Healing plants*

M. S. Valiathan

Though India has a rich tradition in the use of medicinal plants, the effort to develop drugs from plants has had limited success. The global market for herbal drugs however claims US $20 billion and promises to grow even further. Herbal drugs are prescribed widely even when their biologically active compounds are unknown because of their effectiveness, minimal side effects in clinical experience and relatively low cost. It is imperative that India launches a programme on drugs from plants, based on clues from traditional knowledge and harnessing modern technologies for the development of new chemical entities.

THE second half of the twentieth century was marked in Kerala by the birth of the Trivandrum Medical College. Those of us who joined the college in 1951 as students had outstanding teachers who had retired after long years of service from the Medical Colleges in Madras and Visakhapatnam and moved on like itinerant Rishis. They believed, like Rabbi Akiba, that 'more than the calf wishes to suck does the cow yearn to suckle'. It so happened that some of them had been contemporaries of Yellapragada SubbaRow in the Madras Medical College. SubbaRow's name stood out as the only Indian name in our text book of physiology by Best and Taylor, but it came alive through our teachers' vivid references to him.

When SubbaRow joined the laboratory of Folin at Harvard in 1924, biochemistry was quivering with discoveries in quantitative analysis, which drew upon colorimetry. Following the development of a process for the estimation of creatine in tissues, Folin and associates worked out a method for the estimation of phosphorus by converting tissue phosphorus with ammonium molybdate to phospho-molybdic acid and breaking it down with hydroquinone into a blue substance which could be measured by colorimetry. This method had the drawback that the colour faded quickly and made the analysis difficult.

SubbaRow began his close association with Fiske by successfully developing an improved method for phosphorus estimation. In searching for a better reducing agent which would break down phospho-molybdic acid quickly, SubbaRow and Fiske discovered 1,2,4-α-amino-naphthol-sulphonic acid which gave accurate readings in the presence of ten times more inhibiting material than would be permissible with hydroquinone. As he noted 'the rapid colorimetric method for the estimation of inorganic phosphorus, organic phosphorus, organic phosphates and lipid phosphorus in blood and urine is correct to 1/100,000th of a grain'. No wonder phosphorus estimation was a favourite subject in our biochemistry course.

His name burst forth again in connection with the study on muscle contraction. Shortly after the demonstration by Meyerhof that lactic acid formed during muscle contraction is a breakdown product of glycogen, A. V. Hill showed the conversion of glycogen to lactic acid partly accounts for the heat produced during muscle contraction. Hill and Meyerhof shared the Nobel Prize for medicine and physiology in 1922 for explaining muscular contraction in terms of the conversion of glycogen to lactic acid. But the award was premature because Fiske and SubbaRow were to demonstrate shortly thereafter that phosphocreatine and ATP were the sources of energy for muscle contraction. They were robbed of due recognition for their key discovery, and the only glimpse of nobility in the unhappy episode was SubbaRow's spirit of self-denial at a time of great personal privation. He renounced all personal credit for the work to advance Fiske's appointment as the Head of the Department!

In therapeutics, SubbaRow's was a recurrent theme. We learnt of the development, by his Pearl River group, of a liver extract which cured pernicious anaemia. Then came sprue which had killed his brother and barely spared him, and the discovery of folic acid which was curative of the fatal disease. Other discoveries followed; notably, hetrazan – unmatched till now – for the chemotherapy of filariasis, and the first broad-spectrum antibiotic—aureomycin. Each of these life-saving discoveries was the outcome of prodigious effort, punctuated by setbacks and egged on by fierce competition. As medical students we took pride in SubbaRow's genius and contended that he was denied due recognition because of his Indian origin. Little did we know that SubbaRow's rule was to put his younger colleagues' names ahead

*Text of the Yellapragada SubbaRow Lecture delivered at University of Hyderabad on 7 August 1998.

M. S. Valiathan is in the Manipal Academy of Higher Education, Manipal 576 119, India

of himself, if not absent himself, in major publications and presentations! Many years later I also found a reference to SubbaRow in a totally unexpected source. In SubbaRow's tireless striving for panaceas, Swami Ranganathananda found a perfect example of Sraddha, 'with its richness of imagination, out of which comes not only science but also humanism'[1].

The bits and pieces I had picked up on SubbaRow fell into place when I read his splendid biography which lit up little known aspects of his life and work[2]. Who ever had heard of his flight from home in Anaparthi as a boy with dreams of making millions by selling bananas in Varanasi? Or his determination to join the Ramakrishna Math during the initial years in the Medical College? How little was known about his serious interest in *ayurveda* and his services as Vice-Principal of the Madras Ayurvedic College under Lakshmipathi? The original application for his admission to a course in tropical medicine in Harvard was prompted by the 'ambition to work out the theory of the three humours and place the innumerable Indian herbs on a standardized basis so that they will be useful for all systems of medicine'. That Richard Strong, Dean of the School of Tropical Medicine, reacted adversely to the Ayurvedic project and SubbaRow himself turned his back on Indian medicine, only adds to the interest of the SubbaRow saga. Death claimed him at 52 and left behind a legend of genius, suffering and tragedy, which is so reminiscent of Srinivasa Ramanujan.

The lure of plants

Even though SubbaRow broke out of the spell of *ayurveda* and plunged into medicinal chemistry, he never forgot the therapeutic promise of *ayurveda*. In the chemical race to find a cure for sprue which was his personal foe, he harked back to his own severe illness in 1919 which responded to Lakshmipathi's treatment with the fresh juice of Bhringraj (*Eclipta alba*) leaves. He knew of course that his was by no means an isolated example. *Ayurveda* could not have flourished for two thousand years without any scientific basis.

The fascination of *ayurveda* is both theoretical and practical. The history of Indian medicine traces the development of medical concepts from their origins in miracles and empiricism to the awareness of the fundamentals of a science of life. The doctrine of *tridosha* which fascinated SubbaRow, so central to the practice of Indian medicine, continues to pose interesting questions for the historian of science and the physiologist. Medicinal plants of India, on the other hand, found clinical applications from the time of *Atharva Veda* (circa 1500 BC) and takers in the ancient West as they figure in Hippocratic writings. The *Atharva Veda* refers to many herbs which were believed to act supernaturally like charms. But the *Atharva* mantras reveal beyond doubt that physicians and a pharmacopoeia did exist then and perhaps flourished. By the late vedic centuries the therapeutic value of medicinal herbs was increasingly recognized and a charm became a leaven of faith. The use of medicinal herbs progressed from magico-religious to empirico-rational and, as noted by Kutumbiah, *bhesaja* which originally meant a charm came to denote herbs and minerals during the transition from vedic to the *Samhita* period in *ayurveda*. The *Samhitas* of Charaka and Sushruta abound in discussions on the characteristics of soil; collection and storage of seeds; classification, cultivation and recognition of plants; crop rotation; use of manure and many other aspects of plant economy. The wealth of description and classification of plants in the ancient literature impressed William Jones so much that he claimed that Linnaeus would have adopted the old Indian system for classification of plants if he had access to the Sanskrit texts! Among the many classifications of plants, one was based on medical applications which, according to Charaka, accounted for fifty groups. The study of medicinal plants continued to progress after the classic *Samhita* period as shown by the advanced plant science of *Sarangadhara Samhita* (circa 1300 AD). The native traditions and sources set the stage for the brilliant studies of Gracia D'orta, Vaan Reed, Roxburg and other Europeans on plants from the sixteenth century. They did not explore an uncharted field, unaided: nor did they operate in a vacuum.

Vegetable products dominated *Indian Materia Medica* which made extensive use of bark, leaves, flowers, fruit, roots, tubers and juices. The theory of *rasa*, *vipaka*, *virya* and *prabhava* formed the basis of Ayurvedic pharmacology which made no clear distinction between diet and drugs, as both were vital components of treatment. A thorough knowledge of the various articles of food and drugs was therefore a prerequisite for a physician. According to Charaka, 'The goat-herds, the shepherds, and the cow-herds, who frequently go to the woods, and those who live in the woods, know the plants by name and appearance. It is not, however, by mere knowledge of names and appearance that one can be said to know the plants completely. He who knows the names and appearance of plants and can combine them (according to their properties) is said to be a knower of plants. He who knows plants fully (their names, appearance, properties, actions, applications) is a physician: but he who is acquainted with their applications according to the considerations of time and place, after having observed their effects on individual patients should be known as the best of physicians'[3]. Charaka divided medicines, including mostly plant products, into fifty classes according to their supposed action on different organ systems[4]. The basic principle of the treatment was to use medicines with 'virtues' opposed

to the symptoms of the disease. Charaka observed, 'when particular ingredients in one's body become reduced, we restore them to their proper measure. When particular ingredients increase into abnormal proportions, we reduce them to their normal measure. By treating diseases with medicines imbued with virtues opposed to their originating causes, we succeed in fully restoring the patients to their normal condition'[5]. Classification of medicinal plants, added Charaka, was an aid to the humble practitioner, but a tool for the wise in advancing knowledge.

The advent of Western medicine in the eighteenth century was a setback to the practice of *ayurveda* which suffered considerable neglect at the hands of the colonial administration. What was more galling was the attitude of the Indian scientific establishment, including its medical counterpart. With a few exceptions, they made light of Ayurvedic medicine and distanced themselves from its history, science and practice to keep in step with the colonial masters. Sporadic efforts were made to scrutinize the alleged curative effect of Ayurvedic medicinal plants; but they were poorly planned and largely unsuccessful. The first success which drew international attention was the antihypertensive drug reserpine, an alkaloid of the plant *sarpagandha*, which had been part of Ayurvedic formulary for many centuries. The initial clinical observation on *sarpagandha* was made by Rustom Vakil of Mumbai[6], but the drug became a reality thanks to the CIBA of Switzerland. There were a few other success stories. An enormous amount of characterization of medicinal plants was done in many laboratories and University Departments for over a century; but the outcome was discouraging because the effort was 'disorganized, thinly spread and non-focussed'[7].

A recent success

After reserpine, many decades passed before success greeted the endeavour on Indian medicinal plants. The story of the evolution of *Commiphora wightii* gum into a hypolipidemic drug has been told by Satyavati, who was one of the pioneers[8]. *Guggul* had been widely used for conditions like arthritis in *ayurveda* since the *Samhita* period. The hypolipidemic effect of *guggul* was first reported in Satyavati's doctoral thesis and her inspiration came from a passage in the *Sushruta Samhita* which dealt in 'an extra ordinarily lucid and scientific manner with the etiology, pathogenesis and treatment of obesity and associated lipid disorders and their complications'. Indeed, an *atharva vedic* hymn had claimed that diseases flee away in all directions from *guggul* 'like horses and deer'. The discovery of the hypolipidaemic activity of the gum resin was followed by a series of systematic and careful investigations. While the chemical studies were carried out by Sukh Dev at the National Chemical Laboratory, the pharmacological part was done by Nitya Nand at the Central Drug Research Institute. The chemical investigations revealed that *guggul* resin is a complex mixture of various classes of compounds such as lignans, lipids, diterpenoids and steroids[10]. Experimental studies showed that guggulipid – a standardized ethylacetate extract prepared by Sukh Dev – reduced the serum cholesterol and triglycerides and altered the HDL/LDL ratio in hyperlipidemic rabbits and rhesus monkeys[11]. Regression of atheromatous lesions was also noted in the animals. A number of subsequent studies in patients in different parts of India confirmed the lipid lowering effect of the gum guggul and a few of its fractions[12]. The average lowering was 17.5% for cholesterol and 30.3% for triglycerides and guggulipid was demonstrably effective in reducing lipid levels in type II B and type IV hyperlipidemias[13]. In 1988 the Drug Controller of India gave approval for marketing the drug which is now sold as Guglip. The story of the guggul gum illustrates the amazing insights that existed in ancient Indian medicine, and the complexity of transforming an ancient insight into a modern clinical product.

Rauwolfia and *guggul* are indicative of the untapped wealth of the medicinal plants of *ayurveda*. Sukh Dev lists 15 crude Ayurvedic drugs which have received support for their therapeutic claims[7]. There must be many more waiting to be discovered, not only in the ancient texts, but also in the catalogues on Indian medicinal plants published by the Indian Council of Medical Research and private publishers and the innumerable reports on the characterization of medicinal plants by investigators in India. A data base needs to be created on the published information which is currently scattered and poorly accessible.

Plant to drugs

Drugs of plant origin are no relics of an ancient tradition, but a major segment of therapy and business today. In industrialized countries, substances derived from higher plants constitute 25% of prescribed medicines[14]: the percentage will be obviously much higher in India. Medicinal plants are used in *ayurveda* as complex mixtures wherein the biologically active compounds may not have been identified. In contrast, the herbal drugs which are increasingly used in the West are standardized, single plant extracts. Their safety and efficacy are also proved even though their biologically active compounds may not be known. The global market of herbal drugs accounts for US$ 20 billion excluding the traditional preparations used in India, China and other ancient societies. The great popularity of herbal drugs has to do with their effectiveness, minimal side effects in clinical experience, and moderate prices.

Drugs derived from plants are in everyday use – digitalis, ephedrine, morphine, quinine and many more; others, less often used, like reserpine, guggulipid, and

artemisinin are equally well known. The starting point in the development of all these drugs is some reference to the use of that plant as an indigenous cure in the traditional system of medicine or in folk medicine. This is borne out by the story of guggulipid. But the development of a drug from plants is a long and arduous process which involves many disciplines. The plant must be collected and identified botanically; extracts must be made and analysed chromatographically; pharmacological screening of the extracts must be done followed by activity-guided fractionation; isolated compounds must be purified and their structure determined; large scale isolation should be done to carry out toxicological tests – this is a partial list! Furthermore, assuring a continuous supply of plants is difficult and creates ecological problems; higher plants, trees in particular, may take many years to regenerate. Plant culture which sounds like an attractive alternative has not been very successful in drug development due to a variety of problems including the sensitivity of plant cells to stress and poor understanding of biosynthesis in the plant culture. Despite all this, the interest in screening plant extracts grows because higher plants constitute a largely untapped source of structurally novel compounds that might serve as leads for developing new drugs. However, instead of a random search of plants, a selective search based on traditional knowledge would be more focussed and productive, and certainly more economic.

The effort to obtain drugs from higher plants has grown enormously in cost and complexity since its start five decades ago. The National Cancer Institute, for example, screened 114,000 plant extracts from 1551 genera and 35,000 plant species for cytotoxicity *in vitro* and antitumour activity *in vivo* between 1956 and 1981. Similar, but less extensive, programmes were carried out in China and France with considerable vigour. The search for antineoplastic compounds yielded vincristine and vinblastine from *Catharanthus roseus* (G. Don) (Apocyanaceae), which are used primarily in treating acute lymphocytic leukemia and Hodgkins lymphoma. Other antitumour drugs include etoposide from *Podophyllum emodi* (L.) (Berberidaceae) and taxol from *Taxus brevifolia* (Nutt) (Taxaceae).

As malaria claims 200 million patients annually and kills nearly 2 million, the resistance to chloroquine by *P. falciparum* became a global problem, which was compounded by the resistance of *Anopheles* mosquitoes to DDT. The original antimalarial – quinine – was derived from *Cinchona ledgeriana* (Rubiaceae) and the searchlight therefore once again turned toward plants. A remarkable success followed and artemisinin was developed from the Chinese plant *kwing hasavu* or *Artemisia annua* (Asteraceae) which had been used in China for 2000 years as a febrifuge. Artemisinin represents a completely new chemical series of antimalarial compounds with strong schizontocidal activity against strains of parasites resistant to all known antimalarials. Higher plants have also been the source of drugs against platelet activation.

A few years ago, combinatorial chemistry seemed to offer an alternative to plant-based drugs. Here was a technology which could put together different combinations and create up to 40,000 compounds in a single experiment. Add to this 'high through put screening' – highly automated tests that can scan a million compounds a week—one had the ultimate technology for drug development. So, at any rate, it was claimed. But the enthusiasm ebbed because products frequently failed to pass the tests for pharmacological function.

There is also belated recognition that nature is infinitely more inventive than chemists and that natural molecules have withstood many tough tests of survival for millions of years. An effort is now on to revive culturing of plants *in vitro*. A biotechnology firm in the USA, Phytera, has, for example, set up and stored plant cell cultures of 5000 species in glass vials. If an interesting compound is discovered in a culture, it would then become possible to grow more cells from the relevant species *in vitro*. Plants adapt to the stresses like changes in temperature, light and nutrients; and these adaptations may involve the production of new biochemicals which may have medicinal value. A plant picked at a given time would lack the biochemicals that might have been produced under stress at a different time. This is incidentally reminiscent of the stipulation in the *Samhitas* on the collection of medicinal plants at particular times and in certain seasons. The culture method has now made it possible to challenge the cells by subjecting them to a variety of stresses and extract the compounds released as a response to the stresses. It is claimed that this technique has already yielded a new antifungal agent. Combinatorial chemistry and other chemical processes may still come in handy for synthesizing compounds based on the new chemical entities derived from plants: they are however unlikely to replace plants.

Needed – A technology mission

Plants have returned to the centre stage in drug development as medicines, as sources of active molecules, and as leads to the discovery of new drugs. The realization that nature is the largest and best combinatorial library and that some of the newer and powerful techniques like 'high through put screening' could be used to evaluate natural product extracts, has heightened the interest in medicinal plants. Given the fact that no more than 2% of world's reservoir of plants have been tapped, the opportunities for developing plant-based drugs are seemingly limitless. No wonder multinational companies, whose interest in this area was minimal for three decades,

have reentered the field with gusto. With immense bioresources and living traditions of her own, India is exceptionally well placed to mount an integrated programme for the development of plant-based drugs for diseases which are important for public health and for the global market. The new programme should seek clues from traditional knowledge and employ modern tools for the development of new chemical entities and their validation as drugs. The traditionalists need have no fear that the search for biomolecules would impoverish or weaken *ayurveda* which would be to the investigators what the earth is to the prospectors of bacteria.

India's achievements in the production of bulk drugs and formulations and the development of state-of-the-art technologies for many important drugs are well recognized at home and abroad. However India is only a marginal player which supplies low-cost generic products to the rest of the world. In particular, India has failed to make an impact on the global market with drugs derived from plants, and the gap between India and other countries is widening rapidly in the herbal field. The circumstances which tend to frustrate a major developmental initiative for herbal products are many sided in the country: (i) There is no clear definition of the targets to be achieved or a time frame within which the targets, if any, should be achieved. (ii) There is no co-ordination among the national laboratories, ICMR institutions, and groups funded by the DST, DBT, and DAE who are investigating medicinal plants. (iii) A serious dialogue between publicly funded institutions and the industry is conspicuous by its absence. (iv) A mechanism for regular interaction between the experts in *ayurveda* and R&D groups on medicinal plants does not exist. At the political level, *ayurveda* is constantly extolled, but no effort is made to unify the scattered and thinly-spread efforts into a powerful course of action with specified goals in the development of herbal drugs.

It would be an act of high prudence during the fiftieth year of independence to launch a Technology Mission for the development of plant-based drugs. I would go out on a limb to suggest the development of five drugs in seven years from the leads which already exist in the country's disorganized data bank. Sukh Dev's list of candidates is illustrative of the kind of data which can become inputs for a meaningful and time-bound programme on herbal drugs. While India sleeps, others are wide awake like a French laboratory which forges ahead with the development of a biomolecule reported by Asima Chatterji in the nineteen sixties! The selected drugs should aim at diseases and conditions which affect large numbers of people, and my favourites would include antimalarials, antimitotics, immunomodulators, anti-diabetics and age modulators (*rasayanas*). The Mission should be headed by the Prime Minister's representative with full authority to coordinate a national effort which would involve the Planning Commission, Ministries of Health, Science and Technology, Environment and Forest, Chemicals, Commerce and Law besides the pharmaceutical industry and professional organizations. The march from 'molecule to market in 2500 days' is exacting and demands a radical change in our fragmented approach and leisurely style. It is time that we in India choose to become subjects of scientific history and not remain its helpless objects.

Conclusion

Dharampal[15] refers to an episode in Japan's phenomenal development as an industrial nation. After closing the doors to foreigners for two centuries, Japan guardedly reopened a window on the West by sending a few bright young men to Europe in the late nineteenth century. One of the pioneers was Maeda Masana who was initially overwhelmed by the pomp and circumstances of Paris but recovered his confidence after witnessing the Franco-Prussian war and the sack of the French capital. Returning home, he became one of the founders of Kogyo Iken, Japan's ten-year plan for industrial development. The plan said 'which requirement should be considered as most important in the present efforts to our government in building Japanese industries? It can be neither capital, nor law and regulations because both are dead things in themselves and totally ineffective. The spirit/willingness sets both capital and regulations in motion.... If we assign to these three factors with respect to their effectiveness, spirit/willingness should be assigned five parts, laws and regulation four, and capital no more than one part'. Nothing great is ever achieved without spirit or ardour. SubbaRow's endeavour in Boston and Pearl River was ablaze with a kind of ardour verging on fire. India lacks neither the capital, nor the law and regulations of Masana; the question is whether we have the spirit, which animated Indians like SubbaRow, to rebuild the country.

1. Swami Ranganathananda, *Science and Religion*, Advaita Ashrama, Mayavati, 1978.
2. Gupta, S. P. K., *In Quest of Panacea*, Evelyn Publishers, New Delhi, 1987.
3. *Charaka Samhita*, Sutrasthana, **1**, 120–123.
4. *Charaka Samhita*, Sutrasthana, **4**, 9–19.
5. *Charaka Samhita*, Sutrasthana, **10**, 6.
6. Vakil, R. J., *Br. Heart J.*, 1949, **11**, 350.
7. Sukh Dev., *Curr. Sci.*, 1997, **73**, 109.
8. Satyavati, G. V., *Economic and Medicinal Plant Research*, Academic Press, London, 1991, vol. 5, p. 47.
9. *Sushruta Samhita*, Sutrasthana, **15**, 32.
10. Sukh Dev., *Proc. Indian Natl. Sci. Acad. Part A*, 1983, **49**, 359.
11. Nityanand, S., Asthna, C. P., Gupta, A. P., Kapoor, N. K. and Dhawan, B. N., *Indian J. Pharmacol*, 1981, **13**, 59.
12. Malhotra, S. C. and Ahuja, M. M. S., *Indian J. Med. Res.*, 1971, **59**, 1621.

13. Kuppurajan, K., Rajagopalan, S. S., Koteswara Rao, T., Vijayalaxmi, A. N. and Dwarakanath, C., *Indian J. Med. Res.*, 1973, **8**, 1.
14. Principe, P. P., *Economic and Medicinal Plant Research* (eds Wagner, H., Hikino, H. and Farnsworth, N. R.), Academic Press, London, 1989, vol. 3, pp. 1–17.
15. Dharampal quoted by Bajaj, J. K. and Srinivas, M. D., *Curr. Sci.*, 1991, **61**, 419.

Received 10 August 1998; accepted 17 August 1998

Fighting malaria in India

V. P. Sharma

A brief account of malaria problem in India has been described bringing out important landmarks in fight against malaria. Control of resurgent malaria has become a formidable task in view of the problem of vector resistance, parasite resistance, low social acceptability of spraying and inadequate knowledge of malaria in many ecotypes. National Malaria Eradication Programme's current strategy of malaria control has been discussed.

Everything about malaria is so moulded by local conditions that it becomes a thousand epidemiological puzzles. Like chess, it is played with a few pieces but is capable of an infinite variety of situations.

– L. W. Hackett (1937)[1]

HISTORICALLY, malaria is full of examples of the decisive role played by it in war and peace. Malaria destroyed the splendour of Greece, caused the fall of the Roman empire, diminished the Egyptian civilization, and extinguished the ancient culture of Ceylon. In ancient India, malaria was known as the 'King of Diseases'. Malaria and famine formed the vicious cycles of sickness, death and poverty, and thus malaria was largely responsible for the poverty of nations. India remained the hot bed of malaria until the time of independence, generating annually an estimated 75 million cases and 0.8 million deaths in normal years. In this connection it is noteworthy to mention that Ronald Ross' painstaking research on the etiology of malaria led to the discovery of oocysts on the stomach wall of 'dapple wing' mosquitoes (probably *Anopheles stephensi*). This was the first experimental evidence of extrinsic cycle of malaria parasite in the mosquitoes. This discovery was made in Secunderabad on 20 August 1897 and for this discovery Ronald Ross was given the Nobel Prize in 1902 and knighted by the king of England. Later in 1898 Grassi and his colleagues working in Italy demonstrated human malaria transmission through the bite of mosquitoes[2].

V. P. Sharma is in the Malaria Research Centre (ICMR), 22, Sham Nath Marg, Delhi 110 054, India.

Environmental management era

In 1902 Ronald Ross suggested the demonstration and practicability of drainage and minor engineering works in the control of malaria. Mian Mir a cantonment near Lahore (now in Pakistan) was selected for detailed studies. The work was started by S. P. James in 1902 (ref. 3) and supported by the Royal Society, London. Anopheles breeding in rain-filled pits, irrigation ponds, canals, and miscellaneous places was controlled by simple and inexpensive methods of drainage and minor engineering works. After two years of work it was concluded that Mian Mir experiment had failed and the primary reason for its failure was the lack of knowledge of the biology of malaria carrying mosquitoes, thus emphasizing the need for more field research[4]. However, principles of drainage were successfully applied by W. C. Gorgas[5] in 1910 to reduce malaria rates in Havana during the construction of Panama canal and by Malcom Watson in the control of malaria in federated Malay States[6]. In India, Assam Medical Research Society in 1940 supported studies on *An. minimus* and successfully controlled malaria in some selected tea gardens by sluicing and flushing under the guidance of Ross Institute[7]. The anti-malaria campaign in 1942 during the second world war in Assam theatre was successful by clearing jungles and organizing drainage to prevent the breeding of *An. minimus* and thus establish malaria-free zones in Assam, Chittagong and Cox's Bazar[8]. In those days malaria was rampant in development projects and therefore the Government of India in 1946 prepared documents on the subject of antimalaria measures to be adopted by railway board; borrowpits in land acquired temporarily for road construction; Delhi improvement trust on construction