THE CHEMISTRY OF LIFE

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Eight Lectures on the History of Biochemistry

by

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INTRODUCTION

by Joseph Needham

This book, the outcome of a course of lectures which was given by Cambridge biochemists each year from 1958 to 1961 under the aegis of the History of Science Committee and Department, is not the first collective work which has been generated by the modern movement for the history of science in Cambridge. For in 1938 the University Press published *Background to modern science*, ten lectures by leading figures in research who were willing to look back over the previous four or five decades and to say how the development of science seemed to them to have been set forward during that time in their own field. The modern phase of the history of science in Cambridge goes back close on thirty-five years, for it was in 1936 that two events took place: the loan exhibition of historic scientific apparatus in the Old Schools organized by the late Hamshaw Thomas; and the formation of a Committee (under the chairmanship of the present editor and with Walter Pagel as secretary) to arrange for courses of lectures on the history of science. From these small beginnings over the years has grown the present thriving Department of the History and Philosophy of Science (headed by Gerd Buchdahl), with its Whipple Museum of historical scientific instruments and a valuable library used by many students and research workers. The lectures now printed in this book were well attended, and the group was happy to welcome into it one player from away, namely Mikuláš Teich of Prague, one of the few living professional historians of biochemistry. Although our subject is of such fascinating borderline interest, it has so far surprisingly given rise to only one full-scale book, that of Fritz Lieben (1935); perhaps Teich will endow us with another.

Although some far backward glances are here included, effectively most of the material in this book refers to events from about 1800 onwards. If we are to talk about the history of biochemistry, the development of human knowledge of the chemistry of life, we are faced with the problem of defining it. It is quite a tenable point of view to hold that it is not possible to speak of biochemistry until modern chemistry had been born —and that did not happen until the growth of the chemistry of gases in the latter half of the eighteenth century, the 'revolution in chemistry' of Lavoisier, and the founding of modern atomic chemistry by Dalton. But this may well be thought too narrow and rigid, laying the accent also on the '-chemistry' rather than the 'bio-'. By contrast, if one includes all the old ideas, speculations and groping experiments on the chemistry of living things, whether plants or animals, then a vast realm of history lies before us. Nothing that men have ever thought and done on the implicit presupposition that there *was* a chemistry of living matter, can then be alien to us. Some selection from the many trends of thought involved was what I used to contribute in my lecture in the series now before us, but there is such a gulf fixed between ancient and mediaeval ideas and doings on the one hand, and modern post-Renaissance scientific endeavour on the other, that my participation here may better take the form of an introduction to the whole, even though it means compressing a quart into a pint pot. What is needed is some sketch of the background panorama for the contributions which follow, a perspective glass to show that their subjects did not suddenly come into being like a set of extraordinary mutations, but rather that they grew like plants with roots coming up a very long way from the sub-soil of antiquity. Furthermore, it will be found when one penetrates into the bygone origins of biochemical ideas that it is necessary to take the whole of the Old World into consideration, not treating Europe as a self-contained entity, which it never was, but bringing into consideration the great contributions of the Arabic, Indian and Chinese culture-areas.

In the very restricted space at my disposal it will be possible neither to give illustrative quotations, always so moving in the words of the original writer, nor to give precise datings except for names likely to be unfamiliar to the general reader, nor to give chapter and verse for statements that will be made. A select group of references may, I hope, atone somewhat for this. How best in short space to depict that general background already mentioned presents, of course, an almost insoluble problem. One could search the pre-Socratic philosophers (sixth and fifth centuries B.C.) and the Hippocratic corpus (fourth century B.C.) for many interesting speculations about the material basis of life, and to them one could add similar material from the *Suśruta* and *Caraka Samhitas* in India (first to third centuries A.D., revised eighth to eleventh) and from the philosophers of the Warring States period (fifth to third centuries B.C.) further east. Alternatively, one could take a single conception, for example animal heat, and follow it through all its ramifications from the earliest Greek and Chinese statements down to the beginnings of modern knowledge of oxidation-reduction processes in the living cell. I thought however that I should like to follow a different way and dwell less extensively on a small number of key ideas, almost as if they were entries in a kind of Voltairean 'Dictionnaire Philosophique' (without however any undertone of mockery). Let us therefore try to say something about each of the following key-words—Pneuma—Element—Humour—Krasis—Quintessence—Elixir—Conjunction—Ferment.

How many books could be written (and of course have been written) on the 'breath of life'! The association of breathing with life and its cessation with death came down from the earliest historical times and beyond, and it was quite understandable that the functions of the body and all its organs and tissues should be thought of in terms of the movement and nature of a number of imperceptible breaths. This pneumatic proto-physiology and proto-biochemistry was common to all the civilizations of the Old World. For it has been shown in detail that the *pneuma* of the Greeks was equivalent to the *prāṇa* of India, the *ch'i* of the Chinese and later on the *rūḥ* of the Arabs. The universality of this conception prompts the conviction that it originated in the Fertile Crescent, spreading out in all directions, even if so far the Assyriologists have not been able to find much evidence for this. The Indians classically counted and tried to define five sorts of *prāṇa* and the Chinese a good many more. For a millennium and a half European thought on these matters was dominated by the Galenic theory of spirits; *pneuma*, spirit as such, coming from the circumambient air through the lungs, and combining with *pneuma physikon* or natural spirits prepared by the action of the liver on the food, to form *pneuma zōtikon* or vital spirits. The former were distributed in ebb and flow from the right ventricle of the heart through the system of the veins, the latter from the left ventricle through the arteries. Similarly, under the action of the brain, the vital spirits were transformed into *pneuma psychikon* or animal spirits, distributed to all parts of the body through the nerves. Here there was of course some connexion with the Aristotelian doctrine of 'souls', for both the natural and vital spirits were at the level of the vegetal soul (*psychē threptikē*), and the animal spirits were in the domain of the sensitive soul (*psychē aisthētikē*), while for the rational soul (*psychē dianoētikē*), because essentially mental, there was no equivalent in the world of material spirits. Ancient Chinese ideas were much more like those of the Greeks than has usually been supposed, for at about the same time as Aristotle, Hsün Ch'ing and others conceived of a 'ladder of souls', e.g. *ch'i*, *shêng*, *chih* and *i*, representing a very similar ascent. From our present viewpoint, the 'souls' were but names for particular functions of the levels of living, yet we still conserve such names as 'vegetal' for the yolky poles of eggs, and 'vegetative' for parts of the nervous system.

When the Renaissance came, something like nitre and salt-petre was recognized in the external *pneuma*, and the 'nitro-aerial particles', surmised by the Paracelsians and demonstrated by Mayow, pointed the way towards the development of 'pneumatic' chemistry in the eighteenth century. Meanwhile John-Baptist van Helmont (1579 to 1644), who has perhaps as good a title as anyone else to be called the father and founder of all modern biochemistry, separated clearly the ancient *pneuma* idea into his *gas* and his *blas*. From his recognition of the identity of carbon dioxide onwards, the way led clear through Priestley, Cavendish, Black and all the others to the modern discoveries of the transit and carriage of gases in living bodies, the respiration of the cells themselves, and the nature of the energy-providing oxidation-reduction reactions going on inside them. Van Helmont's *blas* was another way of talking about the more spiritual spirits, including those *archaei* which both

Paracelsians and Chinese had visualized as presiding over the activities of every organ (like controllers sitting in front of instrument-panels in glass boxes high above the automatized activities of great factory halls in modern industrial plants). He thus skilfully shunted off all discussions of this aspect of things on to the philosophical loop-line of the mechanist-vitalist controversies. These have been prominent at various times, as in the Naturphilosophie period early in the nineteenth century, the time of the synthesis of urea by Wöhler (lecture 7 hereafter), or again in the Liebig–Pasteur controversy (lecture 3), or again in the present century, aroused by the supposed gas-secretory activity of the lung; but today they have lost much of their intensity with the recognition of the omnipresence of levels of organization, morphology extending down to the level of complex molecules, and chemical processes reaching up to the very substratum of mental activity (lecture 4).

In China also, *ch'i* became more and more material as time went on, and having begun (as we know from the etymology of its ideograph) as the steam arising from cooking rice, it came to mean by the twelfth century all kinds of matter, however gross. This was the time at which the Chinese scholastics, the Neo-Confucians, were able to build their scientific world-view on two conceptions only, *ch'i*, which we might now call matter-energy, and *li*, which we may call organic pattern at all levels, whereever manifested. The pursuit of the *ch'i* led people in China to some striking discoveries, such as that of the existence of deficiency diseases (cf. lecture 6) by a Mongolian physician about A.D. 1325. This was Hu-Ssu-Hui (Hoshoi), Imperial Dietician under four Yuan emperors, who observed that there were some diseases, such as, for example, the last stages of avitaminosis-B, which could be cured by diet alone, without the intervention of any drugs at all. We still possess his book, the *Yin Shan Chêng Yao*.

All this pneumatic heritage has left indelible traces on both our language and our thinking. As I sat down to write these words, builder's tradesmen were loudly singing 'in high spirits' on the other side of the garden wall, and in the newspaper I had read of the evidence transmitted back by Mariner 7 that there is methane and ammonia—therefore perhaps *life*—on the planet Mars.

Introduction

For two thousand years or more before the appearance of the modern conception of elementary substance, during and after the Lavoisierian revolution, all the peoples of the Old World had had the conception of Elements. The classical Aristotelian earth, fire, air and water are well known, and could still inspire modern poets such as W. B. Yeats and Dorothy Wellesley; less well known are the Chinese five: metal, wood, water, fire and earth. These played perhaps a greater role in proto-physiology and proto-biochemistry at the eastern end of the Old World than the four elements did in the West, for in accordance with the elaborate Chinese system of symbolic correlations, elements were associated not only with planets but with specific organs in the body. That they could conquer each other and be generated from one another was again an idea which existed among the Greeks (as in Plato's *Timaeus*) but which was carried much further in Chinese thought. Earth, fire, air and water came right down to the beginnings of modern chemistry, for as late as the last quarter of the seventeenth century it was a great point of dispute (in which Robert Boyle prominently participated) whether or not analysis of mixed bodies by fire could demonstrate either the existence of the classical elements or that of the *tria prima*, salt, sulphur and mercury, which the Paracelsians (cf. p. xx) had partially substituted for them. The Indian Buddhists also had their elements, as usual more like the Greeks with four, but India was particularly characterized by the development of a subtle and elaborate theoretical atomic system, especially in the Vaiseśika school. A good deal of work has been done on this, notably by philosophers, but it has not so far been adequately investigated by historians of science.

Parallel with the elements went the doctrine of the Humours, rounded out (though not very consistently) in the Hippocratic corpus; four fluids, as we should say, with different biochemical characteristics. Broadly speaking, the humours were first, blood, hot and wet (corresponding to air); secondly yellow bile or *chole*, hot and dry (corresponding to fire); thirdly black bile or *melanchole*, something like serum and perhaps derived from the observation of the lower part of a blood clot, cold and dry (corresponding to earth); and fourthly phlegm, cold and wet (corresponding to water). Later on these humours were connected with the liver, gall-bladder, spleen and lungs respectively. Health depended, when not disturbed by trauma or by some invading influences, on the right balance (*krasis*) between the four humours. Such conceptions were actively employed in Western medicine down to the middle of the eighteenth century. In China and India similar note was taken of the characteristic juices and fluids of the body, but the emphasis was different, saliva and semen being more important than the biles. In the early Middle Ages the Taoists developed a particularly interesting theory of the three primary vitalities (*san yuan*), i.e. pneumatic essence (*ch'i*), seminal essence (*ching*), and mental essence (*shen*). These ideas seem to have come through to Europe in the late eighteenth century, and to have affected a number of biological thinkers in the Naturphilosophie period, who distinguished in various ways a tripartite set of bodily functions such as locomotion, secretion-generation and intellection. As for *krasis*, the Chinese made even more widespread use of the idea than the Greeks, for in their natural philosophy two fundamental forces, the Yin and the Yang (pairs of opposites, as darkness to light, female to male, cold and wet to hot and dry, etc.) informed the entire universe in every particular. It was most natural, therefore, that an imbalance between these two fundamental forces in the body would lead to disease, and century after century the physicians of China laboured to restore the natural and perfect equilibrium. No one, I am sure, among the contributors to this volume, inheritors all of Frederick Gowland Hopkins' famous epigram that 'Life is a dynamic equilibrium in a polyphasic system', would want to take exception to the insights of their Greek and Chinese ancestors. An inhibition in the activity of an enzyme or the supply of a substrate (cf. lecture 2) will certainly throw a spanner in the works of that extremely delicate balance on which the health of the cell depends; indeed also the normal activity of the mind itself (lecture 4); and it is needless to say that without the perfect synchronization of the endocrine orchestra (lecture 5), that marvellous symphony performed with no conductor, a hundred things will go painfully wrong with the bodies of men and beasts. We may not use the expressions *krasis* and *t'iao ho* much today, but we still have to think in those terms.

Now for the Quintessence, an idea associated with the technique of distillation which played so great a part in both Arabic and European alchemy from the late ninth century to the beginning of the iatro-chemical period in the sixteenth. Here was something over and above the four elements, not always thought of strictly as a material substance, but more like *rūḥ* or *pneuma*—'a volatile principle that could be separated from a material substance and possessed its characteristic activity in the highest degree'. Thus it was an especially subtle form of matter, intermediate almost between matter and spirit. This may be said to have been the beginning of the conception of 'concentrating' active principles, one of the basic methods of all modern biochemistry (cf. lectures 2, 5, 6). Organic substances had been subjected to distillation either wet or dry since the time of the Alexandrian proto-chemists onwards (first century A.D.). Since eggs were such obvious sources of potential life-force, the yolk and white were often distilled separately or together, giving the Alexandrians various fractions containing sulphur (the *theion hydōr*, 'divine' or 'sulphur' water) which had startling effects on the surfaces of metal alloys. The making and employment of such calcium polysulphides was one of the most interesting of all the Alexandrian procedures, analogous to the preparation of stannic sulphide ('mosaic gold') by the Chinese.

Then someone distilled wine, and things began to happen. The discovery of this quintessence, alcohol, has been placed in Italy in the twelfth or even the eleventh century, but it is more likely to have been developed in the Arabic culture-area where al-Razī was distilling vinegar in the tenth and al-Kindī essential oils of perfumes in the ninth. It may even have started in China, where there are hitherto unexplained T'ang references (seventh and eighth centuries) to 'burnt wine' (cf. *branntwein* and brandy). The Jābirian corpus (about 900 A.D.), of which I shall say more in a moment, has a special 'Book of the Fifth Nature', and elsewhere there is a statement that the distillate of wine catches fire. Nevertheless, the Arab pharmacists seem not to have used *aqua ardens* as a drug, and it caused little stir until the

Westerners began to distil it themselves. It is very prominent in the Lullian corpus (after 1350, cf. p. xix), and the link with alchemy, gold and immortality came in because alcohol was soon found to have the property of making organic bodies 'incorruptible'. The complex liqueurs made by members of the religious orders (such as Benedictine, invented in 1510), with their great variety of plant ingredients, are actual examples of a microcosmic 'philosophical heaven', in which the stellar influences generating the virtues of many plants have been, as it were, captured on earth and 'fixed' for human benefit. From this point it was but a short step to the first use of alcohol as a fixative by Robert Boyle, who in 1666 described 'a way of preserving birds taken out of the egge, and other small faetuses'. As a name and a concept Quintessence died, but the hundreds and thousands of biologically active substances, of pigments, enzymes, hormones, vitamins, and other chemical molecules extracted with infinite labour from large amounts of starting material, are all its lineal descendants. Also we still buy 'eau de vie', and are still asked if we 'have any spirits to declare'.

A quintessence could also be an Elixir—and with this evocative word we are plunged at once into that ocean of words which have been written by and about alchemists since the beginning of our era. This is one of the most complex and difficult subjects of all historical research, but in laying bare the roots of modern biochemistry it cannot be overlooked. Almost from the beginning of historical time, with the life-giving potion of the Indian Vedic literature, *soma*, men have sought for some compounded herbal, fungal, mineral or metallic drug or tincture which would keep that breath of life gently pulsating long after the individual's 'appointed span'. Let no one say that this was an impossible dream, for today when antibiotics and sulpha-drugs have gained the victory over so many diseases formerly rabid killers, we are now facing the social problems not only of incurable diseases prevented in former times from manifesting themselves, but also of what to do with the generations that medical science preserves beyond their time. The word elixir, in the opinion of many, serves well to define alchemy itself, for in its earliest Western forms proto-chemistry was a matter of making various kinds of artificial 'gold', and had little or nothing of the 'macrobiotic' or longevity preoccupation. This came into Europe only with the transmission of Arabic alchemy, and since alchemy is after all itself an Arabic word, we should not speak of it in Europe until after the translations of the mid-twelfth century. It then took some time to exert its full effect, but the emphasis on a longevity which chemistry could produce reached full force in the writings of Roger Bacon (1214–92).

The traditional origin of the word elixir was from the Greek *xerion*, a medicinal powder strewn upon wounds, or the powder of projection which turned the base metal into gold; but now it seems at least as likely that the word is of Chinese provenance, perhaps from *yao chi* (medicinal dose), perhaps from *i chih* (secreted juice). The first words in both these phrases ended with a *k* in old Chinese pronunciation, which would account for the *q* in *iqsir*. However this may be, it is certain that Chinese proto-chemistry was by far the oldest to emphasize consistently the macrobiotic preoccupation; and for the reason that in China alone was there the idea of 'material immortality', the etherealization of the body and spirit so that the individual could continue on earth to enjoy the beauty of Nature without end, uncramped by the needs and limitations of ordinary mortals. Here two points need emphasis: first, the association between the manufacture of the imperishable metal, gold, and the attainment by man of earthly imperishability begins with this earliest alchemy (strictly so-called) of which we have any knowledge, namely, that of China in the second century B.C.; secondly, the thought-connexion between gold and immortality through the centuries was that all the other metals, rusting and corroding, suffered from the same illness as mortal man, so that the 'philosopher's stone', as it came to be called, was the supreme medicine of man as well as metals.

If we were to draw a thumbnail sketch of the pre-natal history of chemistry in the Old World, the summary would be something like this. One has to distinguish half a dozen spatio-temporal entities and phases. Beginning nearest home, there was the Hellenistic or Graeco-Egyptian tradition of proto-chemistry, starting in the first century A.D., continuing through the Byzantine culture, and ending in the eleventh century, from which time the oldest extant MS texts have come down to us. This at least is the case for the philosophical writings, but we have much earlier MSS for the purely practical chemical-metallurgical techniques (e.g. of imitating gold), which centre on papyri of the third century A.D. This practical tradition continued on without much break till the eleventh century, through the *Compositiones ad Tingenda*, translated into Latin about 750, and the technical book of Theophilus Presbyter just before 1000. None of this was alchemy in the full sense, because it lacked the macrobiotic component; people were either imitating gold or believing that they had made an artificial form of it.

Far away at the other end of the Old World, however, there was another tradition in which the making of elixirs, or 'biochemical' medicines of immortality, was closely tied to artificial gold-making. This was the alchemy of China, ancestor of all the rest; it generated the first book on the subject in any civilization, the *Ts'an T'ung Ch'i* of Wei Po-Yang in A.D. 142, and later on, in 848, the first printed book on a chemical subject in any civilization, the *Hsüan Chieh Lu* of Hokan Chi on plant-drug antidotes for elixir-poisoning by heavy metals. So far there has been very little appreciation of the series of priorities and parallelisms between Chinese alchemy and Hellenistic-Byzantine proto-chemistry. The philosopher Tsou Yen (*fl.* 300 B.C.) precedes Bolus of Mendes the Democritean (*fl.* 200 B.C.) just as the metallurgical chemistry of the *K'ao Kung Chi* in the third century B.C. precedes the practical papyri of the third century A.D. In other ways one finds close parallelisms. The first clear connexion between gold and elixirs occurs in the statement of Li Shao-Chün (133 B.C.), but in the middle of the next century Anaxilaus of Larissa and Liu Hsiang were both active in attempting to make 'gold'. The first century A.D. brings the writings of Pseudo-Democritus and his group (Mary the Jewess, Pseudo-Cleopatra, Comarius, etc.) but although most valuable for the origins of chemical apparatus and techniques, they were basically inorganic in tendency and the *Physika kai Mystika* is not an essentially elixir book like that of Wei Po-Yang. Exactly the same contrast holds good of the two great systematizers writing about A.D. 300, Zosimus of Panopolis in Egypt, and Ko Hung (Pao P'u Tzu) in China; and it can be illustrated again by the men working some two or three centuries later, Olympiodorus the Neo-Platonist with Stephanus of Alexandria, on the one hand, as against the great alchemical physicians, T'ao Hung-Ching and Sun Ssu-Mo. Finally there is the strange coincidence that just as our codices of Hellenistic proto-chemical material date from about A.D. 1000, so the first definitive collection of the *Tao Tsang* (Taoist Patrology), home of so many alchemical books, took place in 1019, and the first printing of it in 1117.

Nevertheless, the Golden Age of Chinese alchemy had corresponded with the period of the T'ang dynasty (620–900 approximately). This had been the time of activity of men such as Mêng Shen, Mei Piao and Chao Nai-An. Since it is now quite clear that the alchemy of the Arabic culture-area was powerfully influenced from China, this lends additional significance to the fact that it flourished not as used to be thought in the seventh and eighth centuries, but rather in the ninth, tenth and eleventh. There was a veritable burst of activity around the year 900. The many writings of the Jābirian corpus were approximately contemporary with the lifetime of the great alchemist-physician al-Razī (860–925), but they were quite independent of him and related rather to the Qarmatian scientific group known as the Brethren of Sincerity (Ikhwan al-Ṣafā). This was also the time of the mystical alchemy of Ibn 'Umail and the compilation of the work known to the Latins as *Turba Philosophorum*—a kind of imaginary international chemical congress embodying lively statements of opinions by all the natural philosophers whom the Arabs knew of from the pre-Socratics downwards. A century later came the activity of the great Ibn Sīnā and al-Majritī, so that we are brought almost to the moment when the curtain went up on true alchemy in the Frankish or Latin West.

The first translations from Arabic into Latin were made in Spain, where al-Majritī had worked, from 1130 onwards, and for a whole hundred years after that an abundance of translation continued. Europeans were now excited by the idea of a biochemical medicine of longevity as well as the artificial making of gold; so that the considerable advances in chemical knowledge recorded make the fourteenth century a notable period. It begins with the books attributed to Geber, now recognized as original, not translations, and having nothing but the name in common with the earlier corpus of writings attributed to Jābir ibn Ḥayyān. The unknown author who covered himself with the Latin form of the name was nevertheless well acquainted with Arabic alchemy. Then followed Petrus Bonus (*fl.* 1330) and John of Rupescissa (*fl.* 1345), as well as two important collections of related MSS: the Villanovan corpus called after Arnold of Villanova and dating from the early fourteenth century, and the Lullian corpus called after Raymund Lull, from the late fourteenth. The fifteenth century was a less original time of stocktaking and of compilation, but the beginning of the sixteenth century saw an entirely new period come to birth.

The 'scientific revolution' is generally made to centre around the figures of Copernicus, Kepler and Galileo with all that they did towards the mathematization of natural phenomena, but there are many ways in which the work of Paracelsus (1493 to 1541) was hardly less revolutionary. He it was who broke the link between 'gold-making' and macrobiotics which Li Shao-Chün and his companions had forged in the second century B.C.; this he did with his famous epigram that 'The business of alchemy is not to make gold but to make medicines'. In the year before the death of Paracelsus was born the first of the modern chemists, Andreas Libavius, whose *Alchemia* of 1597 sought to understand the chemical combination and the properties of chemical substances more or less as we understand them now, freed from all the older implications of artificial gold or immortality elixirs. To his younger contemporary, J. B. van Helmont, I have already referred. We are now in the realm of the history of modern chemistry, which cannot be followed further here. Suffice it to name the great seventeenth-century chemists Béguin, Sala, Glauber, Becher, Stahl, Lémery and Boyle. Then the eighteenth century brings Boerhaave and Macquer, ending with Antoine Laurent Lavoisier—and 'la revolution en chimie est faite'.

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Introduction

The new movement introduced by Paracelsus got the name of iatro-chemistry because it was chemistry applied to medicine, and all biochemists therefore are particularly interested in this period. One has to understand the very mixed character of the Paracelsian contribution, for while on the one hand it called insistently for ever new experiments, and did indeed make many fresh discoveries in chemistry, it had at the same time a world-philosophy derived from Neo-Platonic, Gnostic and Hermetic sources. This was strangely similar to certain Chinese world-views involving the macrocosm-microcosm doctrine, the principle of action at a distance, the unification of the spiritual and corporeal worlds, the idea of the inter-connexion of all things by universal sympathies and antipathies, and a tendency to numerology as opposed to real mathematics and quantification. So far did this resemblance go that one of the English Paracelsians, Robert Fludd, invented two words, 'volunty' and 'nolunty', for which he could just as easily have chosen Yang and Yin if he had known of their existence. In time the Paracelsians or 'chymists' came into sharp conflict with the adherents of the traditional herbal pharmacopoeia, the 'Galenists', in a famous controversy towards the end of the seventeenth century.* In the Eastern civilizations this could not have happened because they had never had the prejudice against metallic and mineral remedies that Greek medicine had bequeathed to Latin Europe. What here concerns us more, however, is the fact that in China also there was an iatro-chemical movement, though it started considerably earlier. Since it led to what was perhaps the greatest achievement in all the pre-natal history of biochemistry, something must be said about it here.

In order to understand this, one must know that as Chinese

* These were the circumstances in which arose the first biochemical organization, so to say, in this country, the Society of Chymical Physitians, founded in 1665 by William Goddard, Marchamont Needham and others, just as the Great Plague was beginning to ravage London. It did not long survive that emergency, but the medical profession gradually adopted by general consent those chemical remedies that experience showed to be effective. Since the subject does not arise elsewhere in this book, it may be of interest to add that in 1808 a group of Fellows of the Royal Society, including Humphrey Davy, Charles Hatchett, Everard Home and Benjamin Brodie, founded a Society for the Improvement of Animal Chemistry, which lasted a couple of decades. Finally in 1911 came the establishment of the present Biochemical Society, convoked by J. A. Gardner and R. H. A. Plimmer.

alchemy pursued its way during and after the T'ang period, it developed two entirely different strains of thought and activity, the 'outer elixir' (*wai tan*) and the 'inner elixir' (*nei tan*). The former was the standard term for all the longevity preparations made from metals and other inorganic substances as well as products of plants and animals. The latter signified the school of all those—and there were many, eventually preponderating in number—who said that nothing important would ever be effected by trying to act upon the human body pharmacologically from outside; what was necessary was to engage in a variety of special practices which would bring about the formation from the body's own tissues and juices of a truly organic elixir of immortality. These procedures were elaborate but essentially psycho-physiological; e.g. meditational, respiratory, gymnastic, photo-therapeutic, and sexual. They were all carried on in the conviction that 'the only true laboratory is the body of man himself'—that was to be the reaction-vessel in which the marriage of contraries, the *conjunctio oppositorum*, would take place. It will be seen that this Chinese system was quasi-yogistic, and it is easy to point to the Indian connexions, though the direction and extent of the transmissions still remains unclear. In any case the Chinese conceptions were distinctly more materialist and 'biochemical' than anything in the Indian mind, for the Chinese pictured the elixir formed in the body as a definitely chemical thing, a 'self-made medicine'. Although in the later centuries there were great exponents of practical, laboratory, inorganic alchemy such as Ts'ui Fang and Wang Chieh in the eleventh century, and P'êng Ssu around 1225, most of the great names belong to the *nei tan* tradition, e.g. Chang Po-Tuan (d. 1082) and Ch'en Chih-Hsü (*c.* 1330). From all this it can be seen that Chinese *nei tan* alchemy had nothing to do with the allegorical-mystical-psychological trend which tended to dominate in European alchemy, especially as its sands ran out and modern chemistry began to take over.

And now comes the dénouement, for in the Chinese iatro-chemical movement, current from the Sung to the beginning of the Ch'ing dynasties (eleventh to seventeenth centuries), the methods of the *wai tan* alchemists began to be applied, especially under medical influence, to what one might call *nei tan* materials. Take urine, for example. Textual evidence shows in great detail that during the centuries just named the Chinese iatrochemists worked up large quantities of it almost as we should say 'on a manufacturing scale'. And they subjected it to evaporations, heatings, precipitations (even with saponins), re-solution and further precipitations, ending with sublimation procedures at strictly controlled temperatures. In this way they were able to prepare, centuries before the nature of the steroid ring-system could have been conceived of, mixtures of crystalline steroid sex-hormones, and these the physicians used for just the same conditions as those in which they are prescribed today. By choosing the age and sex of the donors varying mixtures of the crystalline products could be obtained. The whole process must be called quasi-empirical rather than empirical because some fairly sophisticated theories were at the basis of it, though they were not those of modern science. This *ch'iu shih* is only one example of the Chinese iatro-chemical preparations, for many other materials were also worked up, e.g. placenta, menstrual blood, testis and thyroid gland; animal sources being often used. This was what I ventured to call perhaps the greatest achievement in the pre-natal history of biochemistry.

In order to complete the picture, something must be said of the Indian contribution. It seems on the whole to have been truly alchemical from the very beginning, combining the idea of gold-making with that of the elixir (*rasa*). On the other hand it does not seem, so far as we can tell at present, to be as old as Hellenistic proto-chemistry, let alone the alchemy of China. The beginnings are over-shadowed by the figure of the Buddhist patriarch Nāgārjuna, who may or may not have been the eminent alchemist that later generations thought he was; perhaps there was another person of the same name working in the third or fourth century A.D., the latter time being the date of the earliest document, the Bower MS. Very little early mediaeval literature has remained, however, and it is only after the *Rasaratnākara*, which is dated to the seventh or eighth century, that texts become at all numerous. The bulk of the literature is rather of the tenth to the fifteenth centuries. Elucidating the development of Indian alchemy as such is a particularly difficult task, partly because the dating of any document in Indian culture is a ticklish matter, and partly because a wealth of MSS still lie unexamined in the Indian libraries. Particularly interesting results are to be expected from the further study of the Tamil literature of the south. In general one can hardly say more for the present than that the contacts between the Indian, Chinese and Arabic culture-areas were often quite close, but that India remains still by far the most obscure of the three.

Only two more key-words now remain to be considered—Conjunction, and Ferment. The idea of the conjunction of opposites in synthetic reaction has already appeared in passing as the aim of *nei tan* alchemists, but in fact it was the objective of all alchemists everywhere, and nowhere was it more enthusiastically sought than in the Latin world. It is of course nothing less than the ancestor of the modern doctrines of chemical affinity, fundamental in biochemistry as elsewhere; yet its roots go right back to the ideas about sympathies and antipathies which preoccupied Liu An about 125 B.C. no less than his senior, Bolus of Mendes, and his junior, Pseudo-Democritus. Whether like tends to react with like, or like with unlike, was a problem that worried everybody for two millennia before Lavoisier's time; the Paracelsians and the Galenists tended to take opposite sides in the matter, and the Arabs had also discussed it. About the sixth century the Chinese took a notable step forward in sophistication by arranging chemical substances, including some of biochemical interest, in categories (*lei*) as well as the vertical Yin-Yang classification, members of the opposing sides of which must necessarily be expected to react. But if they did not belong to the same category (*t'ung lei*) then no reaction would take place. Such are some of the ancient ideas, originally always with a sexual nuance, from which men slowly passed to our more exact conceptions of valency, affinity, steric hindrance and the like; recognizable still, it may be, even in the activity constants of enzyme proteins (cf. lecture 2), and the points of action, whether stimulatory or inhibitory, of hormone molecules (cf. lecture 5).

It was not so many years ago that an enzyme was known as a

Ferment, and this is the last key-word which there is time to consider here. In biology the idea of a small amount of leaven leavening a great mass was taken over simply from the empirical human technology of beer and bread; the 'domestication' of yeasts which must go back at least to Babylonian times. Very early the development of embryos was seen as a fermentation; morphological differentiation, with the appearance of complex organs, muscles, nerves and vessels, being analogized in a rather simple-minded way with the varied textures, shapes and colours which appear in maturing cheese. In the Jewish Wisdom Literature, produced just at the time when the biological school of Alexandria was at its height, Job (x. 10) is made to say 'Hast thou not poured me out as milk and curdled me like cheese? Thou hast clothed me with skin and flesh, and knit me together with bone and sinews'. Aristotle had said the same thing—for him the menstrual blood was the material basis of the foetus and the semen provided the form, acting upon it just as rennet acts upon milk. This idea, though followed little further, remained a commonplace throughout the Western Middle Ages, prominent for example in the visions of Hildegard of Bingen (1098 to 1180), and related to what Albertus Magnus had in mind when he said that 'eggs grow into embryos because their wetness is like the wetness of yeast'. This line of thought when further traced leads directly into the first work on the nature of proteins. The fascination which the Alexandrian proto-chemists had felt about the yolk and white of eggs a millennium and a half earlier, was felt again by Sir Thomas Browne (1605–82) in his chymical elaboratory at Norwich in the middle of the seventeenth century. For there he carried out many experiments with the chemical apparatus and equipment of the period to try and find out more about the proteinaceous substances which seemed endowed with such marvellous potentialities. Work paralleling this on the amniotic and allantoic fluids was done in 1667 by Walter Needham, and further efforts to unveil the secrets of the proteins of eggs were discussed at length by Hermann Boerhaave in his *Elementa Chemiae* of 1732, but no real break-through in the understanding of protein structure was possible of course until the development of organic chemistry in the nineteenth century, and the classical work of Emil Fischer stood nearer the end of that than the beginning.

What we have been talking about is nothing less than the beginning of man's knowledge of the phenomena of catalytic action; but this has a separate, rather different root, concerned not with biological events of any sort but with metallurgical techniques. In fact it goes back to what we should now call simply the 'debasement' of gold. The Graeco-Egyptian papyri of the third century constantly speak of the imitation of the precious metals by alloying them with others such as copper, tin, zinc and lead, but at least some of the gold and silver mixture (*asem*, *electrum*) had to be there, though quite a small amount would do. Hence the philosophers talked of the *diplosis* or *triplosis* (doubling or tripling) of *asem*, the necessary amount of which was sometimes thought of as a 'seed' or, as we might say, a nucleus of crystallization. However, in the Hellenistic proto-chemical corpus (first to seventh centuries) the idea that a small amount of something can act on a large amount of material to turn it into precious metal, the process that was later called projection, is already fully present, and the action of the small amount of substance (corresponding to the later 'philosopher's stone') tended rather to be likened to the action of yeast (*maza*, *azymon*). So for Zosimus (*c.* 300) the effect of projection was a fermentation. It is an extraordinary yet little-known fact that exactly the same idea of projection can be found as early as the first century B.C. in China; but whether we are to think of a Westward transmission or of some intermediate common source remains as yet quite uncertain. From the Chinese literature, and from the Hellenistic-Byzantine writings, the idea of the metallurgical 'ferment' passed into the alchemy of the Arabs, where nearly all the writers have it—the Jābirian corpus and Ibn 'Umail, also the *Turba* and the eleventh-century 'Book of Alums and Salts'. Thence to Geber about 1300 and to the Villanovan corpus of the early fourteenth century, where *massa* has become the regular word for the philosopher's stone as ferment, actual gold or silver still being thought of as necessary elements in its composition. Indeed a garbled etymology at times derived *alchemia* itself from *archymum* (*azymon*), so that all chemistry was synonymous with the 'yeasty craft' (*maza pragma*), as in the early fourteenth-century Byzantine Greek translation of Pseudo-Albertus. Now this replication process whereby a certain thing could make more of itself *ad infinitum* was surely a strange and not often recognized ancestral foreshadowing of the knowledge we now have about the self-replicating ribonucleo-proteins. Perhaps it well exemplifies the truth that 'the alchemists took a path just the opposite of chemistry today, for while we seek to explain biological processes in terms of chemical ones, they conversely explained inorganic phenomena in terms of biological events'.

There is still a little more to say about ferments, however, because the ancients and the early mediaeval people knew about digestion and the fundamental changes which it could carry out at strikingly low temperatures. All the common phenomena of fermentation and putrefaction were involved in their thinking about this. Hence even when they were in hot pursuit of the philosopher's stone, they were sometimes convinced that certain processes ought to be carried out slowly at low temperatures; which explains the frequent use among the mediaeval alchemists of fermenting horse-dung, by the aid of which temperatures of some 65 degrees could be maintained for prolonged periods. It was the same preoccupation which inspired the Chinese alchemists of the Sung to devise extraordinary systems of cooling coils in their reaction-vessels, so that they could control the temperatures attained. More fanciful was the tendency of some Western alchemists, especially the writers of the Lullian corpus of the late fourteenth century, to give their vessels the shapes of organs of the body—the stomach, the uterus, or the egg—and the age-old sexual nuance of chemical combination was mirrored in the paired alembics used at this period for reflux distillations. In the second iatro-chemical phase the nonsense was largely cast off, and van Helmont laid down that all the reactions of organic life were controlled by ferments of one kind or another. Disease also was thought by him and his followers to be due to 'alien ferments', their new version of the *contagium vivum*. Van Helmont recognized in the body (not only in the gut) six primary digestions, and here again the hidden parallelism between Chinese and Western thought reveals itself, for in 1624 van Helmont's contemporary, Chang Chieh-Pin, was explaining the doctrine then quite old in China, of the 'three coctive regions' (*san chiao*). Such correspondences invite much further research and I cannot say more of them here. But we have seen enough to realise that the idea of organic catalysts (cf. lectures 1, 2, 7) goes far back into the past, involving all the aspects of proto-chemistry and alchemy through the long course of the centuries.

This brings me to the end of what there is space to include by way of background panorama for the lectures which follow. The fact that they are now gathered together in print is very largely due to the persistence of Frank Young, the present head of the Sir William Dunn Institute of Biochemistry in Cambridge, who could not bear to see so interesting an assembly of perspectives restricted to oral tradition. I cannot end, however, without a filial tribute to that great man of whom most of us are the descendants, Frederick Gowland Hopkins, the *fundator et primus abbas* of biochemistry in this country. All of us who were privileged to follow his lectures for many years will remember how he never lost an opportunity of referring to events of historical interest in our subject. Whether it was van Helmont capturing the 'wild gas' in breweries, or Captain Lind protecting his men from scurvy with citrous fruits, or Berzelius finding lactic acid in the muscles of hunted stags in 1808, or Fick and Wislicenus romantically climbing the Faulhorn to settle the relation of protein metabolism to muscular work—all were brought in to give colour and perspective, to enlarge our understanding of our past. The present book may thus be considered one more laurel-wreath for 'Hoppy', yet at the same time adequate enough, we hope, to these present days of electron microscopy, refrigerated ultracentrifuges, the refinements of chromatography and electrophoresis—and the examination of Moon dust or Mars dust for forms of life that had not been dream'd of in our philosophy.

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