-Susruta period (circa first to fifth century A.D.). Accumulated experience enabled Charaka to evolve fifty groups, each containing ten herbs, which he thought "enough for the purposes of an ordinary physician." His classification is made on a pharmacological basis and, to epitomize, there are quoted as emetics, salt, mustard seeds, and copper sulphate; as

purgatives, castor oil, cassia fistula, turpethum, and sulphur and mercury preparations; and, as an anthelmintic, embelia. Cannabis was recognized to be sedative, and datura as inebrant, but nux vomica seems to have been regarded as narcotic. Cardamoms, chiretta, and cane sugar had also been brought into use.¹² This rapid development of Hindu medicine is often regarded as a result of Grecian influence, but this is difficult to accept, since most of the remedies are indigenous. It seems more likely that investigation of native herbs by the Brahmins was inspired by travellers from Egypt and Assyria in a period (Ayur-Veda) anterior to Charaka.

About 1000 B.C. Egyptian and Mesopotamian therapy began to influence Greece; thus Homer tells of Helen receiving from the Egyptian Polydamna her knowledge of a soporific, which was probably opium, to abolish grief and pain, and he testifies to the superior skill of Egyptian physicians.¹³ Homeric therapy shows little trace of theurgy, but in the Asklepiian temples drug therapy became subordinate to mysticism,¹⁴ and it was only when the Asklepiads divorced themselves from the priesthood at Cnidos and Cos that medicinal substances received appropriate homage again. The majority of the drugs in the Hippocratic collection are of Egyptian origin, and there are traces of resemblance in some prescriptions to those of the Ebers Papyrus; the few remedies of Indian origin were probably acquired through Phoenician traders.

I must not delay to eulogize Hippocrates: historical times have been reached, with a substantial *materia medica* derived from ancient civilizations; the list was constantly being increased by addition of herbs collected by the physicians themselves or brought to them by the pharmacopoli, botanologi, and rhizotomoi. This knowledge was collated by Theophrastus in his *De Historia Plantarum*, a treatise describing some five hundred herbs. That the actions of these drugs were imperfectly understood needs no emphasis, but attempts were made in the Alexandrian school by Herophilus and Heracleides to determine their activities and regulate their mode of administration—for example, those of opium as a soporific. In the same period the insecure tenants of thrones instituted pharmacological experiments upon their subjects, and to Mithridates VI, King of Pontus, or his rhizotomist, Krateras (120-63 B.C.), is due the universal antidote mithridation and the conception that tolerance to poisons may be acquired. During this period the doctrine of the four humours developed, and its extension to the four qualities of drugs, which did much to obscure their actions during the dark ages; the doctrine, although ascribed to the Pythagoreans, was, there is little doubt, founded on Egyptian religious tenets.

With Rome as the centre of culture there commenced a period of polypharmacy and uncritical empiricism, when the rarity, secrecy, or complexity of the compound was its chief claim to virtue, as in the famous theriacum of Andromachos—a panacea of some seventy ingredients—which remained in vogue till the *London Pharmacopoeia* of 1746. The Roman period, however, was not entirely decadent, and Dioscorides deserves recognition for his attempt to simplify therapeutics by his succinct descriptions of the remedies of his times.

I must leave the early results of empiricism with the statement that, by making a rough classification of the present vegetable *materia medica*, we can discover that 30 per cent. of the crude drugs are mentioned in the Ebers Papyrus, Assyrian tablets, or early Brahminical treatises; that 37 per cent. were known in classical times; and, by including the drugs introduced by the Arabian school, we reach 50 per cent. of the whole. Among the remedies handed down from antiquity occur practically all the demulcents, flavours, or carminatives, purgatives, and anthelmintics; of bitters, gentian occurs in Dioscorides and chiretta as a febrifuge in Susruta; orange and lemon escaped Greco-Roman notice and were introduced by the Arabians. Of vegetable astringents, galls, myrobalans, and bael fruit were used, but astringent metallic salts were preferred; squill, which was probably only an emetic with the Egyptians, was a diuretic for dropsy in classical times. Opium was recognized as a soporific, and hyoscyamus and datura as deliriant narcotics; knowledge

of the sedative properties of cannabis seems to have been transferred from India to the Arabians.

It may be said that, with the exception of the drugs introduced by the Arabian school—namely, rhubarb, senna, camphor, nutmegs, cloves, sandalwood, cassia, and tamarinds, which probably emanated from India—the *materia medica* of Dioscorides was the foundation upon which medicinal treatment was based down to the advent of the renaissance in medicine, and that confusion of the pharmacological facts discovered by the ancients resulted from the doctrinal controversies concerning therapy which were waged down to within comparatively recent times.

The next important source of new remedies was the discovery of America, but the accounts of the introductions give us little concrete information as to the original reasons for their selection. Tobacco was discovered in Cuba in 1492, and guaiacum wood (*lignum vitæ*, *lignum sanctum*) reached Europe from San Domingo shortly afterwards. Freind states that Gonsalvo Ferrand, in search of a cure for syphilis, found guaiacum used with success in the West Indies, and was the first to import it;¹⁵ but Oviedo is also credited with its discovery in 1514.¹⁶ Its fame as a treatment for the "French Pockes" must have spread rapidly, because its virtues were extolled in 1519 by Ulrich von Hutten, whose work was published in English by Thomas Paynell in 1536;¹⁷ and it was mentioned in conjunction with mercurial inunctions and fumigations by Fracastoro in 1530.¹⁸ It was Paracelsus, of course, who popularized the employment of mercury internally in the disease.

A little later sarsaparilla was introduced from New Spain and Honduras, and from about 1553 was recommended in the sudorific treatment of syphilis.¹⁹ Jalap root was found in Mexico, and the Spanish physician Monardes refers to it in 1565 as the "rhubarb of the Indies"; the same author seems to have introduced the balsams of tolu and Peru.²⁰ The use of ipecacuanha for the "bloody flux" in Brazil is recorded in 1625 on the authority of a Portuguese friar,²¹ but it was not until 1680 that Helvetius, acting on information gleaned from a Paris merchant, advertised its virtues in dysentery and, having successfully cured the Dauphin of France by its aid, sold his secret to Louis XIV for 1,000 louis d'or.

The mode of introduction of cinchona is almost mythological. Local legend suggested that the waters of a lake, into which cinchona trees had been overthrown by an earthquake, were found curative of ague, but it seems more probable that the value of the bark was known in Peru, and that a grateful servant imparted the knowledge in 1630 to the Governor of Loxa, who transmitted it eight years later for the treatment of Countess Ana of Chinchon, wife of the Peruvian viceroy. Her cure led to its use a year later in Madrid under the name of "Countess's powder." By 1650 it had been widely distributed by the Jesuit priests, and acquired the name "Jesuits' powder." Thomas Willis mentions its value, and Sydenham in his *Methodus Curandi Febres* (1666) describes its use; but Sir Robert Talbot, an "irregular" practitioner, was mainly responsible for establishing its use by effecting with it the cures of Charles II of England and the Dauphin of France.²²

The seventeenth century gave birth to physiology and histology, but the irrational and unsavoury list of nearly 2,000 remedies which in 1618 constituted the first *London Pharmacopoeia* was an infant in which the sins of its fathers for more than the third or fourth generation were apparent; even Culpeper, immortal quack, could make merry at its expense!

The eighteenth century has a more creditable record; the fourth and fifth *London Pharmacopoeias* were still redolent of skatological, astrological, and folk therapy, but the critical essay *Antitheriaka*, by William Heberden (1745), was successful in banishing mithridate, theriac, and other superstitious nostrums from the sixth *Pharmacopoeia* of 1788, in which were approved the "diaphoretic powders" of Thomas Dover and of James, kino, which we owe to Fothergill, and senega, which, used by the Indians for rattlesnake bite, was advised by Dr. Tennant, a Scotsman in Virginia, for pleurisy and pneumonia.

About this period Thomas Fowler, an apothecary of York, who had acquired an Edinburgh degree, analysed a patent medicine which was advertised as "Tasteless ague and fever drops," and found it to contain arsenic. He devised the well known "Fowler's solution" (1786), and reported its effects in agues, remitting fevers, and periodic headaches; credit for the rational use of arsenic is thus due to a quack remedy.

Two triumphs resulting from the observation of folk medicine were the establishment of vaccination by Jenner in 1796 and the introduction of digitalis by Withering, an Edinburgh graduate, in 1785.²³ Ergot also was probably derived from folk medicine; it was known as an abortifacient during the sixteenth century, but did not come into general use as a uterine stimulant till the beginning of the nineteenth century.

The rapid advances in the nineteenth century were consequent on the development of chemistry with its discovery of the alkaloids, and upon the knowledge gained through experiments upon animals; Magendie (1821) was a pioneer in determining the actions of bromides, strychnine, and morphine, and in showing their therapeutic applications. Magendie's mantle descended upon the Edinburgh school, and I need merely mention the names of Sir Robert Christison, David Wardie, Sir James Young Simpson, Alexander Crum Brown, Sir T. Lauder Brunton, Sir Thomas Fraser, and Sir E. Sharpey-Schafer to recall to mind the therapeutic advances for which experimental investigations were responsible. Another cradle of experimental work was Dorpat, through which passed to larger spheres of influence Dragendorff, Buchheim, Schmiedeberg, Kobert, and Hans Meyer.

The number of drugs introduced by modern experimental methods has been large; those which have survived the test of clinical experience are familiar to all, and I need do no more than remind you of some outstanding examples. Carbolic acid was introduced as an antiseptic by Lord Lister in 1867; amyl nitrite for angina pectoris by Brunton in 1867; chloral by Liebreich in 1869; cocaine as a local anaesthetic by Koller, and antipyrine by Filehne in 1884; strophanthus by Fraser in 1891, and adrenaline by Sir E. Sharpey-Schafer in 1894.

The late Sir Clifford Allbutt once said of Freind's *History* that "he spread his net too widely"; the present endeavour to epitomize the evolution of remedies suffers from the exigencies of time and space, but its imperfect generalizations will, I trust, induce some of my readers to elaborate and qualify the principles which in various periods have been involved in the introduction of new remedies.

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