Indian Journal of History of Science, 43.1 (2008) 109-118

The Gifts of Chemistry to Modern Medicine*

Introduction

Human body is a physico-chemical consortium. Human biochemistry or clinical chemistry reflects changes inside the body in health and disease. Chemistry offers a very useful tool in diagnosis of diseases and in their follow-up while under treatment. Advances in the field of medicine have been always on three lines: better chemicals, better instruments and better quantification.

The marriage between chemistry and physico-pathological activity in human health and disease is a natural phenomenon The thought of explaining all biological activity on chemical basis - iatro chemistry (Greek: "iatros", physician) as initiated by Paracelsus (1493-1541), Aureolus Theophrastus Bombastus von Hohenheim, Jean Bapiste Van Helmont (1577-1644), Franz De Le Boe (1614-1672), Franciscus Sylvius and others is comparable to that of explaining all such activity on mechanical iatrophysical basis as postulated by Galileo Galilie (1564-1642), Sanctorius Santorio (1561-1636), William Harvey (1578-1657), Rene Descartes (1596-1650) and others. Iatrochemistry is the study of chemistry in relation to physiological and pathological processes, and treatment of disease by chemical substance as practiced by a shcool of medical thought in the 17th century. Iatrophysics is physics (its laws) as applied to medicine during the same period. Needless to say the gifts of physics to modern medicine in various aspects of diagnosis and treatment of diseases are enormous and spectacular in our time (Majumdar, 2004).

The evolution of chemical pathology/clinical chemistry needs to be studied on the kaleidoscope of some major technological advances in more recent years in the context of historical observations from pre-technological era (Donaldson, 1999).

* Contributed by **Dr. Sisir Kumar Majumdar**, Hasiniketan, 200 Summer House Drive, Wilmington, Darkford Kent DA 2 7PB, England, UK. Email: majumdar@tiscali.co.uk

The gifts of chemistry to modern medicine have been moulded in the crucilble of today's chemical pathology. Its evolution from the pre-technological times to the technological age is exciting. It is a relatively new science. The advance of chemical pathology has followed the development of medicine, of biochemical knowledge, of advances in molecular biology, and of chemical analytical techniques. It is the study of the changes that occur in disease in the chemical constitution and biochemical mechanisms of the body.

As a fundamental science, it applies physiology and biochemistry to the elucidation of the nature and cause of disease. As an applied science, it seeks by analysis of body fluids and tissues to aid the doctor/clinician in diagnosis and treatment – here comes chemistry as the saviour.

By the middle of the 19th century physicians could analyse gastric juice for hydrochloric acid, urine for sugar (glucose) by Fehling's test evolved by the German chemist – Herman Von Fehling (1812-1885), for protein by boiling with acidification, and for bile by nitric acid. The classical "Lectures on Chemical Pathology" of 1847 by the British physican Henry Bence Jones (1814-1873) were based on quantitative analysis of urine. However, there were no important developments in the 19th century in general application of chemical knowledge to medicine by performance of biochemical analysis. But in the first two decades of the 20th century important advances in methodology were made, notable pioneers being Bernhard L. H. Bang (1848-1932), Danish veterinarian and physician, Otto Knut Olaf Folin (1867-1934) US biochemist and D.D. Van Slyke (1883-1971), US physican and chemist. By the early 1920's vene puncture had become routine practice, visual colorimeters were widely available, and analytical methods requiring only 1 ml of blood were generally adopted. This was the first revolution.

Antiquity: A Peep into The Past

The first proven reference to what could be termed the nidus of chemical pathology emanates from the ancient Indian Ayurvedic Medicine. Here there is mention of ants and other insects accumulating around the sites where certain people urinated in the fields; it was, we now realise, glucose in the urine of diabetics that attracted these creatures (Bolodeoku and Donaldson 1996). The second anecdote hails from the account of the

Peloponnesian War (431-404 BC) by Thucydides (460-400 BC); he noted the very high death rate during the Plague of Athens, observing that those who had the plague themselves and who had recovered from it (Thucydides, himself suffered this illness around 430-427 BC – and survived it) never had it again – or, if they did, had it only in mild form (Thucydides, 1954 translation). This was, surely, one of the first pertinent observations, nowadays so obviously referable to the basic understanding of 20th century immunology. The third quote is from the voyage of Vasco da Gama (1469-1524 AD) with his 140 Portuguese sailors, commencing from Lisbon in July 1497; it was seven months later that many of the men fell ill with what, in retrospect, was clearly scurvy. The point of note in this instance is that at the end of that voyage there was presented an opportunity to purchase oranges from Moorish traders (Moorish rule in Spain: 711-1492 AD) who approached the boats; there was also the subsequent comment in the historical records, just 6 days later, stating that, "all our sick recovered their health for the air of this place is very good". It was, of course, the ascorbic acid (Vitamin C) content of the oranges that was responsible for the rapid restoration of health (Carpenter, 1988).

Evolution of Chemical Pathology

It was Thomas Willis who, in 1674, succeeded in tasting the sweetness of urine from a patient with diabetes – but this observation differed from the previous anecdotes in that it involved the use of a silver spoon as receptacle for the urine. The spoon could, therefore, be construed as the simplest possible piece of technology being applied in an early scientific test (Bolodeoku and Donaldson, 1996). Nevertheless, the story advances yet further when one brings Mathew Dobson of Liverpool into the discussion; it was he who, a century later, established that the presence of "sugar" was responsible for sweetness of the urine. However, he relied upon rather more sophisticated laboratory technology in his scientific confirmation than did Thomas Willis in his observations of 1674.

Over the years there has been increasing complexity and ingenuity in both thought and development of scientific aids and apparatus – in the continuous quest for establishing scientific truth. Urine was, in fact, one of the earliest biological fluids to be analysed – largely because it was so readily and freely available (Bolodeoku and Donaldson 1996); blood testing

came later (Bolodeoku, Olukoga and Donaldson, 1998). In the early years progress was very slow. Large volumes of blood were required for chemical tests in those early days; moreover, the duration of laboratory procedures was long and only one or two tests could be dealt with at any one time. New techniques developed in response to the challenges occurring. Smaller volumes of blood came to be needed as technology advanced, the spectrum of tests became wider and tests themselves became shorter in duration. Alongside all of this greater numbers of tests could now be accommodated and it became possible, therefore, to increase the frequency of testing on any one patient. From this increased frequency of sample testing emerged evidence of biochemical and biological variations – and then followed the exciting possibility of opening up a way of identifying the physiological responses to stimuli of various types. Later still, came the confirmation of circadian, menstrual, annual and other biological rhythms.

From then onwards unfolded a sequence of advances – at first involving early instrumentation and later concerning development of the early laboratory; there was invention of the hypodermic syringe, spectroanalysis, colorimetry, the photoelectric cell, the centrifuge, the Bunsen burner, emission spectroscopy, electrophoresis, blood gas analysis, chromatography, radioisotopes and detectors, mass spectrometry, automation and computerisation – together with, in very recent years, telephonic communication, photocopiers, fax machines, e-mail communication and access to the internet. All these inventions – and the very many others which could have been iterated, are fundamental to the modern day chemical pathology/ biochemistry laboratory. From early times laboratory testing has involved the application of many types of analytical procedures – including gravimetric, volumetric, titrimetric, gasometric, monometric, chromatographic, colorimetric fluorimetric, trubidimetric, nephelometric, osmometric and radiometric, to name but a few. Moreover, in the growing organisation that has occurred additional issues must now be heeded, e.g. quality control, health and safety, accreditation, etc.

Four Fundamental Historical Pillars of Chemical Pathology

In order to present a more graphic account of applied technological development a selection of four inventions, across the board, has been made; these are illustrative of progress over the centuries. The names of their

inventors – or those responsible for publicising their use, will be briefly quoted (Olukoga, Bolodeoku and Donaldson, 1997).

The hypodermic syringe : The First Pillar

Although not actually a laboratory instrument, the syringe is of fundamental importance in providing a link between the patient and his/her quantitative blood results; it provides the means of extracting blood in a rapid and convenient manner. Names linked in the development include Francis Rynd (1803-1861) who introduced the hypodermic syringe in 1845, Alexander Wood (1817-1884) who was responsible for its modification in 1851 and Charles Gabriel Pravaz (1791-1853) who made further changes in the form of adding a plunger to the syringe; the latter adaptation made it eminently applicable for administering drugs by the intravenous route.

The Bunsen burner

The second technological illustration stems from Robert Wilheim Bunsen (1811-1899) of Gottingen, Germany, who was a scientific inventor and one of the great experimental inorganic chemists of the 19th century; he was responsible for a multitude of widely ranging major discoveries. Contrary to popular opinion he did not actually invent the Bunsen burner - but he introduced and first used it in 1855 - adapting it from a design by Michael Faraday (1791-1867), the British chemist and physicist; it does seem, however, that Peter Desdega also had involvement in its design. The Bunsen burner was for many years (and currently continues to have some application in microbiology laboratories) a basic piece of apparatus in many laboratory settings world-wide; it must be mentioned, however, that it was the forerunner of both the gas-stove burner and the gas furnace. Its ability to combine air and flammable gas in a controlled manner helps to create a very hot flame - up to a temperature of 1500° C. Although modern methodological procedures avoid the need for presence of a naked flame (thereby significantly limiting the danger of fire and explosion), in some less developed parts of the world Bunsen burners are still frequently used.

Spectroscopy

The third topic in this section is that of spectroscopy. Among the many scientific inventions credited to Robert Wilhelm Bunsen (1811-1899)

of Gottingen in Germany, was that of spectrum analysis and chemical spectroscopy - he was a pioneer of these tools; it was his work with Gustav Kirchhoff (1824-1887), in or around 1859, that led to the observation that each element emits light of characteristic wavelength. Each chemical element possesses, therefore, its own unique spectrum. Indeed, the dark Fraunhofer lines found in the solar spectrum were attributed by Kirchhoff in 1859 to absorption, by the elements in the cooler atmosphere of the surface of the sun, of the continuous spectrum emitted from the hotter interior. Applications of spectrum analysis extend both far and wide to include, in astronomy, those of the solar and stellar systems; it is in this way that the identification of certain elements in distant stars can be confirmed. The work of both Bunsen and Kirchhoff established the immense value and importance of spectroscopy in chemical analysis. More down to earth, however, but also linked with this technique, were Bunsen's and Kirchhoffs discovery of caesium and rubidium in 1861. Emanating from this very basic investigative technique has evolved many sophisticated analytical procedures including spectrophotometry in all of its many current forms - ranging from infra-red, visible, and ultraviolet spectrophotometry to photochemistry magnetic resonance spectroscopy (MRS), which is a powerful technique for analysing both the quantity and structure of chemical compounds in complex mixtures in solution, is currently being developed - although it has not, as yet, achieved wide application in chemical pathology/clinical chemistry.

Electrophoresis

The fourth illustration chosen is that the electrophoresis; the moving boundary apparatus was devised by Arne Wilhelm Tiselius (1902-1971) in 1937. Application to clinical practice permitted great advancement in the knowledge of protein chemistry; subsequent advances opened the way of electrophoresis of proteins on starch gel, filter paper, cellulose acetate, agar gel and acrylamide gel etc. It is the presence of positive and negative charges, on the amino acids within the protein molecule as a whole, that determines the rate of migration of proteins (within serum or other biological materials) when exposed to a potential gradient along the strip - when a voltage is applied across the electrodes. The combination of applying an electrical gradient, together with various subsequent immunological techniques, has made possible enormous advances in the knowledge of proteins. Protein

electrophoresis now comprises a very fundamental part of daily laboratory life; in cases where there is clinical suspicion of moncional and polyclonal gammopathies (e.g. including myelomatosis) and of globulin deficiency states these procedures are nowadays so vitally fundamental.

Nano-chemistry and Medicine: The New Promise

Today's most intriguing, curiosity-driven and promising area of technology is by far the "nanotechnology". Technology concerns the building of useful things based on known scientific principles. Thus 'nanotechnology' means building useful things of dimensions at the nanometre level. Various words with prefix *nano* are often used by the scientific community to describe various phenomena occurring in these tiny structural domains. Understanding of the science of nanomaterials is important and curiosity-driven not only because of the fascinating nature of the subject itself but also for its overwhelming and novel applications of various nanosacle systems in almost all branches of technology. Nanotechnology cuts across disciplines without a thought. From physics, we have tools that allow us to see and manipulate matter at unprecedented small scales. From chemistry, we have methods for synthesizing and assembling molecules, from materials science, we know that matter at these length - scales can exhibit novel and unusual properties. And from biology, we know that this is also the scale of a cell. The reason that nanotechnology is causing so much excitement is the potential to bring together all these disciplines to tackle common problems - and, of course, solve them with a plethora of new applications.

The origin of the term 'nano' comes from the Greek word for 'dwarf", but in scientific jargon, nano means 10^{-9}. So, a nanometre (10^{-9} metre) is a billionth of a metre, that is, the size of ten atoms or so, or 1/80,000 of the diametre of a human hair, or 10 times the diametre of a hydrogen atom. Therefore, nanotechnology can be best be considered as a 'catch-all' description of activities at the level of atoms and molecules that have applications in the real world. Obviously, the nanotechnology is an anticipated manufacturing technology that allows thorough, inexpensive control of the structure of matter by working with a few number of atoms, thus leading to the production of machines or devices at the nanometre scale. It is, therefore, a scientific advancement that is as important as the discovery of the first

tool. However, unlike metallurgy, natural substances are not used as the starting materials, but atoms – the ingredients of the universe.

The concept of nanotechnology, however, dates back to the history of the famous lecture that Nobel Laureate Richard P. Feynman (1918 - 1988), Nobel Laureate in Physics (1965) gave in 1959 : "The principles of physics, as far as I can see, do not speak against the possibility of manoeuvering things atom by atom".

As technology has advanced, things have gradually been miniaturized. Machines that were a metre in size have been reduced to a hundredth the size (centimetre) and even smaller. For example, the integrated circuit components used in microelectronics operate at the micro (10^{-6}) level. In fact, blood capillaries are of micrometer (10^{-6} metre) dimensions. The ever-increasing quest of miniaturization of electronic devices has been driven by the need for faster and more powerful electronics. In fact, the dwindling size of circuits in electronic chips drives much of the interest in nano. In addition to the importance of developing new generation electronics, materials on the nanoscale often exhibit interesting quantum phenomena as electrons, when confined to nanostructures, follow quantum mechanics and exhibit their wave-like natures. Therefore, the question naturally comes: "can we build machines one size smaller than micro, that is at the nano level?" Obviously, there is no reason why it will not be possible if nano-dimensional structures can exist in biology? A typical example is the 'ribosome' that has a dimension of few thousand cubic nanometers and can manufacture almost any protein by binding together amino acids (building blocks of proteins) in a precise linear sequences. Cells can do everything and it is the proteins that hold the key positions in the working of the cells. Therefore, proteins are the action molecules of the biological kingdom. The structures of protein molecules are all different, because they have evolved to fulfil different tasks in different ways. Proteins and other biological macromolecules normally act individually carrying out one highly specific task in the nanometre-sized network of the cell's business. Therefore, nanometre is the length scale in which the macromolecules of the living cell store information, process it and convert it into function. Deoxyribonucleic acid (DNA) is in charge of the information storage, while proteins fulfil the mechanical or chemical functions. Ribonucleic

acid (RNA) can do both. It serves as an information career between DNA and the machinery making proteins and it has functional roles both in protein synthesis and in editing of genetic information.

Life consists of a whole collection of machines. For example, apart from ribosomes, it contains a large number of copies of tiny machines that convert carbohydrates to carbon dioxide and use the heat energy generated in the chemical reaction to perform life functions. The action of such nanomachines is very much analogous to that of a gigantic thermal power station where coal serves as the main source of energy similar to the role of hydrocarbons in biology. Again, similar to solar cells a living organism coverts light energy to electrical energy as a brain response when light rays fall on a human eye generating brain waves that essentially cause responses for the vision. There are many more macroscopic examples of nanomachines that work in a biological system.

However, biological nanomachines are much more sophisticated and have the capacity of reproduction.

A key-property of biological nanostructures is the molecular recognition, leading to self-assembly and the templating of atomic and molecular structures. To date, most successful bio-mimetic component, used for self-assembly has been DNA itself. For example, it is-wellknown that two complimentary strands of DNA will pair to form a double helix illustrating two features of self-assembly. The molecules have a strong affinity for each other and they form a predictable structure when they associate. Those who wish to create defined nanostructures would like to develop systems that emulate this behaviour.

Therefore, building nanomachines is not a science fiction, rather it is a reality. Because such machines have the dimensions of the size of atoms, few atoms or groups of atoms - molecules - must be used. Nanotechnology is more concerned with observing atoms and molecules and manipulating them through visual observation at the nanometre level. It may be a combination of chemistry, physics and molecular biology. The discovery of nanotechnology in the broadest sense has immediate implications, since we can design a whole new range of machines or devices from nanoscale objects.

The Epilogue

The application of newer inventions in physics and chemistry to modern medicine in various fields of diagnosis, prevention and treatment of diseases has a chequered history in the 20th century (Majumdar, 2000). Over the years it has become clear that technological advances in science, generally, have been determinant of progress in the laboratory based science of clinical chemistry. A chemical pathology laboratory comprises, overall, physics (i.e. laboratory machinery, pressures, voltages, etc), chemistry (i.e. the chemical solutions flowing through the tubes of the machinery, at the correct concentrations, etc) and biology (i.e. the personnel in charge of the technology and computerisation); it is interaction between these three that collectively constitutes the working laboratory. It is, furthermore, the chemical pathologist who provides diagnostic interpretation of the results being produced - in the context of his awareness that the variability of values being produced falls within acceptable statistical limits (as judged by quality control schemes integrated into the total working system).

References

J Bolodeoku, D Donaldson, "Origins of urinalysis in clinical diagnosis", *J Clin Pathol*, 49 (1996) 623-26.

J Bolodeoku, O A Olukoga and D Donaldson, "Historical perspectives on health, Origins of blood analysis in clinical diagnosis", *J Roy Soc Health*, 118.4 (1998) 231-36.

K J Carpenter, "The explorers' sickness (1498-1700)", *in The History of Scurvy and Vitamin C*, Cambridge, New York, New Rocelle, Melbourne, Sydney: Cambridge University Press, 1988, pp. 1-28.

D Donaldson, "Chemical Pathology – A Brief Evolutionary History from Pre-Technological Times", Historical Medical Equipment Society, London, *Bulletin No. 5* (1999) 3-7.

O A Olukoga, J Bolodeoku and D Donaldson, "Laboratory instrumentation in clinical biochemistry: An historial perspective", *J R Soc Med,* 90 (1997) 570-77.

S K Majumdar, "History of Medicine in the Twentieth Century: An Overview," *Bull. Ind. Inst. Hist. Med*., 30 (2000) 117-150.

S K Majumdar, "The Gifts of Physics to Medicine", Historical Medical Equipment Society, London, *Bull. No. 11* (2004) 11-14