Clinical endocrinology in India

N. Kochupillai

An estimated 108 million people in India suffer from endocrine and metabolic disorders, with the poor mainly bearing the brunt of the disease. Several of these diseases are caused by environmental factors, are preventable and can be also be effectively treated at affordable cost. Yet a majority of them remain undiagnosed and untreated due to the lack of technology use. There is an urgent need for policy initiative at the national level to facilitate wide, cost effective and reliable use of immunoassay technology to measure hormones and metabolites and thus help diagnose and treat endocrine and metabolic disorders in the country.

CLINICAL endocrinology is a specialized branch of internal medicine. The discovery of immunoassay technology, which permitted reliable measurement of picomolar or femtomolar concentrations of hormones in body fluids led to phenomenal growth of this specialty during the past four decades. Application of knowledge and know-how in this branch of medicine is now saving hundreds of thousand of people from death or disability annually, in developed countries. The inventors of the immunoassay technology were awarded the Nobel Prize in Medicine in 1977 (ref. 1).

Unlike in developed countries, endocrine and metabolic disorders are predominantly caused by environ-
mental factors in India and perhaps in other developing countries. Hence their prevalence is several-fold higher in developing countries like India. The estimated disease burden in the country due to these disorders is approximately 108 million (Table 1). The poor bear the major brunt of this disease burden.

**Nature of endocrine and metabolic disorders**

Hormones are key bio-regulatory molecules elaborated and secreted into the circulation to achieve timely growth and development of organ systems as well as to adaptively regulate metabolism to achieve bodily homeostasis. Because of the all-embracing nature of hormone action, disorders of endocrine glands affect functions of multiple organ systems. Conversely disorders of different organ systems can, in turn, influence endocrine functions. Therefore, hormone measurement has now assumed a position of pivotal importance in the practice of scientific medicine. Because hormone concentrations are infinitesimally small in body fluids, their precise measurements in the study and diagnosis of endocrine disorders are quite a demanding venture in terms of the technical skill and scientific insight.

**Table 1. Magnitude of endocrine and metabolic disorders in India**

<table>
<thead>
<tr>
<th>Endocrine and metabolic disorder</th>
<th>Countrywide prevalence (in millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid disorders</td>
<td>42</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>25</td>
</tr>
<tr>
<td>Metabolic bone diseases</td>
<td>15</td>
</tr>
<tr>
<td>Reproductive endocrine disorders</td>
<td>12</td>
</tr>
<tr>
<td>Clinically significant growth problems and pituitary disorders</td>
<td>8</td>
</tr>
<tr>
<td>Adrenal disorders</td>
<td>4</td>
</tr>
<tr>
<td>Miscellaneous (all varieties of rare endocrine and metabolic disorders)</td>
<td>2</td>
</tr>
<tr>
<td>Total national burden of endocrine and metabolic disorders in India</td>
<td>108</td>
</tr>
</tbody>
</table>

*Projection on total burden of thyroid disorders in the country are based on our recent countrywide studies on thyroid disorders among adolescents and young adults, in the post salt iodization phase as well as our countrywide experience on the epidemiology of thyroid diseases in India over the course of the last three decades.

*On the basis of a countrywide study done by P. V. Rao and M. M. S. Ahuja as part of a Ph D research programme.

*Projections made from published data on countrywide prevalence of excess fluoride ingestion through water as well as published epidemiological studies on endemic fluorosis in north India; our own recent studies on vitamin D deficiency in north India and our clinical experience on metabolic bone diseases in India during the last three decades.

*Projections based on clinical experience with reproductive endocrine disorders seen in north India.

*Projections made from three decades of clinical experience on these problems at AIIMS which serves as a national referral centre for pituitary disorders from all over the country.

*Based on our recent study on adrenal involvement in clinical tuberculosis.

A unique feature of endocrine disorders is that early and reliable diagnosis is possible only by sensitive and specific hormone measurements. Endocrine disorders most often present with vague symptoms early in their natural history. The full blown syndrome emerges late, and by then several systemic complications would have set in as a result of damage to vital organs. Thus adult hypothyroidism, if not diagnosed and treated early, may cause heart diseases or affect the functioning of the brain causing memory loss, hearing defect, depression and even psychotic disorders. Congenital hypothyroidism, if not diagnosed and treated promptly at birth, may cause mental retardation which cannot be corrected by late hormone treatment. Indeed, congenital hypothyroidism is among the few treatable causes of mental retardation and therefore, in most developed countries new-born are routinely screened for this condition to prevent mental retardation.

Another important feature of endocrine disorders is that, once the diagnosis is made, the treatment is perfectly scientific with predictable outcome. Besides, the hormones or hormonal substitutes required for treatment are widely available at affordable cost. The clinical outcome of the treatment hardly has any adverse consequences. Even endocrine surgical interventions, wherever required are cost effective and potentially available widely in the country. Thus effective treatment and cure at affordable cost is a hallmark of most endocrine disorders.

As already mentioned, the bulk of endocrine disorders in India is due to environmental factors. Therefore, their prevalence is several-fold higher and their clinical biology considerably modified in the country. These two facts make it imperative that hormone measurements are reliably, cost effectively and widely used in the country to investigate and understand as well as to diagnose and treat these disorders to prevent related death or disability. The sad fact, however, is that the immunoassay technology used for hormone measurement is neither widely available nor reliably or cost effectively used in the country. Such use of immunoassay technology alone can help bridge the currently existing gap between knowledge and its application in endocrine and metabolic biomedicine, to alleviate the sufferings among the millions affected countrywide.

**Magnitude of endocrine and metabolic disorders in India**

**Thyroid disorders**

Thyroid disorders are the most common among all the endocrine diseases in India. Though endemic goitre and
related problems of human health and development caused by nutritional iodine deficiency were thought to be confined to Himalayan and sub-Himalayan regions, isolated studies by independent investigators as well as a multi-centric national study by the Indian Council of Medical Research in the eighties showed country-wide prevalence of endemic goitre. Largely regarded as a cosmetic problem by most professionals, endemic goitre assumed new significance as a health problem as a result of two pioneering discoveries by scientists at the All India Institute of Medical Sciences (AIIMS) 1,2. 

Till 1973 it was believed that goitrous enlargement of the thyroid in iodine-deficient populations was adaptive in nature resulting in functional euthyroidism in all but exceptional situations. However, AIIMS scientists showed that majority of the subjects with larger grades of goitre were functionally de-compensated and hypothyroid in severely iodine-deficient regions. These observations, confirmed subsequently by several workers in other endemic regions of the world, helped focus attention on the serious nature of nutritional iodine deficiency as a health problem. This new awareness also spurred further scientific efforts at AIIMS to investigate the more important question of neonatal thyroid status in severely iodine-deficient regions of the country. During the period from 1975 to 1984, a cost effective and appropriate technology to measure thyroid hormone in dried cord-blood spots on filter paper, was developed. This was made possible by collaborative interactions with Rosalyn S. Yalow, who was awarded the Nobel Prize for Medicine in 1977 for discovering the radioimmunoassay technique. Adopting this technology, over 22,000 newborn were screened for neonatal hypothyroidism from different parts of the country with differing iodine nutrition status and endemic goitre prevalence. The results showed that in severely iodine-deficient districts of Uttar Pradesh, an average of a 100/1000 babies born were severely hypothyroid (T4 < 3 µg% and TSH > 50 µU/ml) and faced the risk of mental retardation. In view of their major public health significance, these findings were critically evaluated and discussed in depth in an international symposium on ‘Iodine Nutrition, Thyroxin and Brain Development’ wherein leading scientists working worldwide on the subject participated. In the aftermath of these developments, UN agencies like UNICEF and WHO provided new momentum for prevention of nutritional iodine deficiency worldwide. An international council for control of iodine deficiency disorders was launched to provide focus to this effort. In India, at the wake of these developments the languishing National Goitre Control Programme was revived and given new momentum. Salt iodation to prevent nutritional iodine deficiency was included in the Prime Minister’s 20 Point Programme in 1984. Subsequently the Central Council of Health, Government of India approved a policy to iodize the entire edible salt in the country. Iodized salt production increased several fold to meet the new demands. Currently there is national and international recognition that successful salt iodation has virtually eliminated nutritional iodine deficiency in the country. Studies done to assess the impact of salt iodation on incidence of neonatal hypothyroidism in the same districts, where pre-salt iodation studies were done, showed remarkable decline in the incidence from a 100/1000 birth to less than 18/1000 birth. The salt iodation programme is thus saving millions from neonatal hypothyroidism-related mental retardation and other iodine deficiency disorders in the country.

There are several other functional disorders of thyroid found in the country. Thus, thyrotoxicosis is a widely prevalent disorder of the thyroid in north India. We have extensively studied this problem and reported a large number of its unique features as seen in India. These scientific studies and documentation of the unique facets of thyrotoxicosis as seen in India were made possible by the extensive use of radioimmunoassay for thyroid hormone developed, internationally validated and cost effectively used in our laboratory. This large body of information generated is now helping physicians all over the country and elsewhere in the world to understand and manage the disease better, besides promoting relevant education on thyrotoxicosis in the country.

Recently a countrywide study was done to assess the prevalence of common thyroid disorders in the post-salt-iodation phase among school children, NCC cadets as well as army recruits from all over the country, with fund support from the Defence Research and Development Organization (DRDO), Government of India. The results of these studies, to be published, show 23% residual goitre prevalence among school children countrywide, with normalized urine iodine excretion, indicating elimination of nutritional iodine deficiency. Functional studies of the goitrous subjects showed overall prevalence of 5.4% hypothyroidism, 1.9% hyperthyroidism. 7.5% prevalence of autoimmune thyroiditis was demonstrable by fine needle aspiration biopsy among female goitrous students. On the basis of this countrywide study and other related studies, it can now be estimated that the total burden of significant thyroid disease in the country in the post salt-iodization phase is approximately 42 million. The data of this recently concluded study are under publication. These studies involving tens of thousands of thyroid hormone assays were made possible because of availability of reliable and cost effective in-house assays.

**Adrenal diseases**

Diseases affecting the adrenal gland is another example of environmentally induced endocrine diseases in India.
High prevalence of adrenal insufficiency results in avoidable morbidity and mortality among hundreds of thousands annually in India. Our recent studies show that all varieties of clinical tuberculosis, on adrenal reserve testing, show adrenal involvement in 46 to 56% instances. Besides, 16% of such cases show adrenal involvement by sophisticated imaging techniques. In fact, clinical tuberculosis is the commonest cause of adrenal insufficiency in India and its prevalence is several-fold higher when compared to Western countries where it is predominantly caused by a rare autoimmune disease, which occurs relatively infrequently among individuals with predisposing immuno-genetic haplotypes. With the advent of AIDS, however, this scenario is changing and there is presently recognition that AIDS can cause adrenal insufficiency either by direct involvement or by causing specific infections (for example, tuberculosis of the adrenals). Adrenal insufficiency is a life-threatening disease. The diseased adrenals fail to secrete adequate cortisol to cope with psychophysical stresses. The consequent adaptive failure results in cardiovascular collapse and death. It is important to point out that in India, most patients with adrenal insufficiency die due to acute stress-related vascular collapse. In such cases the cause of death is unknown. For early diagnosis to prevent such deaths due to tuberculous involvement of the adrenal gland, reliable measurement of cortisol is required. In the absence of such facility, the disease remains largely undiagnosed and untreated. Yet, if diagnosed promptly, the cortisol hormone required to treat the illness is widely available in India at a cost affordable even to the poor. The estimated disease burden of tuberculosis adrenal involvement with adrenal insufficiency is 4 million countrywide.

Reproductive endocrine disorders

Sexual maturation and reproductive functions are entirely dependent on hormones in both the sexes. However, hormone-dependent reproductive functions are more complex in women. The monthly cycle of menstruation, pregnancy and lactation are all critically dependent on a variety of hormone-mediated processes. Women are therefore prone to endocrine disorders of the reproductive system. While several of these can be managed empirically by the use of hormones by trained gynaecologists, there are large number of such disorders which need to be managed by expert endocrinologists on the basis of reliable hormone measurements. With rapidly advancing knowledge in reproductive biology, the number of disorders that can be successfully treated in the above manner is also increasing. The recent progress in assisted reproduction (such as in vitro fertilization) is an example of such progress. Diagnosing the cause of and effectively treating infertility by such means greatly depends on reliable hormone measurements as well as astute use of hormones in therapeutic intervention. Similarly, more and more sexual disorders like impotence, age-related sexual debility, sexual immaturity and related growth and development problems, menopausal problems in women, and several human cancers related to reproductive organs are all managed, with improving results, by appropriate endocrine intervention. With these dramatic developments in clinical endocrinology, the areas of effective clinical intervention with the use of hormones is rapidly expanding. Unfortunately much of the therapeutic know-how and knowledge is not effectively used to relieve human suffering in India because of inadequate and unreliable use of hormone measurement techniques. Besides, reproductive endocrine disorders remain largely neglected in India under the negative impact of state-driven fertility regulation programmes as well as culturally-driven obscurantist outlook towards sexual disorders in the country. The estimated burden of major reproductive disorders countrywide, on the basis of clinical experience of experts, is 10 to 12 million. Since effective remedial measures are available to most of them on the basis of scientific diagnosis, failure to bridge the gap between knowledge and its application to prevent or cure reproductive illness and thus promote the right to reproduction and reproductive health would be a major area of medical negligence.

Metabolic bone diseases

Metabolic bone diseases due to a variety of hormonal disturbances, nutritional deficiencies and environmental toxins acting together or in isolation constitute a major bulk of endocrine and metabolic disease burden in India (Table 1). On the basis of the experience at AIIMS, the biochemical features of these disorders are unique and often confusing in the context of knowledge acquired from textbooks written on the basis of experience in developed countries. In such cases reliable measurement of hormones and metabolites such as parathormone, calcium, phosphorus, magnesium, etc. are important in making the correct clinical diagnosis. Most of the metabolic bone diseases in India are either caused, or their clinical picture markedly modified, by environmental factors. Therefore, their prevalence as well as clinical severity is of far greater magnitude than what is reported from Western countries. They are the commonest cause of physical disabilities such as short stature, repeated and disabling bone fractures as well as bone and joint deformities, including pelvic deformities. The latter is among the dominant causes of obstructed labour in India. There is reported scientific data showing far less mineralized bone mass among Indians in both sexes in all decades when compared to Cauca-
sians. In view of this and also considering the increasing life expectancy in India, the nation is entering a demographic phase wherein age-related metabolic bone diseases such as post-menopausal osteoporosis are sharply on the increase. We have recently demonstrated wide prevalence of vitamin-D deficiency-related disturbances of bone mineral metabolism even among apparently healthy people belonging to middle or upper socio-economic strata of north India. There is clear scientific appreciation that chronic vitamin-D deficiency-related hyperparathyroidism is an important contributory factor in post-menopausal osteoporosis.

It is well known that fluoride ingestion through drinking water (hydric fluorosis) is widely prevalent in India. We have recently demonstrated significantly higher fluoride content even in normal Indian bone specimens at autopsy when compared to French bone specimens. Our recent studies have also demonstrated the adverse impact of chronic fluoride ingestion on renal phosphorus conservation, which worsens the consequences of vitamin-D deficiency in India. This is an example of more than one environmental factor acting in synergy to distort bone mineral homeostasis, leading to retarded or defective growth and development of bones among Indians. The estimated burden of clinically overt metabolic bone disease in India is 15 million.

**Pituitary disorders**

The pituitary gland, a pea-sized gland situated at the base of the brain, in relation to the hypothalamus, is a master gland and orchestrates hormone-mediated bioregulatory processes in the body. During pregnancy this gland enlarges to meet the special metabolic and endocrine needs of the mother and its blood supply increases several folds. The pituitary gland of the pregnant mother is very susceptible to anoxic injury. If there is abnormal blood loss during delivery, the pituitary gland gets damaged, resulting in a chronic disease characterized by failure of lactation, atrophy of breast, absence of menstrual cycles, progressive weakness, weight loss, frequent loss of consciousness and ultimately death in a state of extreme psycho-physical debility. On the basis of experience at AIIMS, this disease is by no means uncommon, yet it is hardly diagnosed even by relevant specialists. Presumably for every patient who comes to an advanced tertiary care center like AIIMS, there are several scores in nearby communities who are sick with the undiagnosed disease. With the largest number of daily births, the highest rate of home deliveries and unacceptably high prevalence of maternal anaemia in the northern states, India must be having the highest death rate due to post-partum pituitary failure. If one also considers the fact that snakebite is an important cause of pituitary failure in India, it can be surmised that pituitary insufficiency of environmental causation can be widely prevalent in India. Obviously, the disease is neither diagnosed nor treated to prevent death and disability among women, due to inadequate professional expertise and poor use of hormone measurements for diagnosis and management of endocrine diseases. The estimated burden of pituitary disorders in India is 4 to 6 million.

**Diabetes**

On the basis of careful countrywide studies, the total estimated burden of diabetes in India is 25 million (ref. 32). There is now recognition worldwide that Indians are among the most susceptible ethnically to develop diabetes. Also, the syndrome of diabetes as seen among Indians, is distinctly different from that among Caucasians. To investigate and understand this problem scientifically and clinico-epidemiologically, several hormones like insulin, glucagon and related gut hormones should be measured specifically and sensitively in thousands of biological specimens. I am not aware of any source of purchase of bulk reagents in India to perform adaptively and cost effectively, as well as with precision, hormone measurements required to do any meaningfully designed clinico-epidemiological study to understand the pathogenesis of diabetes among Indians in the Indian socio-medical settings. Such studies may well pave the way for developing effective strategies for primary prevention of the disease. Yet the potential for scientific investigations and related possibility of preventive interventions to reduce the prevalence of diabetes in the country is not availed of due to the use of poor technology.

**Technology adoption and use in clinical endocrinology**

Immunoassay technology can be used either by adopting trained manpower-based labour-intensive methods or by importing kits and using it cook-book fashion, adopting technology not understood or assimilated by the user. On the face of it, the latter approach may look easy, yielding quick results, while the former may appear more demanding in terms of developing skilled manpower with required scientific understanding. Besides, such approaches would be time consuming.

In the market place conjured up for us by Western techno-business and marketing strategies, we are made to face a great measure of ‘befuddlement’ by commercial offers of systems which are claimed to be ‘user friendly’ adopting ‘state-of-the-art technology’! Such commercially driven assay use enslave us by forcing upon us technologies which are neither familiar nor es-
sential to the task at hand, namely measuring hormones! I would like to illustrate this point by an example. It is imperative to use a tracer tagged ligand in the immunoassay technology used to measure hormones. The earliest tracer to be used in this regard was radioactive isotope-tagged tracer, which permits quantitation of the ligand by measuring radioactivity. Later, several other varieties of tracers were used for the purpose, such as enzymes, fluorescent and chemi-luminescent compounds, etc. Of these, technological sophistication for quantifying fluorescence and chemi-luminescence has presently reached a state wherein fluorescent and chemi-luminescent tracers permit assay sensitivity and precision similar to radioactive tracers. Many manufacturing companies who have developed and patented these technologies have commercially maneuvered themselves to occupy key positions in the multi-billion dollar immunoassay business by touting the safety (lack of so-called radiation risk), ‘acute sensitivity’ and ‘precision’ of the ‘state-of-the-art-technology’-based kits. Companies with patent for complimentary technologies merge, monopolize the market and pressure-sell their newfangled products. However, despite all the commercial hoopla, a moment of reflection would reveal the well-conceived deception in these marketing gimmicks. Buying a chemi-luminescent immunoassay kit means using a sophisticated instrument to quantify chemi-luminescence. It also means purchasing the tracer ligands from companies who hold patent for the technologies. Quite often companies with different and complimentary technologies merge and the resulting commercial monopoly would sell kits, including the tracer as well as the quantifying machine in a package. Some packages offer free use of the quantifying machine on condition of purchasing extremely expensive kits for a predetermined amount at regular intervals, as the conditionality for retaining the machine. Some kits are relatively less expensive, but the machine needs to be purchased at prohibitive costs with the hassles of repair and maintenance, for most of these machines are ‘black boxes’ incorporating technical secrets of commercial nature which are not revealed. Therefore they cannot be repaired and maintained in an autonomous manner. Besides, many of them quickly get outdated because of the fast pace of technical progress and therefore no spare parts would be available to permit long use of the purchased machine. Ultimately the laboratory would be left with no choice other than buying a new machine by spending a huge sum all over again. All these result in prohibitive costs of hormone assays for the patients. For example, a simple thyroxine assay costs anything up to Rs 150. The net cost of performing $T_4$ measurement using an autonomously developed in-house assay system, with indigenously prepared radio-tracers and radiation quantifying equipments is not more than Rs 10 per assay. Obviously the capital-intensive approach, using patented instrument and reagent imported from abroad for hormone measurement will never permit effective permeation of technology used widely in the matrix of the socio-medical milieu of the nation. On the contrary, labour-intensive efforts based on well-trained manpower and using indigenously available technology and equipments would permit cost effective assay use widely in the country. Our own work and accomplishment during the last two decades at AIIMS has shown that such autonomous assay development and use are not only feasible but imperative for adaptive and cost effective technology use to study, understand and manage endocrine and metabolic diseases in India’s unique medico-social milieu.

Affordable cost as well as appropriate and adaptive technology use are pivotal requirements to promote wide use of hormone assay in the country. Promotion of such use of hormone assay is the only way to bridge the gap between scientific knowledge and its application to prevent death and disability due to endocrine and metabolic diseases in the country. To achieve this, there is a need to appropriately train and deploy manpower competent in the development and usage of immunoassay technology. There is also a need to promote indigenous efforts to prepare and distribute high-quality standardized immunoassay reagents in bulk, cost effectively. Besides, a network of laboratories should be organized by empowered bodies for quality control of the life-saving bio-measurements in the country. In these days of high technology medicine, such standardization is as important as quality-controlling pharmaceuticals. Thus there is a need for urgent action to prevent deaths and disability due to endocrine and metabolic diseases among millions in our country.

The farmers' protests against field trials of genetically engineered Bt-cotton in India highlighted the controversies surrounding genetic engineering technology in agriculture. Molecular biology informed, democratic decision making.

The technological and societal issues were neither well characterized, nor well separated; scientists that information available to the public was incomplete, irrelevant, or obfuscated such that and, thereby, to suggest the level at which such problems are best addressed. The analysis suggested in order to identify the level of organization at which known and potential problems arise.

Commercial interests, and governments of both developed and developing nations, who believe that it provides the only means of producing enough food to feed people. It is strongly opposed by environmental groups and, especially in the media of developed countries, as if polarized across the developing/developed line. There appears to be a complex set of technological and societal issues. Although the issues involved were purely technological (i.e. molecular, organismal or ecological), there appears to be an unifying theme for controversies involving genetically engineered crops, especially the Bt-cotton issue, involving parts of the molecular biology community, including many scientists. The promise and problems of genetic engineering (GE) in agriculture is conducted across the world have united in protests against GE and developed nations. Much of the debate regarding applications of GE agribusiness, state and national regulatory agencies have united to try to block GE crop products. The US and Europe have been strongly opposed to GE crops, while a few Asian countries areتوره hypoxanthine-guanine phosphoribosyl transferase (HGPT) gene. The transgenic Bt-cotton plants were resistant to lepidopteran pests and were not killed by the Bt toxin. Nevertheless, unlike non-transgenic cotton, Bt-cotton yield was reduced by an average of 4.8% due to insect feeding.

The farmers, who had been following the experimental plots for a few years, were aware of the yield and income benefits. However, the farmers were not aware of the Bt toxin activity. Hence, they opposed the commercialization of Bt-cotton without conducting any field trials.

The farmers organized themselves into several non-governmental organizations (NGOs), while the Bt-cotton controversy was strongly opposed by environmental groups and, especially in the media of developed countries, as if polarized across the developing/developed line. There appears to be an unifying theme for controversies involving genetically engineered crops, especially the Bt-cotton issue, involving parts of the molecular biology community, including many scientists. The promise and problems of genetic engineering (GE) in agriculture is conducted across the world have united in protests against GE and developed nations. Much of the debate regarding applications of GE agribusiness, state and national regulatory agencies have united to try to block GE crop products. The US and Europe have been strongly opposed to GE crops, while a few Asian countries are currently allowing GE crops. The farmers, who had been following the experimental plots for a few years, were aware of the yield and income benefits. However, the farmers were not aware of the Bt toxin activity. Hence, they opposed the commercialization of Bt-cotton without conducting any field trials.