

EVERYMAN'S SCIENCE

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* Lord Rutherford unfortunately passed away before the Science Congress and Sir James H. Jeans presided over the Congress in his place.

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EDITORIAL

SAFETY, HEALTH AND ENVIRONMENT AT WORK-PLACES

Productivity of a person working in the premises of any organization—manufacturing or service—depends on the design, maintenance and modification (from time to time) of the workplace. This is true for all levels of workers and for all types of work, though the dependence could vary in nature and extent from one category of workers to another, and from one type of work to a second. Since modifications involve some design considerations and maintenance has to take into account the design, work-place design assumes a very important role in determining productivity—something that we all want to optimize.

Work-place (in relation to productivity) includes the place used by a worker individually as well as the over-all situation in which the entire organization works. Work-place has to be comprehended in terms of physical as also psychographic (human) features. Physical features include considerations of adequacy (of space), cleanliness, safety, noise level, illumination and ventilation, and the like besides access to safe water and pure air. Psychographic features relate to the nature and extent of interactions among workers, peer relations and relations between superiors and sub-ordinates, and more importantly stress caused by the work as also the policy of the organization affecting working life. Incidentally, safety is an umbrella term and has to be viewed against various types of exposure to unhealthy, dangerous or difficult situations faced by individual workers e.g. radiation hazards or chemical hazards as well as situations which affect workers in a particular area or in the whole organization, like fire hazards. In fact, agricultural workers handling poisonous chemicals like pesticides or insecticides or even using chemically polluted water are exposed to serious health hazards.

Given that Industry and Agriculture have to exist and have to adopt advances in technologies including those which are associated with risks and noting that workers in other places also are

vulnerable, attempts are being made to minimize the deleterious effects of unsafe, unhealthy and environmentally poor work place. Safety, Health and Environment at work-places have to be understood in terms of identifiable and measurable parameters ; permissible upper or lower limits for each such parameters have to be developed, and action has to be taken by organizations to ensure conformity to such standards. Apart from attempts to conform to prescribed limits for individual parameters, usually fraught with findings of non-compliance occasionally, organizations should develop and maintain systems to ensure safety, health and friendly environment at work-places. And as is true for other systems, systems required to ensure these drivers of productivity should be based on four components, viz. organization, processes, procedures and resources.

Among the important standards which address these and related issues, the most well known is the Environment Management System standard ISO 14001 and the British standard BS 8800, released in 1996, relating to occupational health and safety management system. However, unlike the international standard ISO 14001, the British standard does provide guidance in the matter and is not a standard against which certification for compliance can be issued, helping the organization to identify its weaknesses which could be acted upon. Several Certification bodies came up since then to develop an widely accepted protocol, viz. OHSAS 18001 which allows auditing and certification. In fact, the International Labour Organisation deplored as late as December 1998 the absence of an international standard in the matter, noting that OHSAS is not an international standard and lacks the edge of an ISO specification.

A meaningful and effective implementation of any standard or protocol in this area calls for commitment on the part of top management. Fortunately, with a growing consciousness all around, top management has been held responsible whenever standards are

violated, particularly when such violations cause casualties in some recognizable form or the other. In fact, the number of cases where top management has been booked for such violations in legal disputes has become quite noticeable in some industrially advanced countries. Of course, it is very true that people consciousness at all levels is a key factor in maintaining a safe, healthy and environment-friendly work-place. Beyond consciousness, training of people in using and operating safety devices, in observing needs of personal hygiene, in maintaining cleanliness, in meeting emergency situations, etc. are quite important.

Coming back to work-place design, besides taking full advantage of ergonomic principles, we have to understand and implement a few actions scientifically and take recourse to some calculations (statistical in nature) in order to reduce risks and review situations. Thus, we have to (1) analyse tasks to be carried out by a worker ; (2) identify hazards associated with materials to be handled or accessed or accepted, processes to be carried out, procedures to be followed, checks to be exercised, (3) calculate risks for different types of hazards and take actions based on these. Risk is usually computed in terms of a risk priority number (RP), more or less on the lines of a Failure Mode and Effect Analysis (FMEA), based on three inputs, viz. frequency of occurrence, severity of occurrence and impact or consequence. More often than not and thanks God for that-adequate data do not exist to allow an easy computation of risk. This is why sophisticated statistical techniques for evaluation of very small probabilities have to be used in a scientific determination of risk.

Human aspects of safety, health and environment are gradually gaining momentum and attention is being paid to such matters as problems of lone or solitary workers, physically or mentally challenged workers, segregated workers, and so on. Studies on human behaviour in emergency situations and on alertness to avoid hazards etc. are being recognized as important inputs in our efforts to ensure safety, health and good environment to all our workers. Emphasis is also being

placed on emergency preparedness and on drills and mock exercises like firefighting.

All this is in relation to work-places in the organized sector, being overseen by a number of regulatory bodies. A lot remains to be done to improve the situation in the relatively ignored unorganized sectors of manufacturing or service. Of particular concern are the unhealthy environment in which children and adolescents work or are forced to work, and even handle hazardous materials and processes, with little provisions to take care of associated risks. Large numbers of male and female children and adolescents are involved in the Match and Fireworks Industry in Sivakasi, Bidi Industry in Vellore and Murshidabad, Diamond-cutting Industry in Surat, Glass Industry in Ferozabad, Pottery Industry in Khurja, Lock Industry in Aligarh and Carpet Industry in various parts of U. P. In most of these cases, whatever we are going to discuss here are just not heard or are just not taken into any serious concern.

It will be not merely desirable but also imperative for us to raise matters relating to safety, health and environment in different types of enterprise with reference to their specific features and not just issues that are common to all and mostly known to all and, may be, mostly taken care of, or mostly ignored. We have to think of responsibilities and obligations of different stakeholders—people who work, people who design and maintain work-places, people who decide on investments in health and safety, people who are meant to act as watchdogs, people who handle emergencies and disasters, and people who design and develop methods and practices to improve work-places. A segmented approach rarely yields the desired results and it may be a good idea to form a forum of representatives from the different stakeholder groups, equip the same with some wherewithals and charge it with some specific responsibilities.

Prof. S. P. Mukherjee

No one gossips about other people's secret virtue

— Bertrand Russell

PRESIDENTIAL ADDRESS

THE ROLE OF SCIENCE IN THE RECENT PROGRESS OF MEDICINE

* SIR U.N. BRAHMACHARI, KT., M.A., M.D., PH.D., F.S.M.F., F.A.S.B., F.N.I.

Your Highness, Ladies and Gentlemen,

We happily meet this year at Indore in the famous land of Mālava, watered by the beautiful Siprā. Not far from here are the sites of the sacred cities of Māhismatī, Ujjayianī and Dhārā, whose names conjure up glorious visions of the past. The town of Maheswar is connected with the hallowed memory of the saintly Ahalyā Bāī, an illustrious ruler of the Indore State, whose piety and generosity are even today a household word throughout India. Ujjayianī was a famous seat of learning in the olden times.

In the fitness of things the Indian Science Congress has been invited to hold one of its sessions in this historic place, thanks to the hospitality of its most enlightened ruler, His Highness Maharajadhiraj Raj Rajeshwar Sawai Shree Yeshwant Rao Holkar Bahadur, Maharaja of Indore. In the annals of Indian history, the Holkars hold an honoured place for their achievements in the fields of arms and of peace.

Under the able guidance of His Highness, the city of Indore now ranks amongst the great industrial and highly cultured cities of India. It is an important educational centre with an excellent plant research institute, many high schools and colleges, an excellent institution for the training of the sons of Chiefs and a medical school, and with palaces and beautiful gardens. Indore must feel proud that His Highness has recently introduced so

many reforms in his State, has given her a magnificent aerodrome with a splendid landing ground, and has inaugurated many beneficial schemes, such as, geological and mining surveys, vocational education and development of new industries and encouragement of industrial research. Within a few miles of the city are the great waterworks of Badarkha with the largest syphon system in the world which, I understand, is an extraordinary feat of engineering skill. By the generosity of His Highness and the cooperation of his officers, hosts and guests have met today under a happy augury of success and we have every reason to congratulate ourselves on his gracious hospitality and kindness.

In rising to address you at this annual meeting of your Congress, I feel I am hardly worthy to occupy an office which is associated with the names of those with whom I cannot compete in greatness. A few years ago, Lord Rutherford stated at a meeting of medical men that the hopes of the world rested upon their successes and ever-growing usefulness. Aviation, wireless and television have now been accomplished, but one thing still left to wish for, Lord Rutherford very truly remarked, was long life and health, and it was the medical profession with whom it lay to give that guerdon to humanity. For "Happiness lies, first of all, in health".

"O blessed health! thou art above all gold and treasure....

..... He that has thee has little more to wish for and he that is so wretched as to want thee, wants everything with thee."

* General President, Twenty-third Indian Science Congress, held during 31st January to 5th February, 1936 at Indore.

Standing here today as your president, I think I should show no partiality towards Science of Medicine by choosing it for my address because I happen to be a medical man. As it is customary in the annual meetings of scientific societies for the president to refer to the recent advances in Science and as the progress as well as the future achievements of Medicine, which is concerned with the preservation and restoration of normal activity of living matter in the human machine, depends to a great extent upon the help that she has had and may yet get from the Sciences that you profess, you would perhaps expect me, as far as practicable within the time at my disposal and as far as lies in my power, to give a review of the important contributions made by some of your Sciences in recent times towards the advancement of Medicine. I shall take cognizance of our recent knowledge of some aspects of living matter, as Medicine is intimately connected with life, and I shall refer to some recent facts revealed by your Sciences which may apparently have no particular relation to Medicine in the present day, but may be of medical interest in the futures.

The future happiness of mankind depends on the solution of the problems of life. These problems are much more complicated than those of Physics and Chemistry, and still more is this the case with the Science of Medicine, which deals with the pathological aspects of living matter. I shall probably be able to say nothing that is new, but presentation, from a different viewpoint, of things already heard may perhaps be profitable.

BIOCHEMISTRY

I shall begin by saying a few words about our present day conception of dietetics and nutrition.

As a matter of the most vital concern in nation-building, the problem of nutrition demands very careful consideration by statesmen and scientists alike, more so due to the fact, as has been recently observed, that a great part of the world's population

is not consuming the necessary food stuff. An eminent Swiss authority predicts the decay of civilization unless there is a fundamental revision of the people's diet.

Dietetics and Nutrition—Vitamins

It has been stated that the function of nutrition is probably the centre of Medicine from a medical point of view, and that the proper dietary of man is a most important subject for the maintenance of health and prevention of disease. As has been observed by Hopkins, during the whole history the needs of nutrition and the kind and amount of food geographically available have played a great part in determining the destinies of races. It has been stated "tell me what you eat and I shall tell you what you are." "Man's place in future history will depend in no small degree on the food he eats." Nutrition is one the essential functions of life and its value cannot be too much emphasized.

Up to 20 years ago, the reign of calories was supreme in the field of nutrition, and it was held that if the proper amount of energy required for maintaining nutritional equilibrium could be worked out in terms of calories, then the last word would be said about the problem of nutrition. But it has now come to be recognized that certain substances that had eluded detection in the past, are indispensable in our dietary for the normal activity of the tissue cells and the prevention of certain diseased conditions. Further the study of the problem of nutrition has increased in recent times from the quantitative to the qualitative standpoint, especially with respect to the proteins.

Though it was long known that diseases like beri-beri were due to deficiency in the food of certain substances of unknown chemical nature, it was Hopkins who made in 1912 the monumental discovery of the value of the "accessory food factors", or the "vitamines" as they were termed by Casimir Funk, in the maintenance of normal functional activity and growth. The progress of

research upon the nature, distribution and functions of vitamins has been very intense in recent days. To attempt to summarize all that is known about them is beyond the limits of my lecture. The discovery of vitamins has led to the relief of a considerable amount of suffering and disablement that is particularly true in regard to rickets. Many of them are simple chemical substances and it is possible that each of them possesses a strict specificity in its action, though lack of more than one vitamin may be responsible for the causation of the complex phenomena manifested by disease.

The function of vitamins and the pathological lesions due to their deficiency are known to those among you, who are biochemists or who belong to the medical profession. I shall not discuss them here.

It is possible that the lack of vitamins does not play such an important part in the causation of disease as has been claimed by some observers and that the symptoms following a deficiency of certain vitamins may be attributed to a disturbance in the gastro-intestinal canal. It is realized today that the processes of digestion are much more complex than was hitherto thought. The secretion of the intrinsic factor is but a case in point. It is now known that vitamin B₁ deficiency is the cause of lack of appetite and defective movements in the elementary canal. It requires but little imagination to conceive that these effects must have some fundamental cause and that they could lead to a number of abnormal sequelæ, such as, defective absorption, stasis and toxæmia, to mention a few.

Requirements of Proteins, Carbohydrates and Fats in A Dietary

The minimum amount of protein required for the dietary of man has been a matter of dispute for a long time. Originally found by Voit at 119 gms, it was afterwards raised by Atwater to 125 and subsequently lowered by Chittenden to 60. Sherman quotes it at about 44.4. It has now been recognized that the quest for a protein minimum is really an

illusion, as it depends not on the quantity but on the kind of protein supplied. The work of Hopkins on the essential amino acids in connection with nutrition has come into prominence in the present day. As has been pointed out by him, the food proteins which can be used with the greatest economy in the body are those which contain all the amino acids in such relative proportions as will correspond most nearly with their proportion in the living tissues of the consumer. These are the proteins of so-called high biological value, constituting the first class proteins. It has been observed that the average consumption of Cambridge undergraduates, those in training being excepted, is about 80 gms of protein.

The Problem of Perfect Diet

There are many problems that await fuller investigation by physiologists and biochemists in future before the perfect diet can be proclaimed. A food in order to be effective, must be ingested by a body both physically and psychically sound. It is possible to be well-nourished on the simplest of dietaries. Who can say for certain what is the optimum protein diet or the optimum intake of fat? What about the food of the Eskimos, the human carnivores of the world, who live for long periods on purely animal food? Hindhede has emphasized the superiority of the high fat, low protein diet of the Danish farmers over the high protein, low fat diet of the neighbouring Finlanders. But is this applicable to all mankind? There has been much talk about the energy value of different foods expressed in calories. But, as Cathcart has said, are not these merely convenient units of measurement? How are we to explain the deleterious effects of "very high" cereal dietary and how are they corrected by "protective" foods, such as milk and leafy vegetables? Do the cereals contain any toxins, which are neutralized by a proportional quantity of the protective food? What definite information is available as to the body needs of the different kinds of vitamins? A further question is the problem

of hypervitaminosis, as also the actual part played by vitamins, and any difference which may arise from taking synthetic or natural vitamins.

Nearly 90 years ago, Chevers taught that the dietary of the Hindus with a very moderate quantity of animal food was the fittest for a tropical climate. Thus he wrote, "It is certain, that the law-givers, who prescribed for the people of India a diet consisting mainly of vegetables and water, the lighter kinds of animal food, such as fish, pigeons and goat's flesh, being only occasionally introduced in moderate quantities, judged almost as physiologically as they could have done, had they studied at the feet of Liebig and Prout". Similarly in a discussion on the dietary of man, the meatless diet of some of the finest soldiers of His Majesty's Indian Army who fought in the last great world war was highly extolled. This is an interesting subject for research in the quest of minimum animal protein required for human consumption and the future may show that it may be influenced by climatic conditions. Recent researches of Berg tend to show that factors which determine the minimum quantity of protein necessary to preserve nitrogenous equilibrium, such as, the particular protein the subject is accustomed to taking and the ratio of inorganic based to inorganic acids available to or formed in the body of the subject.

This brings me to the question of animal versus vegetable protein. Investigators of the present-day hold that, in general, proteins of animal origin are superior to the vegetable proteins for the purposes of nutrition and that the testimony of human vegetarians is useless in determining the amount of animal protein requirement of man, because they were probably not vegetarians during the first part of their lives.

Are there first class fats? At present we know little about the nutritional value of different fats, but some work goes to show that certain fatty acids of the linoleinic series may be essential. It has been stated that the synthetic fat intarvin may be

used by fasting persons of normal health without the development of acidosis. Do not these adumbrate the possibility of the existence of first class fats? Further work is also necessary to determine if there are essential carbohydrates.

Mineral Constituents of Diet

In recent years there has been an advance in our knowledge of the importance of inorganic substances, especially minerals in our dietary. Many of these such as calcium and phosphorus are required for structural purposes and their deficiency gives rise to structural diseases. There are others which are required to be present in minute quantities in our dietary and which are perhaps concerned with the stimulation of the active processes in the tissues. These are copper, manganese and perhaps yet other undiscovered elements. Their deficiency is regarded to be responsible for certain forms of anæmia, though very recently this view has been doubted by some observers. The possibility of the existence of undiscovered mineral deficiency in disease is for the future to reveal, and may I suggest that certain obscure diseases of India, such as, infantile biliary cirrhosis of children may be investigated from this point of view.

Complicated are the inter-relations of the vitamins, the hormones and the mineral constituents of the tissues in the prevention of certain diseases. For instance, bio-chemistry has shown that a supply of iron, copper, vitamin C and thyroxin are the essential factors in the formation of erythrocytes and hæmoglobin, in addition to an active bone marrow. Deficiency of any of these may give rise to certain types of anæmia. A generous supply of calcium and phosphorus together with a liberal supply of vitamin D is essential for the perfect development of the bones and teeth of the child.

Prolongation of Life and Rate of Growth

It recent times, studies in nutrition have been concerned chiefly with the maintenance of normal health and production of a rapid rate of growth. It

has however been observed still more recently that prolongation of life associated with a retarded rate of growth has been noted in many divergent forms, such as, rats and brook trout and that animals kept on a restricted food intake for long periods outlived by a wide margin those that were allowed to eat full from the time of weaning. The inverse relationship of the rate of growth and the time of onset of senility is also apparent from other investigations. Evans has noted that animals injected chronically with preparations containing growth hormone of the hypophysis show evidence of premature senility. On the other hand, Lee and Schaffer have shown that administration of the pituitary growth hormone results in retention of juvenile chemical characteristics by the tissues. Other clues for the study of these problems are furnished by the facts that thymus extracts greatly increase the rate of growth and maturity while pineal extract seems to retard growth. Wetzel in his work on "Motion of Growth" has shown that excessive rate of growth during infancy and childhood is associated with excess of wasteful heat production and that this may have grave consequences. It is apparent that some of the current tenets in the field of nutrition require reconsideration in an effort to determine the optimal rate of growth for each period in life.

It seems, however, that the preponderance of evidence indicates that the increased growth achieved by well-considered improvement in the diet is accompanied by general physiological betterment and definite improvement of the species. By intelligent improvement of nutrition of experimental albino rats through successive generations there has been developed a new species of these animals.

Environment and Improved Nutrition

In the present day, physiologists realize that a diet which appears to be adequate is not invariably the optimum diet. Better environment and improved nutrition will improve hereditary character and

bring mankind to a higher level of physical development. Newer knowledge of nutrition may lead to the development of a larger stature, greater vigour, increased longevity and a higher level of cultural attainment (McLester).

Indian and Indo-Japanese Dietary

In a recent investigation into the diet of the Indo-Japanese in the Dutch Indies, it has been observed that on a diet which appeared hardly adequate from a European point of view the people of the country lived in a fairly good health, though their weight was of a somewhat low standard. The subject requires further investigation to determine what would constitute a proper dietary for the Javanese.

Coming to the Indian dietary, in recent times some interesting work has been done with the balanced diets for Indians by Tilak and his assistants. The dietary worked out by them is the inclusion with the staple food grains in common use by the people of India, of soya-beans, dried skimmed milk, rice polishing, fresh groundnut cake and preparation of sprouted seeds. Such dietaries, if confirmed, may help in solving the problem facing large masses of people in India, i.e., how to obtain a reasonably good diet for 5 to 7 rupees a month. Aykroyd has found that diets which in paper at least, adequately fulfil human requirements can be bought in Madras for about Rs. 4/- per month. "Cheap balanced diets" of this nature must, of course, be subjected to the test of practice.

Perhaps millions of the people of India, especially among the poorer classes, suffer from various degrees of malnutrition which leads to lessened power of resistance to infection. McCarrison's work in this field is well-known. Sanitation and nutrition must go hand in hand in all countries especially in India, where so many diseases-epidemic and endemic-prevail.

Gastro-enterology

Alimentary auto-intoxications, allergic conditions from imperfect metabolism, and auto-

infections from the alimentary tract play an important part in Medicine and the gastro-enterologists are claiming today that the Science and practice of nutrition is becoming an independent and complete speciality, which is to be identified with theirs. Perhaps the Science of Nutrition, including the problems of the dietary of the people of a country, will, one day, form part of the department of preventive medicine of the State, as it has already begun to be in certain countries.

Dietary in Diabetes

In India where diabetes is common, the proper dietary of the disease is an important subject, and I shall very briefly refer to it. Since the epoch-making discovery of insulin in the treatment of diabetes, the pendulum is swinging from the fat diet of Newburgh and Marsh to "high" and "higher" carbohydrate diet of Sansum and others. Recently, it has been observed that administration of carbohydrate stimulates the production of an unknown insulin kinase, the insulin acting as a substrate in the metabolism of sugar (Himsworth). On the other hand, large amounts of fat may inhibit the action of insulin. On this view a "high" or "higher" carbohydrate diet for diabetes aided by insulin finds a rational support and it is possible that, by the adoption of such a diet, the life of a diabetic may be more prolonged and death rate from diabetes more reduced than what has been achieved in the present-day, in spite of the introduction of insulin.

Hyper-vitaminosis, Hyperhormonism, Antihormones

In speaking of vitamins in connection with maintenance of nutrition, one cannot help making a brief reference to a condition discovered in recent times and known as hyper-vitaminosis. This consists of a series of toxic symptoms following the administration of excessive doses of certain vitamins such as A or D. It may be incidentally mentioned here that excessive production of the internal secretions of the ductless glands in the

system, and administration of an excessive amount of the same may also give rise to toxic symptoms. The condition may be described as *hyperhormonism*. Further it is possible that inhibitory principles may be produced as a response on the part of various hormones, and that the clinician in his endeavour to correct a hypo-glandular state may actually add to the gravity of the condition by causing an overproduction of inhibitory principles, as a result of too persistent treatment with hormones (Collip). In diseases due to the deficiency of hormones, their artificial administration must therefore be intermittent and regulated according to the needs of the patient, just as they are normally manufactured and distributed according to the needs of the body in health. Whether inhibitory principles may be produced by excessive use of vitamins I cannot say.

Biological Catalysts

Before I leave this portion of my address, may I make a passing remark about the biological catalysts. The catalysts of a living cell are the enzymic structures which promote reactions within the cells and determine their direction. Perhaps in the maintenance of the normal reaction within the living cells, the vitamins, the hormones and the minute mineral constituents play an important part. The action of medicines and diseased products upon the permeability of the cells and upon the action of enzymes within them must be an important field for research and may be of great value in Medicine for the study of chemotherapy and immunology.

PHYSIOLOGY

No one can doubt that physiology has had a great influence upon the whole field of Medicine in recent times.

Recent researches have thrown light on the mechanism of the fundamental reflex reaction for

the protection of the animals and have shown how with the evolution of an anti-gravity mechanism and of extended movement, the brain stem has become evolved to take over this increased responsibility. Magnus has analyzed the various nervous stimuli from the periphery which are concerned in this very delicately coordinated mechanism. The new data have completely revolutionized our conception of the nervous stem, and signs and symptoms of disease which hitherto could not be properly understood have now become capable of analysis.

In more recent years Sherrington and his school have worked more exactly on the relation of the nervous system to responses produced when it is active. These fundamental studies will no doubt throw much light on the changes so often observed in disease. His researches have shown that the centripetal impulses do not pass straight through the spinal cord, but at certain stations in the cord they are transferred into an enduring excitatory state which may in turn set up fresh impulses yielding the reflex discharges.

Adrian's researches have also added greatly to our knowledge regarding the exact nature of the impulses which pass along nerves in different conditions. With a most admirable technique he has studied nerve impulse and its origin with highly profitable results. He has come to the conclusion that change of potential may be of fundamental importance in the activity of nerve cells. He has shown that damaged nerve fibres set up impulses at very high frequencies and these perhaps play a part in sensation of pain, though sometimes impulses in the smaller, slowly conducting nerve fibres may also be concerned in the physical mechanism of pain. He has been able to observe the activity of a single nerve cell and has shown that human voluntary contractions are regulated in exactly the same way.

In Russia Pavlov and his school have elaborated the reflex reactions of the higher parts of the

nervous system. Their results are capable of considerable application to many of the higher human activities.

A. V. Hill has studied the nerve impulses with exquisitely sensitive apparatus from the point of view of thermal phenomena accompanying it and it is becoming clear that the nerve impulse consists of a transmitted physico-chemical event, the whole cycle of event comprising activity and recovery in the nerve being supported by the energy derived from metabolic oxidative processes, associated with the cycle.

Further it is possible to conceive "the nervous impulse as a succession of transformation of chemical into electrical energy, and conversely—these transformations being necessary by the structure of the fibres."

Haldane and his pupils have continued their well-known work regarding the control of respiration. Carbon dioxide, formerly looked upon as a product of excretion, to be got rid of as soon as possible, has been shown by them to be an essential stimulus to respiration. This discovery has been of immense value in modern anæsthesia. Further it has been shown by Yandell Henderson of Yale University that carbon dioxide is also essential for the tone of the blood vessels. Dale and Evans have shown that carbon dioxide is essential for the activity of the vasomotor centre, just as it is responsible for the activity of the respiratory centres. Barcroft has shown the principles by which oxygen is transported by the blood. As a result of the work of Haldane, Barcroft and their co-workers, it is now possible to deal with respiratory distress and failure by more scientific methods than what was possible in former days.

Areas such as the cerebral and pulmonary vessels which were once thought to have a poor vasomotor supply have now been found to be much better supplied than had hitherto been imagined.

With regard to the heart, the earlier studies of cardiac disturbances by Mackenzie have played an important part in advancing our knowledge regarding the physiology of the heart, and the work of Starling and of Lewis has placed much of it on a strict experimental basis in more recent times. A new interpretation of the electro-cardiogram in disease has been recently evolved.

The discovery of the function of the carotid sinus by Hering and its study by Heymans have been of great value to physiology and to pharmacology as well. By the recognition of the activity of this sinus and its possible variations one can now explain many of the differences in response which hitherto have been a great drawback in experimental work. In the nerve connection of this sinus and the effect of pressure on it lies, according to some observers, the explanation of sudden death under gas anaesthesia.

One of the most important new facts discovered in recent years regarding digestion is the relationship of the proper functioning of the stomach to the production of blood, and the subsequent application of this to the treatment of pernicious anaemia. This work had its origin in the physiological studies of Whipple on the normal regeneration of blood after haemorrhage and administration of liver. Following the same line of research Minot and Murphy found that administration of fresh liver had a remarkable curative effect on pernicious anaemia. This led to the recent liver therapeutics for treatment of the disease.

The researches of Castle, however, connected the etiology of pernicious anaemia with defective gastric secretions. Recent experiments of Meulengracht have shown that pernicious anaemia in human beings may be due to atrophy and inactivity of that part of the stomach which comprises the pyloric gland region and may be said to have localized the seat of origin of pernicious anaemia in human beings. Thus stomach preparations for the treatment of pernicious anaemia may with advantage be producible from the pyloric gland region.

From a physiological point of view, these experiments give the pyloric glands a function. As we know, it has hitherto been difficult to ascribe such a function to the pyloric glands and the special pyloric gland cells. Now it seems possible that the pyloric glands are the seat of special secretory function and secrete the substance Castle's "intrinsic factor" that is essential to the blood and the nervous system.

These experiments open up the theoretical possibility that under certain circumstances pernicious anaemia may be due to an isolated atrophy or inactivity of the pyloric gland organ without a simultaneous atrophy or inactivity of the fundus gland organ, i.e., without simultaneous apepsia or achlor-hydria ("dissociated achylia") although judging from present clinical experience this possibility does not appear to be of much practical importance.

It has been shown by Loewi that the vagus nerve inhibits or checks the activity of the heart by the liberation of a chemical substance which directly influences the myocardium. This is a finding of great importance, as there is increasing evidence that the activity of all nerves may take place through the agency of similar chemical substances. Cannon and co-workers believe that they are capable of appearing in two forms of combination, one producing only the augmentor and the other only the inhibitory effects of sympathetic nerves.

Extensive investigation as to the nature of the process by which nerve impulses influence the effectors has been carried out by Dale and it seems fairly established that all different messages eventually produce the desired effect by the liberation of either acetylcholine or of a substance like adrenalin. Dale distinguishes such nerve fibres as "cholinergic" or "adrenergic" according to the nature of the active substance liberated. The preganglionic fibres of the autonomic system, the motor nerves, and the post-ganglionic fibres of the parasympathetic belong to the 'cholinergic' category

while the post-ganglionic fibres of the sympathetic usually fall under the "adrenergic" group. It has been pointed out by him that Langley and Anderson's evidence, long available, as to the kinds of peripheral different fibres which can replace one another in regeneration, can be expressed by the statement, that cholinergic fibres can replace cholinergic fibres, but that nerve fibres of different chemical functions cannot replace one another. This discovery has no doubt an important evidence on our new conception of the mode of action of "neuromimetic" drugs.

Certain recent experimental studies tend to show that living tissues may be the seat of radiation able to produce effects at a distance, and that certain activities in one cell of a tissue may influence activities in a neighbouring cell and that chemical reaction may be accompanied by radiations, and events in one cell may thus influence other cells without material transmission.

The Endocrine Glands, the Glands of Destiny, the Pituitary

It has been held that the ductless glands are the "glands of our destiny" and that "these potent overlords of our bodies are dictators of our minds and personalities". It may be possible that the future may reveal that genius, intelligence, beauty, character, morality, and other human characteristics are dependent upon diverse combinations of the secretions of these bodies, just as their deficiency or excess may give rise to disease.

Insulin has completely changed the prospect of the treatment of diabetes. The discovery that parathyroid extract mobilizes the calcium of the bones has revolutionized the treatment of disease due to calcium derangement. Our knowledge of the interaction of endocrines has increased in recent times. I would just mention a remarkable fact that, as shown by Houssay and co-workers, there is no glycosuria when both the pituitary and the pancreas are removed, and further that the injection of

extract of the anterior pituitary is followed by the appearance of glycosuria.

May I end this portion of my address by making a little more reference to the pituitary, which seems to have a multiplicity of functions. It may be regarded as the headquarters for the hormones or the chemical messengers which control most of the other endocrine glands and thereby probably almost every cell of the body. The Chemistry of the pituitary is by no means closed and it may be that the most important discoveries in the pituitary chapter have yet to be written. It has been held that "the integration of the endocrine system is based on the influence of the diencephalon upon the anterior pituitary, which through complex hormones acts on the other endocrine glands, stimulating or inhibiting the production of simpler hormones in them. These hormones are closely related chemically to other substances concerned in normal activities such as, the growth of the embryo, the growth of bone and calcium metabolism, as well as abnormal activities such as malignant growths." Further, "in general we can see a division of labour between nervous and hormonal events, and accordingly between the respective regulators, the central nervous system, and the anterior pituitary lobe. The central nervous system regulates principally the specific, acute functions; therefore it also influences those neurogenic endocrine organs, the adrenal medulla and the posterior pituitary lobe, the hormones of which cause acute changes. The regulator of the non-neurogenic hormonal system, the anterior pituitary lobe, regulates mainly the development and state, and partly also the secretion, of the remaining endocrine organs, the hormones of which bring about longer lasting changes of the conditions of many other organs" (Loewi).

In studying the developmental history of the remarkable endocrine gland, the pituitary, one finds that by the seventh week of embryonic life, as the base of the skull is being laid down between the roof of the pharynx and the floor of the fore-brain,

the stalk of the Rathke's pouch which forms the anterior and intermediate lobes of the pituitary body is drawn out and lies at the posterior border of the nasal septum. Usually some fragments of the pituitary stalk persist in the mucous membrane of the roof of the nasopharynx. Cases have been observed in which the whole pituitary body lies in the posterior part of the nasal septum. By the ninth week the stalk usually disappears, but occasionally a canal in the body of the sphenoid bone of the adult—the craniopharyngeal canal—marks the site of the embryonic stalk. Herring, very recently, has referred to the functions attributed by the ancients to the pituitary. We may make here a reference to the remarkable claims made by the ancient *Yogis* of India who practised what is known as *Khechari Mudra*. They elongated the tongue slowly by practice and manipulation aided by cutting its fraenum, if necessary, and carefully introduced it into the nasopharynx. The *Yogis* claimed to have developed remarkable powers of their body and mind in this way. Did they conceive that the tongue mechanically stimulated the secretion of the glandular structures in the nasopharynx (pituitary?) which might be subsequently absorbed into the system, in the same way as adrenalin is absorbed when put under the tongue, and interact with the secretion of other endocrine glands? Will some future investigator test the validity of the above claims?

Tissue Culture

May I now say a very few words about tissue culture.

“Tissues cultivated *in vitro* show two types of growth, which are sometimes termed “somatic” and “uncontrolled” respectively.”

“In somatic growth, which is usually seen best in cultures of early embryonic tissues, the explanted fragment behaves to some extent as if it were still part of the body. It may increase in size by any or all of the three methods observed *in vivo*, viz., by the multiplication of cells, by the enlargement of

cells and by the formation of intercellular material, and if removed from an embryo at an early stage of development often continues to differentiate during cultivation. For example, undifferentiated skeletogenous mesoderm will form cartilage and bone *in vitro*, explants of the undifferentiated retina give rise to nerve cells and rods and cones, and in cultures of the early mesonephros typical kidney tubules may develop.”

“The second type of growth—uncontrolled growth, is perhaps more characteristic of tissues cultivated *in vitro*. Its main features are the progressive simplification of the original histological structure of the explant correlated with a diffuse outgrowth of the cells multiplication only. Even in uncontrolled growth, however, cells never wholly depart from their original type, and epithelial and connective tissue cells remain distinguishable as such even after prolonged cultivation.” (Fell and Willmer).

The Carrel strain of fibroblasts is the oldest set of cultures in existence, but there is evidence that certain types of epithelium and various forms of malignant tissue can also be made to live and multiply indefinitely *in vitro*. These results suggest that at least some types of vertebrate cells may be potentially immortal, just as certain types of protozoa or the flat worm may be kept indefinitely alive. It has been claimed by Wells and co-writers that “if Dr. Strangeways had lived in the time of Julius Caesar and set a series of sub-cultures growing from a scrap of him, fragments of that eminent personage might, for all we know to the contrary, be loving now”.

The recent invention in the Rockefeller Institute for Medical Research jointly by Carrel and Lindbergh, of a “Life Chamber”, a sort of artificial body of “heart, lungs and bloodstream”, has enabled scientists for the first time to keep the organs alive, functioning and even growing for a long period outside the body. The method of Carrel-Lindbergh

consists of the transplantation of an organ or of any part of the body into a sterile chamber and its artificial feeding with a nutrient fluid through the arteries. In this way the thyroids and ovaries of animals have been artificially cultured, and made to grow. The perfusion fluid consists of protein hydrolytic products, hæmin, cystein, insulin, thyroxin, glutathione, vitamins A and C, blood serum and other substances according to the necessities of the particular organ to be perfused. There is no doubt that tissue culture is likely to be of immense importance in the study of the human body and in the preventive and curative treatment of diseases.

I have briefly outlined how the Sciences of Biochemistry and Physiology have been laid under contribution in the recent progress of Medicine. There are, no doubt, various other facts worthy of note in their application of Medicine, but I have refrained from mentioning them for want of space and time.

It is pleasing to know that many of the investigators whose names I have just mentioned have been Nobel laureates for researches in the subject group of Physiology and Medicine.

Genetics

I hope it will not be regarded as transgression of the ambit of my subject if I pay a passing tribute to the recent activities in the field of genetics.

The account of Mendel's epoch-making experiments in his cloister garden, on the crossing of varieties of the common pea, somehow or other sank into oblivion for thirty-five years. But such was the potentiality of his work that, when rediscovered, it not only laid the foundation but also gave a new impetus to the study of the Science of heredity. In recent times Mendel's theory of what called by him *factors* (now known as *genes*) has received confirmation in the hands of Morgan and others. Their physical existence in the chromosomes has been proved and it is now known

that the chromosomes are indeed the bearers of the hereditary units and that to their very reliable mechanism we owe the regular behaviour of the inheritance of characteristics from parents to children. Heredity is really a most remarkable phenomenon. The production generation after generation, of offspring identical in all but minor peculiarities with their parents is indeed one of the great mysteries of life, and it is by the orderly division of the chromosomes and their contained genes life can be maintained. It is becoming more and more established that "the general laws laid down by Mendel have as wide a validity for genetics as have Dalton's for Chemistry".

The practical outcome of the application of the principles of genetics as demonstrated by the magnificent work in research laboratories such as those at Cambridge, Edinburgh, Aberystwyth, and Aberdeen, has been of immense value in improving crops and live-stock. The boundless possibilities in heredity revealed by the Science of genetics have placed great power in the hands of breeders of plants and animals and they can now tell with approximate accuracy what to expect from matings. This knowledge has revolutionized breeding in all directions, and resulted in the production of bigger and better plants and animals used for food, clothing or pleasure. In the course of time man may be able to replace the natural selection of more fertile mediocrity and the artificial sterility of the high-grade parents by human selection and the artificial fertility of high-grade parents. Sooner or later the frequency of the latter would increase in geometrical progression and control and guide the qualities of mankind in any way it desires for the good of man. The future trend of creative evolution, including man's own destiny, depends on his response to the new knowledge and on his intelligent application of genetical discoveries, in the near as well as distant future (Hurst). Genetics aided by better environments may also be able to prevent the transmission of hereditary weakness and hereditary diseases, some of which are sex-linked. In this way

it may lead to the production of better type of men, free from diseases of the mind and body that are propagated from father or mother to their children and thus the difficult task of medicine for averting or curing hereditary diseases or diathesis will be reduced to a minimum.

CHEMISTRY

It has been recently remarked by Lord Moynihan that perhaps in the relation of Physics and Chemistry to Medicine, we stand on the very threshold. Let us see what advances have been made at this threshold in recent times.

I begin with the recent contributions in therapeutics due to the application of Chemistry. If I were to attempt to enumerate the various compounds that are brought every day to notice of the medical profession in recent times, as hypnotics, anaesthetics, analgesics, antipyretics, antiseptics, or for other therapeutic purposes, then their number will be legion and my task may be impossible. I shall therefore refer briefly to a very few principle therapeutic chemicals of recent times.

How complicated is the mechanism of chemotherapy is shown by the fact that a slight alteration in the constitution of a compound may bring about a complete change in its physiological properties. This is well-exemplified in the preparation of the various amino-quinoline derivatives for antimalarial purposes. A slight change in the constitution of these compounds leads to a complete disappearance of these properties. 6-amino-quinoline and 8-amino-quinoline have no action on paramoecia in strength of 1:4000. The introduction of OH into 8-amino-quinoline and quinoline-8-glycine-amide raises their toxic action on paramoecia to a remarkable degree and the methylation of 6-oxy-8-amino-quinoline by replacement of H of OH by CH₃ reduces its action on paramoecia to nil (Brahmachari and co-workers). Diethylmonosulphone is without hypnotic action, while both dimethylsulphonedimethylmethane and

the isomeric diethylsulphonedimethylmethane (sulphonal) are strongly hypnotic.

Anaesthetics and Hypnotics

Amongst the more interesting synthetic drugs introduced in recent times are those recommended for producing anaesthesia, when given by injection, preliminary to and partly replacing the use of volatile anaesthetics.

Though it may be held that inhalation anaesthesia seems to hold its own which is, to a great extent, due to the development of the gas and oxygen method, yet attempts are being made to introduce, in recent times, other synthetic compounds which may be used for anaesthesia.

The new basal anaesthetics include tribromoethyl alcohol (avertin), urethanes and some of the newer substituted barbituric acids. Most of them are sodium compounds, such as soneryl sodium, amyalsodium, evipan sodium, pernocton, and nembutal. Among the general anaesthetics that have been introduced in recent times may be mentioned evipan sodium, and cyclopropane and di-vinyl ether.

To one coming from Calcutta, the history of anaesthetics has a peculiar interest, because Waldie, who was one of the pioneers of chemical research in India and who lived in Calcutta, was associated with the discovery of the anaesthetic properties of chloroform in 1844. To his memory there is a tablet in the rooms of the Asiatic Society of Bengal. To all of you, the same must also be of great interest because the first Chloroform Commission was held in India.

There is no doubt that general anaesthetics have been conducive to the advance of all branches of Medicine. "The medical sciences, physiology, pharmacology, pathology and bacteriology would have remained inaccurate and incomplete handmaidens of Medicine, had it not been made possible by the aid of anaesthesia to critically examine, corroborate or disprove the claims, hypotheses and tenets of workers of all types." (Standar)

Synthetic chemistry has produced numerous local anaesthetics better than cocaine. A new era has been opened to the operating surgeon. His visitations on the most delicate parts are performed, not only without agonizing screams he has been accustomed to hear, but sometimes with a state of perfect insensibility, and occasionally even with the expression of pleasure on the part of the patient. Who could have imagined that drawing the knife over the delicate skin of the face might produce a sensation of unmixed delight! That the turning and twisting of instruments in the most sensitive bladder might be accompanied by a beautiful dream! (Warren.)

We are steadily approaching the solution of a perfect analgesia for labour.

In recent times, much work has been done in the quest of a suitable hypnotic. The demand for a good hypnotic has grown more and more intense of late, because due to the stress and strain of modern life, many ask for an ideal draught or a tablet or a pill which would quickly put them in possession of "tried nature's sweet restorer, balmy sleep". From the hypnotics of olden times to recent ones, the chemist has travelled a long way, and he is still moving further and further in the search for better hypnotics.

The chief advances in our knowledge of hypnotic drugs in recent times have been

1. the discovery of many new derivatives of the barbituric acid series ;
2. the introduction of a number of drugs other than alkaloids for purposes of basal anaesthesia.

The barbituric acid derivatives are perhaps the most commonly used hypnotics at the present day. Other recent hypnotics not derived from barbituric acid include avertin.

An ideal hypnotic should be free from any toxic effects, should be quickly excreted and should give a quiet natural sleep of normal duration in a short time. Such a hypnotic has yet to come. Further the same hypnotic is not suitable for all types of cases and sometimes methods other than hypnotics are suitable for individual persons for relief of sleeplessness.

May I now refer to the hypnotic properties of the extracts from the root of *Rauwolfia Serpentina*. As early as March 1912 the speaker read a note on its alkaloidal principles and therapeutic properties in a meeting of the Asiatic Society of Bengal. The extracts have marked hypnotic properties and are specially indicated in certain forms of insanity. Since the above paper was read, much work has been done on the Chemistry of the drug and many alkaloids have been extracted from the roots. Its hypnotic properties may be due to these alkaloids.

I now pass on to certain aspects of Chemistry in its application to a few protozoal diseases as revealed by recent researches.

Organic Arsenicals

The best known of trivalent organic arsenicals is salvarsan, for which the non-proprietary name arsphenamine is in common use in the British Empire and the United States. The drug is now generally used in the form of one of its two principal derivatives. The first of these is neo-arsphenamine, the second is sulph-arsphenamine. The first pentavalent organic arsenical used in the treatment of trypanosomiasis was atoxyl. An important derivative of atoxyl is tryparamide. It has been found very successful in the treatment of trypanosomiasis. Other new therapeutic organic arsenicals include stovarsol, etharsanol, proparsanol and carbarsone.

Symmetrical Ureas

The first and best known of the symmetrical urea group of trypanocidal drugs is Bayer 205 or germanin. In 1924 Fourneau and collaborators described the production of a symmetrical urea, which is now obtainable in France under the name Fourneau 309 (moranyl) and is identical with Bayer 205.

Quinoline and Acridine Antimalarial Derivatives

Schulemann and his colleagues succeeded in increasing the antimalarial properties of methylene blue by replacing its short side chains by a longer

chain. Investigation subsequently conducted with the quinoline nucleus led to the discovery of beprochin afterwards named plasmochine or plasmoguin. Similar experiments were made later with other heterocyclic nuclei including acridine and this led finally to the discovery of atebirin. These compounds are of great therapeutic value in certain forms of malaria. In Calcutta a number of amino-quinoline compounds are being synthesized under the speaker's direction and their antimalarial properties tested. Some of them have already been reported to have a marked action upon paramecia.

Leishmanocidal Organic Antimonials

One of the most terrible of tropical diseases, so far as certain parts of India are concerned, is Kala-Azar. Antimony, which was once banned to such an extent that the graduates in medicine of the University of Heidelberg had to swear never to use it, has now been found to be its specific. By the introduction of organic antimonials in its treatment, the mortality of this disease has been reduced from 99% to about 1 or 2% in uncomplicated cases. The terrible nature of this disease in its epidemic form when it ravaged Bengal in the Seventies was well described by a contemporary writer as follows—“The devastation of the epidemic has a very sad tale to tell. Countries that once smiled with peace, health and prosperity, have been turned into hotbeds of disease, misery and death. Villages that once rang with the cheerful merry tone of healthful infants, now resound with loud wailings and lamentations. Huts, which offered too little space for their occupants are left without a tenant. The skulls of human beings now strew the fields at every few yard's distance. The fell disease has mocked every human effort, and absorbed in its powerful grasp, day by day and inch by inch, every blessed spot which once used to be prized for its salubrity” (Roy).

It was doubtless a very great advance in the treatment of the disease from massive doses of quinine to tartar emetic which was the first antimony

compound introduced by Rogers into India for the treatment of Kala-Azar. Soon after the introduction of the latter, the speaker conceived the idea of using sodium antimonyl tartrate (Plimmer's salt) and tartar emetic was soon replaced by this compound.

The next step in the treatment of the disease was the introduction by the speaker of the intravenous administration of metallic antimony in a state of fine subdivision, which was attended with remarkable benefit. It was observed that when injected intravenously the particles of antimony are picked up by the same cells in the spleen as those that harbour the parasites of Kala-Azar, that the two contending agents thus come in closest contact with each other in these tissue cells, and that the fight ends most remarkably in the complete destruction of the parasites in the speediest way.

The next further advance in the treatment of Kala-Azar was the introduction of certain organic compounds of antimony and the use of these compounds in Kala-Azar infection has been the subject of the speaker's research for many years, and in 1920 some of them were prepared for the first time in India in the Calcutta Campbell Hospital.

Early in 1921, the speaker discovered an urea antimony compound for the treatment of Kala-Azar. Its introduction and his other researches on antimonial compounds opened up a new vista in the treatment of the disease in India by means of therapeutic organic antimonials, just as the discovery of salvarsan led to the introduction of organic arsenicals in the treatment of spirochaetal diseases. This urea compound was named “urea stibamine”.

I shall not detain you here with the romance of urea stibamine, however interesting it may be. But I recall with joy the memorable night in the Calcutta Campbell Hospital at Sealdah when after a very hard day's work at about 10 P.M. in a little room with a smoky dimly burning kerosine lamp, the speaker found that the experiments in the

preparation of this compound were up to his expectation. The room still remains, but the signs of a laboratory in it have completely disappeared.

The first series of cases treated with this compound were published early in 1922. Soon after this, most remarkable results were obtained with it by Shortt in Shillong to whom the compound was sent for trial. The value of this compound was quickly recognized. It was introduced, soon after a preliminary experimental trial, by the Government of Assam for the treatment and prophylaxis of Kala-Azar.

Today urea stibamine stands pre-eminent in the treatment of Kala-Azar in India and as a powerful prophylactic against the disease, and it is a matter of supreme satisfaction that this treatment has been the means of saving the lives of a vast population of suffering humanity.

The following remarks from the Annual Public Health Report of the Province of Assam for the year 1933 dated 23rd July, 1934, are worth quoting "It has to be borne in mind that, when no specific remedy was known for this disease, that 98 persons at least out of every 100 were doomed to certain death within a comparatively short space of time. Since 1923, when reliable figures for the disease first became available to the end of the year under report, no less than 328,591 persons have been brought under treatment. It is no exaggeration to say that approximately 3.25 lacs of valuable lives have been saved to the Province".

Further advances have still to be made in the treatment of infections with leishmania donovani, as there are antimony resistant cases, though fortunately few, and the treatment of that ugly skin infection which was first described by the speaker as a post-Kala-Azar condition and known as dermal leishmanoid is frequently unsatisfactory. Cases of this condition may be a menace to a community, as a possible reservoir of the parasite of Kala-Azar.

Chemical Structure and Physiological Properties

Dealing with the relationship between chemical

structure and physiological properties one meets with a remarkable series of compounds in recent times having a common nucleus but possessing varied physiological properties. I mean the compounds having the condensed benzene ring system or phenanthrene, as well as, the reduced phenanthrene plus a fourth five-membered carbon ring or cholane. The cholane nucleus is found in bile acids, cholesterol and other sterols.

A structure of the cholane type is also found in the sex hormones which are responsible for the secondary sex characters of animals. These hormones are oestron, luteosterone and the male testicular hormone or androsterone. They have close structural relationships with each other and with bile acids and cholesterol which probably contain their biological precursors.

The male sex hormone or androsterone has been artificially prepared. Friedmann has pointed out that the aromatic ring, corresponding to ring A of oestrin is not necessary for the development of the oestrogenic effect as the benzene nucleus can be replaced by the furane ring, fural-pyruvic acid being even more active than benzal-pyruvic acid. Recent experiments suggest the possibility of getting oestrogenic activity in ring-free compounds by arranging the carbon atoms 13, 14, 8, 9 of oestrin in a suitable way.

Synthetic hydrocarbons containing the phenanthrene nucleus, such as dibenzanthracene, are found to possess carcinogenic properties. The cancer-producing action of certain tars is due to the presence of a hydrocarbon allied to dibenzanthracene. It has been synthesized and the powerful carcinogenic action of the pure substance has been confirmed. It is perhaps, the most potent carcinogenic substance so far discovered.

The aglucones, that is, the non-sugar parts of digitoxin, strophanthin and several other closely related substances are allied to the sterols as they embody structures of four carbon rings. Bufotoxin has a constitution closely allied to those of the

cardiac aglucones and possesses a characteristic action on the heart similar to that of digitalis preparations. The phenanthrene nucleus is present in some of the most powerful alkaloids, such as morphine and codeine of the opium group, and the corydalis alkaloids and in colchicine.

All hormones of the secondary types contain benzene rings. In some cases the ring is a simple one as in thyroxin, pituitrin and adrenalin. In others it is a complicated one, the condensed phenanthrene ring. The Needhams and Waddington have observed the most remarkable phenomena that the chemical organizer or, as they call it, the evocator which determines certain developments of the embryo, belongs to the same group.

Chemistry of Vitamins and Hormones

X-ray work on vitamin B₁, B₄ and C has been carried out in recent times and the structural formula of C as *l*-ascorbic acid has been established by a close collaboration of crystal analysis with the ordinary chemical methods.

The structure of carotene and vitamin A has also been established by X-ray analysis, as consisting of *cis*-polyene chain which is presumably the chain of polymerized rubber.

Vitamin B₁ possesses two ring systems, one glyoxaline or pyrimidine and the other a pyrrole containing a substituted sulphur. It is not allied to flavins. Vitamin B₁ possesses antiberiberi properties. The crystalline specimens of Jansen and Donath are according to most recent observations, the pure vitamin itself with the admixture only of a small and variable amount of inactivated vitamin.

Vitamin B₂ is a complex, containing flavin and another factor, the absence of the latter and not of flavin being considered responsible for the symptoms of pellagra in rats. The flavin factor exerts a growth-promoting action. A substance identical with lacto-falvin of milk which is allied to vitamin B₂ has been isolated and synthesized.

Examining the oxidation—reduction properties of flavin-cleavage products, Kuhn and Moruzzi were able to sum up the relationship of the flavin group by saying that the parent substance was a reductant; that combined with a ring system which contains a substituted amino group it produced a colour; that the addition of a carbohydrate side chain yielded a vitamin; and that the further addition of a protein group resulted in an enzyme (the yellow respiration ferment of Warburg).

Vitamin C is closely related to simpler carbohydrates and sugars. It is a keto-hexonic lactone.

Vitamin D can be artificially prepared from irradiation by ultraviolet rays. It has been isolated from irradiated ergosterol in a crystalline and apparently pure form, the crystalline compound being known as calciferol. The production of vitamin D by the irradiation of the sterols of the skin by ultraviolet rays of the sun is a most interesting chapter in the history of Medicine, reconciling, as it does, the dispute whether rickets is due to a deficiency in the diet or want of proper sunlight.

Rapid progress is being made today in the isolation of hormones in a chemically pure condition. The hormone thyroxine, the active principle of thyroid gland, the iodine-containing amino acid has been synthesized by Harington and his collaborator Barger from tyrosine from which it is probably formed in the animal body. Kendall of the Mayo Research Institute has succeeded in preparing what appears to be the hormone of the suprarenal cortex, which may be beneficial in the treatment of Addison's disease. Ephedrine and pseudo-ephedrine are alkaloids isolated from species of ephedra and are chemically allied to adrenalin. Physiologically ephedrine and adrenalin behave similarly in many respects. Epinine, a synthetic compound, possesses, in a marked degree, the pharmacological action of adrenalin.

The Specific Carbohydrates

The discovery of type specific carbohydrates is

among the most remarkable triumphs of Chemistry in recent times. It has been observed that a derivative of gun arabic possesses properties resembling those of the specific polysaccharides of one of the types of pneumococcus serum. The value of polysaccharides possessing immunological functions, and the knowledge of their composition, properties and structure must be of great value in medicine. The polysaccharides of the cholera bacilli and of *B. dysenteriae* (Shiga) have been investigated.

Isotopes and Heavy Water in Relation of Life

Vernadsky has put forward a hypothesis that the living organisms possess a selective power between isotopes of an element. Among the plants, Loring and Bruce have shown that in the potassium of potatoes isotope of atomic weight 41 predominates while in ordinary potassium the chief isotope is of atomic weight 39. In the case of man the future may reveal that isotopes of elements play an important part in the maintenance of health and that they may vary in disease.

Barnes has suggested that the polymerized molecules of water are of primary importance in physiological processes. The discovery of the hydrogen isotope (deuterium) of mass 2 and the isolation of quantities of "heavy water", containing this isotope have opened a new field in the physiology of water. Gortner considers that the water in the Medusa is as much "alive" as are the proteins, the fats, the lipids, or the carbohydrates. The water relations and different molecular forms of water in the living organism lie at the foundation of problems concerning both health and disease. It has been held by him and others that in lyophilic hydrosols and hydrogels the water may exist in two states, i.e., in the state of free water which is characteristic of water in bulk and in the state of bound water which is characteristic of the lyophilic system, and that the equilibrium between free and bound water is undoubtedly of major importance in vital phenomena. Two hypotheses have been

presented as to the possible nature of bound water.

1. An oriented adsorption of the water dipoles at the interface, and
2. an oriented adsorption of hydrogen and hydroxyl ions.

The effects of the substitution of the deuterium form of hydrogen in place of ordinary hydrogen and of the isotopes of other elements into organic molecules may have in the future an important application in Biochemistry and Medicine.

I have referred only to a very few achievements in Medicine due to the application of Chemistry in recent times. The advance has been so very great that even in snake venom has been found a therapeutic application for the relief of the terrible pain of inoperable cancer or as a systematic hæmostatic in uncontrollable hæmorrhage. The sex hormones are having therapeutic applications, and the pregnant mare's urine has been found useful in pituitary cachexia with disturbance of circulatory regulation and on the metabolism of carbohydrate and fat. Ovarian extracts have been used in the treatment of hemophilia.

The relation between chemical constitution of compounds and their varied physiological and therapeutic properties, though at present consisting mostly of jumble of empirical facts may one day lead to generalization of vast importance. Therapeutics is moving today from merely qualitative to quantitative foundations. Some of you may live to see that remarkable results may be attained by Chemistry in the treatment of disease like tuberculosis or cancer for which chemical therapeutics has at present day only a limited application in gold or selenium and lead respectively. It may be mentioned in passing the interesting results obtained in Berlin by Fischer on cancerous rats. By keeping these animals in pure oxygen, under a pressure of 1.5 kg. per sq. cm. for 24 hours, he observed that the tumour exploded literally outside of the body, tearing the skin, and

was finally eliminated as sloughing tissue. Crystalline insulin free from impurities is now available. Mandelic acid, phenyl hydroxy-acetic acid and its sodium salt are very recently coming into use in the treatment of *B. coli* infection of the urinary tract, the principle of treatment being based on the fact that a ketogenic diet leads to the production of β -hydroxybutyric acid which is the effective agent in the urine of patients treated with a ketogenic diet and which is allied to mandelic acid. Newer treatment of epilepsy, of myasthenia gravis and of agranulocytic angina are coming in the field due to the triumphs of Chemistry. You may see the synthesis of other newer vitamins and internal secretions as well as extracts from different organs of the body synthesized or isolated in a pure state and used in medicine for the treatment of disease. We look forward to the day when endocrine preparations will be available for oral administration and the dread of the needle averted.

PHYSICS

I now pass on to the contribution of Physics to Medical Science. Its application is partly for the purpose of diagnosis of diseases and partly for their treatment. Further, Physics is slowly evolving conception of living matter by X-ray analysis, by improved methods of microscopy and by the advancing knowledge of the constitution of matter.

It is not my intention to give here an account of the various apparatus that Physics has made available for the diagnosis and treatment of disease as such an attempt will be merely cataloguing. I shall only refer here to some of them that have been of striking value in Medicine or that may prove useful in the study of the structure of organic matter.

The Electro-cardiograph

The Electro-cardiograph is a valuable apparatus for studying certain diseases of the heart. A portable apparatus which can be taken to the patient's house

and which is constructed on the principle of the string galvanometer is now available. Another portable Electro-cardiograph based on the principle of the valve amplifier is also available. By means of a special Electro-cardiograph outfit, simultaneous records of a heart may be obtained in the wards of a hospital for purposes of research showing (1) heart sounds, (2) electro-cardiogram, and (3) carotid pulse by means of Hill's wire sphygmograph. An apparatus consisting of a Stethograph combined with an Electro-cardiograph may prove a valuable aid in cardiology.

The Electro-cardiograph has shown that tracings taken of patients dying of various maladies can demonstrate that for some time after clinical death some cardiac activity could be registered the duration varying from six to twenty minutes. These observations show that in cases in which there is cardiac standstill during anesthesia or in the newborn, resuscitation may be effected by timely cardiac injection or needle puncture. There may be other conditions that may be discovered in future in which the same may be possible.

It may just be mentioned here that a convenient new method of assay of vitamin B₁, based on electro-cardiographic measurements, has been recently described.

An Electro-encephalograph of the Future

One of the most recent advances in Biophysics is the discovery of some electrical phenomena in the human brain, which were originally studied by Berger and subsequently by Adrian and Matthews, the latter observers using the Matthews' Oscillograph constructed on the principle of a valve amplifier. The electrical changes consist of a rhythmic oscillation of potential with a frequency of about 10 per second appearing when the person experimented upon lies quietly with eyes closed and dis-appearing when his attention is fully occupied. Non-visual activities which demand the entire attention, e.g., mental arithmetic, as well as

sensory stimuli demanding the same, abolish the waves.

Berger considers that this "Berger rhythm" represents the normal activity of every part of the cortex of the brain while the experiments of Adrian and Matthews point to the conclusion that they arise from the activity of cortical cells in some parts of the optical lobe connected with vision.

I consider that future researches in this line may be as important in studying, as pointed out by Hopkins, the functions of the brain as the electrical changes in the heart are in studying cardiac diseases. An electro-encephalograph may then be a valuable apparatus in Medicine and may be useful for the study of the diseases of the central nervous system or of the mind, such as, anxiety neurosis or psychosis as the Electro-cardiograph has been in studying the diseases of the heart. Further work in this direction in the hands of Adrain and his co-workers is awaited with keen interest.

Ultraviolet Ultra-microscopy

One of the latest developments in microscopy is the use of ultraviolet light with dark ground illumination.

Barnard's technique and apparatus have made photography with ultraviolet light as certain and reliable as ordinary photomicrography. His microscope has already revealed the structure of some of the viruses and inclusion bodies. We are beginning to learn that there is no clear line of demarcation between the ultra-microscopic viruses and the visible bacteria. I hope that further advances in ultra-microscopy with shorter waves, aided with improved methods of fine adjustment and electrical equipment for producing the spark source, will in future reveal the nature of the bacteriophage, and that of the smaller viruses which is not possible at the present-day without the aid of biological tests. Differential centrifugalization, graded ultra-filtration, the recently developed methods of electron diffraction and micro-dissection may be helpful in this direction.

Thanks to the recent advances in the ultra-microscope the nature of the filterable viruses as a biological problem has assumed a new aspect in recent days. The view that viruses are small micro-organisms similar to ordinary bacteria is being daily confirmed. There is reason to believe that the size of the smallest virus which behaves like living organisms approaches that of the largest organic molecule. Until recently little evidence was available to suggest the existence of what may be termed saprophytic viruses except that of River and Tillett who demonstrated in 1923 the presence in the testicles of rabbits of a virus that is not normally pathogenic. Barnard has however demonstrated by means of refined examination of the deposits, which sometimes occur in medium containing horse or rabbit serum, the presence of minute bodies, which in size, shape as well as general optical properties are in no way different from undoubted pathogenic viruses. These bodies increase in number and are seen to be in process of fission. They have been cultivated to the fourth sub-culture. This demonstrates the existence of viruses which are saprophytic in habit, and tends more and more to lend support to the theory that viruses are living organisms. The recent announcement made by Stanley of the Rockefeller institute however complicates our conception of viruses. He has reported the separation, from the juice of Turkish tobacco plants infected with the mosaic disease, of a crystalline protein that has the properties similar to tobacco-mosaic virus. It is too early to speculate on the eventual significance of this fundamental contribution, with regard to its relation to virus diseases in animals or to other virus infections of plants.

There is experimental evidence in recent times that the casual agent of acute rheumatism is probably a virus.

It is not my intention to continue further remarks on ultraviolet ultra-microscopy but I can foresee that aided by X-ray analysis it will reveal in future more and more new facts about the viruses and the

bacteriophage than what is known in the present-day and that the doubt very recently expressed by some observers whether the viruses will ever be seen will cease. The association of viruses with the specific micro-organisms in bacterial diseases may in future be found to be more common than is imagined at the present-day.

Infrared Photography

Photomicrography with infrared light makes it possible to investigate, with transmitted light, many objects which are black or very dark brown in colour, and which consequently absorb very strongly both white light and for the most part also ultraviolet light. The infra-red rays enable one to photograph the veins of the skin or the diseased condition of its deeper layers or of the iris under an opaque cornea.

The Micropolychromar—Optical Staining of Colourless Objects

In studying under the microscope colourless objects, medical, zoological or botanical, we meet with difficulties, because as a rule they exhibit little optical contrast and are barely visible. The usual procedure of chemically staining such objects is tedious and kills them unless they are stained with vital stains. The micropolychromar opens up a new avenue for scientific investigation of such colourless objects. It provides a means of "staining" them not chemically but optically. This optical staining has the effect of showing up the object brightly illuminated in one colour on a differently coloured background. The objects are not merely differentiated from the background by virtue of their relative brightness but even when the background is as bright as the object, the object and background appear in contrasting colours. By means of this optical contrast staining, the fine structures are revealed with remarkable distinctness, the apparatus combining in one image the advantages of both dark field and bright field illumination. The value of such an apparatus in studying the structures of living cells and tissues particularly chromosome structure may be great.

Ultropak

One of the recent advances in microscopy is due, to a great extent, to changes which have taken place in methods of producing the appropriate type of illumination. Of special importance is the arrangement for polarized light recently evolved for the Ultropak. This arrangement eliminates completely the glare and haze which arises from direct reflection, so that the inner structure of the object may be observed in every detail and with a remarkable degree of distinctness, the image of the object may be observed in every detail and with a remarkable degree of distinctness, the image of the object being formed only from diffused depolarized light reflected from its structure. It is a useful aid for the up-to-date worker engaged in microscopical research in general Biology, Zoology, Parasitology and in Experimental Medicine, in which the observation of living organisms under high microscopic magnification is involved.

X-ray Crystal Analysis—Its Aid to Organic and Biochemistry

But evidently the microscope has its limitations. Sir William Bragg's application of X-rays has led to the discovery of the proper structure of matter which is beyond the limits of the microscope. Until quite recently, the majority of the tissues, such as the hair and skin, were believed to be non-crystalline, but recent investigations by means of X-rays and Crystal Physics have shown this belief to be incorrect and it has even been held that entirely non-crystalline materials are very difficult if not impossible to find. Minute regularities which are beyond the range of the microscope can now be detected by means of the X-rays.

Speaking of the crystal structure, of the solid state, as revealed by X-rays, Sir William Bragg has stated that all the investigations of the solid bodies of every form aim at finding out the connection between their properties on the one hand and composition and architecture on the other. While some of these properties are directly dependent on

the atoms of the unit cell in the crystal, there are others which depend on atomic relations which are not fully developed within the cell. The action of the atomic forces in groups of hundreds or thousands or tens of thousands of atoms must be considered before we can understand these other properties of the solid state. It is within a region of dimension covering groups like these and somewhere in the scale of sizes there perhaps enters, as Sir William Bragg says, the breath of life to control these atomic compositions which enter into living organism. It has been stated that "in structures produced by organisms, forces are active in their formation which are not present in solutions when ordinary crystals are deposited. The presence of these additional forces in living protoplasm prevents a clean-cut regularity in arrangement of the molecules; that is, it introduces irregular arrangement of the molecules, or a degree of amorphousness. If this is the case, then the determination of the space group for a given organized substance will have little value" (Sponser). But it is possible that further improvements in X-rays analysis may prove one day useful in considering the activities which occur in the protoplasmic matrix of organisms, and of structures which are produced through vital process. They may enable us to look into the mysterious protein molecule without destroying it and to discover whether diminution of the above-mentioned forces in any tissue in disease or their cessation in death may be accompanied by a change of the amorphousness of the aggregates of the molecules to some more or less characteristic crystallite or crystalline state.

X-ray method of analysis may be applied one day in the study of the cancer cell and it is hoped that its application may increase our knowledge of cell construction and cell growth, which helped by our future knowledge of the colloidal state in living cells may one day strengthen our power in combating the dreadful scourge of malignant disease. The changes that take place in the tissues in cancer and other

pathogenic conditions have been studied by this method By Clark and co-workers.

The animal fibres are built of stringy protein molecules, which are made of strings of groups of atoms. The length of these groups which are marked by joints at regular distances is always the same but their breadth varies and therefore a protein chain is more irregular than a cellulose chain. The protein chains can be made up in many different ways. The difference between species of animals may be due to changes in the order of the groups in protein chains contained in their body. If due to an accident or disease the order of the groups in a protein chain in the dividing chromosomes of a fertilized ovum was upset, the basic pattern for part of the tissues of the embryo would be changed, and as the tissues would subsequently grow according to the new pattern, the final structure would have a new pattern and different properties. The shuffling of the order of the unit group of protein chains may be a fundamental agency in the process of evolution, normal or abnormal. It is difficult to determine the order of the unit groups in a protein chain by the methods of Organic Chemistry. But X-ray analysis may make the problem easier in future. A comparative study of the order of these groups in the proteins of animals is now becoming possible and may one day enable one to investigate the internal structure of the organs more minutely than what is possible at the present day. There is no doubt that X-ray analysis has opened up a new way for the study of living matter.

Electron diffraction gives information similar to that given by X-rays but with the important difference that a much smaller thickness of material is effective in producing the diffraction pattern. Layers with a thickness of about 10^{-6} cm containing ten molecular layers or thereabouts have been used and the effective thickness can be made smaller still by using slow-speed electrons. Another modern branch of Physics is being developed which may be of practical application in Crystal Physics, namely the technique of molecular rays. These

have up to the present been used chiefly for studying the properties of atoms or molecules of substances which can be obtained in the vaporized state, such as the metals, the common gases, a few inorganic salts, and some organic liquids. Such a technique or that of electron diffraction may one day find application in medical as well as in textile research. The processes of absorption of drugs and dyes in the treatment of disease as also of antibodies as well as many other facts in immunity might in future be studied by these techniques.

Spectrograph

In recent years a new field has been opened up by the spectrograph in the domain of chemical analysis, both qualitative and quantitative. It has now become possible to apply spectrum analysis to biological problems, among which are to be counted all the questions arising in theoretical and practical medicine regarding the metabolism of the heavy metals and its significance for the organism, whether healthy or diseased or the treatment of disease by the administration of heavy metals (Gerlach and Gerlach).

Until recently the only metallic elements considered as playing an important part in animal and vegetable life were sodium, calcium, phosphorus and iron and, to a less degree, potassium and magnesium and to these may be added silicon. The powerful influence sometimes exerted on life by very small quantities of elements, such as, copper, arsenic, mercury, iodine and boron, etc., as revealed by recent knowledge has led to an increasing need for improved and accurate methods of analysis for detecting and estimating minute quantities of elements. Results obtained by the flame method of spectrographic analysis are applicable for the purpose.

As an example of the application of the spectrograph to medicine, 0.1 c.c. of blood may be taken from a patient suffering from severe anæmia every 10 or 12 days to study the effect of treatment.

The blood is rolled up in small places of ashless filter paper and spectrographed on a plate and thereby changes in the various constituents of the blood, such as potassium, magnesium, calcium, iron and copper may be readily followed.

It has been shown by this method that human hair and finger nails contain minute quantities of copper and silver, varying in quantities with the age of the people. By its means the routine determination of the vitamins may be studied. The study of absorption spectrum bands given by the different vitamins has helped in the work for the determination of the chemical nature, the concentration and assay of vitamins. Similar methods of hæmoglobinometry are now available. Spectrum analysis has become of great importance in pathological as well as forensic medicine for detecting traces of metals in human organs. It has been recently employed for studying the nature and the constitution of the amino acids of the protein molecule as well as for their quantitative analysis.

Ultracentrifuge

Studies on the size and structure of the molecules of proteins, as well as upon the molecular weights of certain enzymes, carried out with the aid of Svedberg's ultracentrifuge, constitute a new and promising application of Physics to medical research and valuable work has been done with it in connection with blood pigments and serum proteins. It may be helpful in the study of immunology and the physical chemistry blood.

Ophthalmo-eikonometer

The Ophthalmo-eikonometer has been developed for measuring the size and shape of ocular images and has opened up a new field in Ophthalmology, Psychology, and Neurology. It consists of the study of image size variation in binocular vision.

A technique has been developed, "by means of which the brains of mammals can be stimulated at accurately defined points and a correlation

established between the locus of stimulus and physiological function". Interesting possibilities lie in the determination of the influence of certain part of the brain over some of the organs of internal secretion and over the function of the gastro-intestinal tract, the kidneys, etc.

A method has been recently evolved which permits observation of the form and behaviour of living cells providing a valuable means for studying nervous control of the circulation and the nature of nerve destruction and regeneration.

Micro-manipulator and Micro-dissection

Operative work on the living cells has long been the aim of investigators in cytology and in experimental embryology. By micro-dissection and injection the physical structure of protoplasm has been determined by Chambers and others. Until recently the results obtained by the micro-dissection method related to the viscosity, the differentiation of cortex and interior, the nature of the surface film, the nature of chromatic and achromatic structures in dividing nuclei, internal and surface changes influencing cell division, protoplasmic changes accompanying fertilization, and the effect on the protoplasm of the injection of certain substances.

One of the most important applications of micro-injection methods for the study of cell physiology is the role of electrolytes in the maintenance of protoplasmic structure and function. K and Na are far more toxic when applied externally than when injected, the order of toxicity for the immersion experiments being K, Na, Ca, Mg. CaCl_2 is considered to have the most marked toxic effect on the internal protoplasm MgCl_2 is considerably more toxic to it than either KCl or NaCl. From the above and similar experiments, it is presumed that the maintenance of the colloidal state of living protoplasm depends upon the presence of definitely proportional amounts of different electrolytes. The relative amount of different types of salt present must be in such proportions that the solidifying action of the one is balanced by the dispersive

action of the other, K is said to be a labiliser while Ca is a stabilizer. Ca is essential for the formation and maintenance of the protoplasmic membrane.

The determination of the hydrogen ion concentration of protoplasm has been considerably developed in recent years by micrurgical technique. Both colorimetric and potentiometric methods are possible for the determination of the pH of protoplasm by the use of micro-electrodes. By means of this technique it is found that the living protoplasm of widely different types of cells has, under normal conditions, a remarkably constant pH value. The technique has also rendered possible the study of the oxidation—reduction potential of protoplasm.

The recent investigations in micro-dissection of human polymorphonuclear neutrophiles show no marked divergence from Chamber's excellent description of the physical structure of cells in general. It would seem, however, that the cell membrane, in this case, is more rarely a naked surface film than he ascribes to most cells. The cytoplasm is more liquid than that of the monocyte and clasmatocyte.

Observation by micro-injection method on plant nuclei show evidence of an elementary structure together with a fluid sap in the resting nucleus and supports the view that, in plant cell at least, a persistent framework exists which might account for the genetic continuity of the chromosomes.

Radiology

X-ray diagnosis has improved in the present day to an almost spectacular extent; and radiation therapy has now established its claim to an important place in the treatment of malignant disease.

One of the recent advances in diagnostic radiology is undoubtedly the introduction of cholecystography by Graham and Cole. The radiologist can now visualize the biliary tract and the gall-bladder by means of tetraiodophenolphthalein; by the injection of air he can outline

organs in the abdominal cavity and the sinuses of the brain. By the use of organic compounds of iodine he can make visible the lungs, the air passages, the interior of the uterus, the spinal canal, the pelvis of the kidney and the urinary tract, and, by the use of a radioactive substance called thorotrast, the tissue of the reticulo-endothelial system including the spleen and the liver. Cerebral angiograms may also be taken by means of this substance for the purpose of localizing brain tumours. Modern fluorescent screen enables digestive movements, heart beats or lung movements to be watched or cinematographed. Placenta prævia has also been brought within the possibilities of radiological diagnosis.

Perthes has found that the intensity of radiation falling upon a surface perpendicularly is inversely proportional to the square of the distance of the surface from the focal point of the target of the tube. The cumulative effects of Roentgen rays were also studied by him, as also the fact that harder X-rays produce a longer *latent period*. He observed that X-rays as ordinarily used are composed of mixed rays and filters were first introduced by him to cut off softer rays.

By the standardization of physical and biological doses and the proper intervention of filters the dangers of radiation therapy have been greatly reduced in recent times. Today with the improved technique and modern equipment we can safely work with rays of much higher intensity than before without the slightest danger to man, mind and machine.

X-ray and radium therapy is bidding fair to displace the knife in the treatment of certain forms of cancer. The response of tumours to radiation demands wide study, each type of tumour having a different response, both clinically and histologically. By contrasting the sensitivity of growth with that of skin—in both cases using the minimum lethal dose as the standard—it has been possible to place tumours in different groups—radio-sensitive tumours, epitheliomata, adenocarcinomata and radio-resistant tumours.

Views on radiation treatment have changed today and the single massive dose of X-radiation, advocated in former days, is now replaced by a series of smaller doses spread over a period of time. The real problem of malignant disease lies in the treatment of glandular metastases. For deeper lesions and gland areas we turn either to

1. X-rays which, excited by very high and ever-increasing voltages, tend to approach γ -rays in quality, or to

2. large quantities of radium placed at distances remote from the skin with the object of obtaining the large depth doses possible with X-rays.

The growing belief in the efficacy of "telerradium" is indicated by the rapidly increasing number of large radium units being set up in the world. It is to be hoped that with advances in the technique to telerradium and deep X-rays, better results may be obtained in future in the treatment of cancer.

With improvement in apparatus and technique it has now been possible to distinguish radiologically the softer tissues of the body from each other and the extent of invasion of new growths in them.

Though the explanation of chemical, physiological and morphological changes in normal and pathological tissues on irradiation is very scanty in the present state of our knowledge, yet there is a promising beginning as will be seen in recent developments on the subject, especially in great laboratories in America, such as, the Mayo Clinic, Rockefeller Institute and the foremost medical schools. Special radiosensitiveness of cells has received emphasis in the hands of Desjardins and others.

I may just say a word about the application of X-rays to genetics. The origin of the new genes by mutation has been shown to be speeded up at least two hundred times by X-rays.

Radium and Artificial Radioactivity

Lawrence of the University of California has

succeeded in producing a radioactive form of sodium from common salt, having remarkable properties. This will enable sodium to be introduced safely into the animal system, and is likely to be of great value in medicine, He has announced that it would soon be possible to produce cheap radium for commercial purpose and it has been claimed that the discovery of artificial radioactivity in elements, otherwise inactive, will be of greater importance in medicine than the discovery of natural radioactivity. Proto-actinium may have valuable therapeutic properties. The new artificially produced radioactive elements may before long replace the costly radium for therapeutic purposes and for the study of many biological processes.

Light Therapy and Electro-therapy

I have already mentioned the uses of the ultraviolet and infrared rays photography as an aid to Medicine. They have also had therapeutic applications in modern times. It is generally considered by many authoritative observers that ultraviolet and infrared rays modify each others' effects on the living organism, according to their several proportions in combined relations.

Short-wave and ultra-short wave therapy is one of the latest branches of physical therapy. It is not my intention to give an account of the various branches of electro-magnetic wave therapy. I shall only very briefly refer to short-wave and ultra-short wave therapy.

The better results claimed for the very powerful short-wave instruments may be partly explained by the greater capacity effects obtained in the tissue as the wave-length decreases.

It has been inferred that the more delicate the structure, either of cells or micro-organisms, the greater would be the disruptive action of short-and ultra-short electromagnetic vibrations.

Though some observers hold that there is very slight or even total absence of appreciation of heat during the administration of a short-wave treatment

which may be followed by most satisfactory results, yet many attribute the whole action of ultra-short waves to the heat action. They state that experiments which have been carried out *in vivo* and *in vitro* show that they have no specific action on bacteria or tissue-cells and they have observed that bacteria soaked on to a piece of gauze, placed under the skin of animals and exposed to ultra-short waves and undamaged with lethal dose of ultra-short waves, and there is no change in fragility, sedimentation rate, and bactericidal power of the blood following exposure *in vitro*. They conclude that the action of ultra-short waves appears to be coagulative necrosis and extreme vaso-dilatation, which is similar to the action of diathermy high-frequency current of about 300 metres.

Whatever may be the exact mechanism by which short-wave or ultra-short waves show their therapeutic effects, there is no doubt that the advent of short-wave therapy opens up a field of treatment of great possibilities hitherto totally unexplored. It has been held by some that the outstanding difference between long-wave diathermy and short-wave therapy is the peculiar effectiveness of the ultra-short wave in infections and in conditions of suppuration, where diathermy is definitely dangerous, that this quality belongs only to the ultra-short waves of from 6 to 3 meters and that between 15 and 30 meters there is only heat effect.

I shall not detain you by discussing the principles of diathermy or the various forms of light therapy as they are beyond the limits of my thesis. It may be said in brief that the rays of different wavelengths and frequencies have come into modern practice for the treatment of many diseases with excellent results.

I hope that advances in photo-dynamic sensitization may in future lead to the discovery of therapeutic substances which will be activated by the short infra-red, luminous, red, and orange rays and act as sensitizers in the presence of blood-serum.

When we survey the immense development in the use of light waves, visible, ultraviolet, X-rays, and others in the investigation of structures and the treatment of disease, with their future potentialities, it may be said without conceit—truly we are beginning to see through a glass less darkly.

Bragg-Paul Pulsator—Artificial Respiration

Among the many useful apparatus which Physics has placed at the disposal of Medicine in recent times for therapeutic purposes, I would like to mention here as an example, one devised for prolonged artificial respiration. There has been of late an increased scientific interest in artificial respiration methods. The one mentioned here has been designed by Bragg and Paul and is known as Bragg-Paul Pulsator. It shows the triumph of a artificial apparatus in maintaining one of the most vital functions of the body, i.e., respiration, which it is unable to perform due to a physical disability. There are some conditions, arising both from accident and disease, in which long-continued and regular artificial respiration is required. Bragg-Paul Pulsator consists of a pulsator which rhythmically inflates an air-bag encircling the bony thorax of the patient below the armpits to a definite air pressure as indicated by a manometer. Although the lengthy need of an artificial respiration apparatus is rare, still it must prove very satisfactory in cases where its use is indicated. In one case a patient had artificial respiration on this principle for over two years with satisfactory results.

GEOLOGY

The Geologist has discovered numerous spas and springs which refresh and renovate the human system today. The schemes of drainage and irrigation, and of water supply in general, that are bound up fundamentally with the health of mankind, the public health departments of civilized countries all the world over, look forward to the aid of the geologist. It is perhaps known to you that in one section of a town in an English county, the effects

of calcium deficiency among most of the children were traced by the geologist to the poor-in-calcium drinking water of the clay zone area of the town. In the investigation of silicosis, a disease prevalent chiefly among miners, we find the physician working hand in hand with the geologist who has been charged with the identification of the minute particles of mineral matter that find their way into the lungs of the miner. The application of the geologist's methods has led to the detection of china clay and talc in adulterated food products. In the investigations of the dust problems in big cities, the aid of the geologist is indicated. Endemic goiter has been traced to iodine deficiency in drinking water. Excess of iron may give rise to an endemic disease, the "so-called mottled enamel" in man and some animals in certain places, such as Algiers, Tunis and others.

PSYCHOLOGY

Mental disease, before the advent of Psychology in Medicine, was a *terra incognita*. Recent researches in psychology have thrown a flood of light on the domain of Psychiatry. The significance of a mental approach to the problems of psychology had long been misunderstood, but today not only we have a better understanding of mental diseases by means of the psychological method but also we get extremely encouraging results in the treatment of such disorders and psycho-therapeutics has found a place in the armamentarium of the medical men.

I do not know whether one would agree that the services of Freud to knowledge have been as great as those of Darwin, and whether Freud's extension of the idea of sex will stand the test of time, but there is no doubt that one of the greatest contributions to medical psychology in recent times is the concept of the dynamic unconscious. To trace the genesis of mental disorders one has to dive deep into unconscious region of the mind. That the mind has an unconscious component was not at first accepted by physicians trained in the orthodox school.

Awareness is not an essential characteristic of mental process. Significant changes may go on in the mind without our being conscious of them. It is in this unconscious region that the roots of mental disorder lie.

It has been recognized that the explanation of many fully conscious occurrences—which had previously been left unexplained as simply coming “out of the blue”—might be found in this dimmer region. It was from this region of the mind Lady Macbeth uttered “Here is the smell of the blood still; all the perfumes of Arabia will not sweeten this little hand”.

Attention has now been concentrated upon what might be described as the border region between the psychical and the physical. In fact, some of the psychologists—the behaviourists—might be said to have gone over the border-line altogether and merged the psychical in the physical, but those medical men who have come back again to their own special domain via psychology of this kind, have been disposed to view the physical from the psychological point of view. Today a firm alliance has been concluded between Medicine and Psychology, and medical men have more and more fully recognized the necessity of studying the mental history of their patients. Much work has been done in the study of the unconscious in many institutions., notably, the Nancy School. The aftermath of the great war was seen in many cases of nervous debility which are treated in famous clinics e.g. of Hadfield and others. The power of the instincts and the inhibition of the latent forces, of their release, as well as the phenomena of fatigue, have been thoroughly studied to the great advantage of medical practice and efficiency. Modern psychologist and medical men are paying more and more attention to the aspect of psychological investigation of the bodymind known as sublimation of instincts and emotions. Many medical men at the present-day devote themselves as specialists to the practice of psychotherapy.

It may be that the theories of genetic inheritance perhaps apply partially at least to mental characters. It is important, as Dawson has stated, that the latter should be distinguished and the manner of their inheritance traced out. Much work is being done in recent times for diagnosing and measuring unitary mental traits with the view of satisfactorily studying the genetic basis of mental traits. In this respect the cooperation of the medical man, the psychologist and others is imperative.

To some psychologists there is nothing more noticeable in recent years than the *rapprochement* between Medicine and Psychology due to a fundamental cause. They hold that partly this fundamental cause is that the ultimate character of reality is mental, and that the days of scientific materialism are gone which ruled over advancing thought in the last quarter of the nineteenth century, under the leadership of Huxley, Spencer and those who thought with them. The attempts to explain all phenomena in terms of matter, which were in vogue half a century ago, have been considered to be unsatisfactory by those who hold that mind is no longer to be either ignored or compelled to wait in the ante-chamber assigned to non-descript characters called epiphenomena.

The effect of this has been seen amongst medical men and has made them more disposed to admit a close association between mind and matter. It is recognised by them that mental factors are amongst the most important, and that these may be treated with a considerable prospect of success.

In the present-day, it is all to the good that man should be treated as a unity of body and mind, instead of being handed over as it were to rival practitioners—to medical men on the one hand, and to the psychologists on the other. Therefore the alliance between Medicine and Psychology is to be welcomed. It is fitting that medical men.

‘Should study passion; how else cure mankind.
‘Who come for help in passionate extremes.’

'Who could express with more prophetic vision this subtle relationship better than he who was both poet and physician for in truth the mind is undissociable for what it contemplates.

MATHEMATICS

Bayliss once remarked that the ultimate aim of all Sciences is to express in a mathematical form the discoveries that have been made in them. Though it is a difficult problem to express all facts in medicine in a mathematical equation, yet the application of Mathematics to medicine is increasing in recent days.

Within recent times nomograms or alignment charts have been constructed for finding the total number of calories contained in any diet of known composition, for respiratory quotient, and for colour index of blood. Observers have worked out more or less elaborate mathematical methods for building up a suitable diet for any particular diabetic patient. These has been calculated on a knowledge of the so-called basal metabolism needs of the patient, his body weight, height and surface. The vitamin requirement of man has been put in a mathematical formula. The curve of healing of a wound was developed by Carrel and others during the war.

Various equations and curves have been formulated in connection with disease, such as the periodicity curves of epidemics, theory of happenings in its application to epidemic and endemic diseases, of life tables and of carriers of disease. The latter is of special value in India. I need not dilate upon them in detail here any further.

It has to be remembered that the application of Mathematics to medicine has its limitations. All patients do not react in exactly the same way and some subjects appear to be beyond the control of mathematical formula. The various tables and curves used in modern work are no doubt of great scientific interest but they have their limitations.

Undetermined factors exist in more exact sciences like Physics and Chemistry. It is therefore to be expected that the same might be still more manifest in the Science of Medicine which has to deal with diseases of the body and mind and in which there are many complicated and undetermined factors to operate. In investigating a Science which deals with diseases of the mind we have to employ our mind to tell us about itself, and this we must do as a necessity, since we have no other instrument with which to conduct our investigation. Mind is therefore both executive and judicial, it is both judge and jury in its own cause. In such a Science there must be many undeterminable factors.

CONCLUDING REMARKS

Forecast

From what I have stated, it is clear that the various Sciences can be of great service of MEDICINE. Some of them have contributed very substantially to the relief of human suffering from disease. They can obtain valuable findings for the clinician in diseased conditions which may be helpful to him, but the responsibility finally rests with him as to how to act upon their findings. This shows the great importance of what is called today Clinical Science. Anatomy, the Science of structure of the body, Physiology the Science of function and the meeting ground of Physics and Chemistry in their application to problems of health and disease and Biochemistry the Science concerned with the chemical processes underlying the activities of living matter, can be of great service to the clinician. In recent times, the need for increased application of Physics and Chemistry to Medicine has grown with tremendous rapidity.

"The aim of the medical science is to control suffering, to prolong life and to keep mankind in a state of vigorous health". The science of MEDICINE, which was once mostly limited to the study of disease, is now concerning herself with

the study of health, by the increasing knowledge of nutrition, environment and eugenics. Though some may say that Mathematics or Metaphysics is the queen of sciences, yet I hold that MEDICINE is still another or more properly speaking, she is supreme among the queens of the Sciences. I hope that all your Sciences will serve her duly and to her best advantage, so that the person who professes her may give more and more relief to his patients in the mitigation of their sufferings by the light that he gets through your agency.

The newer conceptions of life advances in recent years have opened our minds as to the nature of the living organism. Evolutionally, we see life adapting itself to many varied conditions and to considerable extremes of environment. The most versatile is man who is found from pole to equator. His capacity for adaptation has been achieved and can be maintained only by the possession of an almost changeless and constant medium, the blood, which acts as the direct environment of his most valuable possession, namely, the brain. Man's whole body mechanism is organized in order to preserve "*La fixite de milieu interne*" as it was called by Claude Bernard. One hears in Physics of the so-called constants of nature such as speed of light or Planck's constant, but surely the level at which the essential blood constituents are maintained may also with justice be called the supreme constant both of and for *Homo sapiens*. It is no passive state; dynamic equilibrium holds it where it is, and preserves for us the sole condition for the progress of the development of man and his civilization. And when disease sets in, MEDICINE comes to his aid to maintain this constant or else he may deteriorate and die.

"Yes and how delicate. Life's mighty mystery all its self propagating organisms exist only within a few degrees of the long scale ranging from measured zero to unimagined heat Nor could they endure were't not that by a secret miracle of chemistry they hold internal poise upon a razor edge that many not even be blunted, lest we sicken and die."

In million million years, the earth's temperature may be reduced to such an extent it would be rash to predict how such a fall of temperature may effect man's life. What then will be his blood constant? I can not say. If then he lives, MEDICINE will still be called upon to mitigate the diseases that may attack man in the dim distant future.

It is immaterial for the purpose of my thesis whether the universe is fast proceeding to dissolution and death, by the rapid increase of entropy, according to the laws of thermodynamics and along with which man will meet the same fate, or whether creative evolution will lead in millions of years to the production of superman with new superkingdoms which are beyond the limits of our imagination. But whatever that may be as long as man exists, MEDICINE will have to deal with the infirmities of the degenerate man or the superman, as the case may be.

The discoveries in MEDICINE and its ancillary sciences in recent times have been phenomenal. We do not despair and say what Richet has said in the "*Impotence of man*" that "with the aid of a few drugs, we succeed in minimizing for a time a few trifling morbid phenomena which cause us discomfort". As Du Nuoy has stated, a day may come when the methods of treatment generally used today, will appear to us gross as do now the methods of Mr. Purgon, of Moliere's "*Malade imaginaire*".

Who knows what the future of MEDICINE after ten or hundred thousand years will lead to. Perhaps, in eons to come, it will be the conquest of old age and in complete immunity from disease. Could we not dream of a day when one shall see "all disease quenched by Science, no man halt or deaf or blind". What sort of bodymind will then be evolved, I shall not speculate to say.

But man's destiny may take a different and darker turn in future. Newer diseases worse than cancer or plague or the worst virus disease of today may attack him in the future. Circumstances

over which man may have no control, may lead to the deterioration of his body and mind resulting in the creation of newer maladies. These may render the task of MEDICINE more and more difficult. Catastrophies may occur in the world and civilization may regress. Such a cataclysm may be a geological one or due to a devastation world war much more terrible than is ever known in history or to a fatal epidemic which may spread from one part of the world to another with terrific rapidity or as Spengler and others hold, it may be a "cyclic process passing through the alternate periods of growth and development on the one hand and decay on the other, as evidenced by the various ancient civilization of the world which have now ceased to exist. But whatever that may be, "MEDICINE and civilization will advance and regress together" for all times to come.

The contribution of MEDICINE to civilization aided by the other sciences is great. A healthy body means a healthy mind, and such minds are less likely to cause internal or external strife. There is no doubt that a large part of the greatly increased comfort and safety that we enjoy today is the result of the phenomenal advances that have been made in the medical sciences in recent times. I would say with Howard Haggard 'And finally the physician'. He rightly holds that "Medical history discloses the forces that have made our modern civilization possible.... That modern medical science is today one of the strongest forces operating for human betterment—it is the religion of healthy childhood, manhood and womanhood".

In spite of recent occurrences, will not a day ever come when one may say that.

"The war-drum throb'd no longer,
And the battle-flags were furl'd
In the Parliament of man, the Federation
of the world?"

I conceive such a day may come and that slowly and slowly, physical warfare will give place to warfare of the intellect. There will be no

jealousy, and superiority or inferiority complexes will cease to exist. Slowly and slowly, man will live not by the destruction of the lives of his neighbours and seizing their property, but by making every part of the world healthy and habitable by improved methods of hygiene and thereby minimizing the need for the control of population, the overgrowth of which has been considered to be, to a great extent, responsible for many wars of the world. There will be no inadequacy of food supply which has led to many wars of aggressive in the world.

With his conception of the horrors of war, the MEDICAL man is a fit person for preaching the gospel of abhorrence of war. He can depict to you scenes in which, with the Sisters of the Red Cross, he picks up the wounded from the battlefield in the midst of most frightful agonies and tries to extract a bullet from the heart or the shattered brain or to transfuse his own and his assistant's blood into the vein of a dying soldier when the guns are roaring in the battlefield, irrespective of whatever camp he belongs to. I hope that in every peace league of the world, the MEDICAL man may have some representation, not as a diplomatist, but as one whose motto is that the well being of mankind throughout the world should be effected without any destruction of a life. A day may come when the war mentality of individual statesmen, which may lead to war psychosis among the people, will be analyzed and corrected by the psychiatrist and the psychologist. In this connection one welcomes the recent manifesto issued by the Committee for War Prophylaxis of the Netherlands Medical Association.

Could we not dream of a day when economic depression and unemployment will be ended, thanks to the increasing scientific development of newer industries and newer fields of fruitful work, and there will be leisure to enjoy the beautiful fruits of the earth that Science may provide, and when man relieved from toil by his mastery over the great sources of power in Nature, will have the opportunity of being richer, happier, healthier and

freer than even before. I conceive that this is possible if, as Jeans has suggested, there is a proper balance between labour-saving devices and industry-increasing discoveries. MEDICINE, which includes preventive medicine may help here in its own way be eradicating and preventing disease and thereby increasing man power and the capacity of the people for work, for taking part in the development of newer industries and agriculture, and for defending the country in times of need.

If one studies the evolution of man, one finds that his intellect is growing out of proportion to his body. The caveman was perhaps stronger in bodily strength than the strongest man of today. Is it possible that man's body may become smaller and smaller, his fierce, destructive, and other base instincts and feelings may be sublimated and his mind grown more and more and in the eons to come become independent of matter. Even then MEDICINE will minister to the "mind diseases" in which perhaps Physics and Chemistry may have no part to play. Or it is possible that after reaching its zenith of development, the mind may begin to regress and body begin to grow and thus a perpetual cycle may continue in which body and mind may alternately undergo growth and decay for eternal time? Or it is possible that, finally, the mind of man may merge into the eternal and infinite Mind and feel "*Soham*" i.e., I am He.

If in dealing with my subject, I have sometimes drifted to a mystic region, I would justify myself by repeating what Einstein said "It is enough for me to contemplate the mystery conscious life perpetuating itself through all eternity, to reflect upon the marvelous structure of the universe which we can dimly perceive, and try humbly to comprehend even an infinitesimal part of the intelligence manifested in nature."

Some of you perhaps say that the progress of science does not afford any evidence that the behaviour of living matter is governed by any other than the laws of Physics and Chemistry

(Bertrand Russell). But who can deny what Gowland Hopkins once said that "there may be yet higher levels calling for discussion in quite different terms"? The mechanism of life can not be explained by the Physics and Chemistry of today, though perhaps some of it may be explained by some ultra physico-chemical laws that may be discovered in the future. Even then one may not be able to say wherein, from the radiations to the bodymind, enters the breath of life.

The bodymind of man is the finest product of the universe even when compared with the most magnificent of the stars and the nebulae. Man's appearance cannot be regarded purposeless or accidental or as a sign of disease. He has discovered the laws of motion and relativity as well as of radio-telegraphy, radio-telephony, aviation and television. He unfolds the constitution of the stars and the nebulae, millions and millions of miles away from the earth. He calculates the weight and temperature of the stars and determines their ages. He finds out the constitution of the atoms and discovers the cosmic rays. He smashes the atoms and produces new radioactive elements. He transforms one element into another. He may, one day, be able to determine the Mathematics of the atom by means of his calculator. He tries to find out when and how primordial life came into existence. He tells the story of the oldest man who existed in the earth a million years ago, and gives the history of his evolution. He discovers the chromosomes and finds out the structures that are responsible for heredity. He discovers and dissects the micro-organisms of disease, and finds the defensive mechanism against their attacks. He studies the specific carbohydrates and proteins, and tries to discover the structure of the viruses and the bacteriophage. He discovers the treatment of diseases once considered incurable. He records the electric changes of the brain cortex of man in various cerebral state, and may one day record human thoughts on a sensitive plate. He studies

the endocrine glands, and synthesizes their secretions. He may one day be able to influence the sex of the embryo at his will. He cultures the organs of the body and studies their growth *in vitro*. Ponce de Leon did not perhaps search for the impossible and unattainable when he sought the fountain of eternal youth, for man may one day conquer old age, disease and death. Though I dare not say what the "final secret" is likely to be, yet the bodymind of man must be today the consummation of the work of the Great Design. In this most complicated machine in which, it may be said, "matter, life and mind translate roughly into organization, organism and organizer (Smuts)", MEDICINE tries to give the healing balm to act as a powerful agent for the maintenance of harmony and strength when disease sets in.

Let me now tell you what MEDICINE may do in other directions.

In the present day one cannot fail to be struck by the great increase in the varied functions that have come to be regarded within the province of the MEDICAL man. "He has in large part taken the place of the parson. He has made encroachments on the functions of the lawyer, the legislator and the judge, of the schoolmaster, the architect and the statistician. He has assumed some of the duties of the parent and guardian, while even the soldier and the policeman are to some degree under his control. In the ordering of their lives, and even in the regulation of their vices and the reform of their shortcomings, men and women are far

more willing to seek the advice and help of the medical man than once they were. The reason is, without doubt, that his advice is much more worth having than it once was" (Singer).

Lastly there is that wonderful influence of the mind of the true PHYSICIAN upon his patient's body and mind. The influence has been well expressed in the following words "Nothing can take his place—not propriest nor minister nor all the clinics that Science can provide. There is a rapport and as a confidence between him and his patient which has been known to accomplish miracles." If this force exists, I call it "personalism", the force that mind may exert upon mind, body and disease.

Thus we see that the functions of the MEDICAL man are manifold. Still with all humility he says

"If I can ease on life its aching
Or brush away one pain
If I can stop one heart from breaking
I'll not have lived in vain.
If I can help one failing brother
Into his strength again
If I can calm one fretted mother
I'll not have lived in vain".

I am afraid my address is "not much better-than that noise or sound which musicians make while they are tuning their instruments.... So I have been content to tune the instruments of the Muses, that they may play that have better hands" (Francis Bacon).

DO YOU KNOW ?

- Q1. Where do you have four seasons, each 40 years long ?
- Q2. How long did it take Victoria Memorial Hall to build ?
- Q3. What is the full form of A.M. ?

DEMYSTIFYING DYSLEXIA

Paromita Ghosh*

Dyslexia is a major learning disability which impedes academic achievement and diminishes the self-esteem of its victims. The basic problem is trouble in reading letters, words and other symbols. Its causes are mainly biological. However, the disorder can be managed effectively by multisensory learning and special computer programs.

Seven year old S. had a trying time at school. His class-teacher was fed up with his futile struggles to read and spell properly. After all, she was doing her best to teach. Or, she thought so. The boy's parents were summoned to the Principal's office and told in no uncertain terms that the boy was mentally challenged. The parents felt devastated. But they could sense that their son did not lack intelligence, the problem lay somewhere else.

Refusing to give up, they knocked at the doors of reputed clinicians. Finally, a competent child psychologist diagnosed dyslexia and suggested remedial measures. So there was light at the end of a dark tunnel for the boy in distress.

NATURE OF THE DISORDER : DYSLEXIA

Not many people know about the disorder termed as dyslexia. The word 'dyslexia' originates from two greek words—"dus" and "lexis" which in combined form mean difficult speech. Dyslexia is just that. It is a disorder manifested early in life in which reading performance is much lower than that expected considering the person's level of intelligence, age and duration of schooling¹. Apart from severe problems in reading, there are drawbacks in other aspects of linguistic ability as

well. Dyslexia is, therefore, a learning disability as it has adverse effects on the person's learning and achievement at school. In fact, it is the most prominent of learning disabilities plaguing school-students. It seems to occur in equal frequency among boys and girls¹.

CHARACTERISTICS OF DYSLEXICS

Persons suffering from dyslexia are known as dyslexics. They display the following general characteristics :

- (i) Possession of near-average to higher than average intelligence.
- (ii) Normal vision and hearing.
- (iii) Trouble in processing sensory information particularly in making sense of printed words. Jumbling of letters of alphabet while reading words are common e.g. reading the word "SUN" as "SNU".
- (iv) Lack of concerted effort in performing academic tasks.
- (v) Loss of concentration in studies at slightest distraction¹.
- (vi) Haphazard approach towards learning tasks.
- (vii) Inability to use memory strategies like mastering lengthy learning materials part by part, revising regularly, etc.

* Human Development, Department of Home Sciences, Calcutta University, Kolkata-700027.

- (viii) Weakness in memory capacity for verbal materials like meanings of words.
- (ix) Poor performance in examinations¹. This comes as no surprise because at primary-school, tests of reading and writing (including spelling)–abilities are integral parts of assessment. Besides, poor reading skills may impair comprehension of what is being read thus hampering performance e.g. reading the word “GEL” as “LEG” may come in the way of understanding the properties of gel. Inability to read arithmetic problems and numbers properly also impede performance in mathematics.
- (x) In the face of bad grades, rebuke and ridicule, feelings of anxiety and guilt mount. Confidence and self-esteem go down¹.

These characteristics describe dyslexics in general ways. But for definite diagnosis of the disorder, specific symptoms have to be delineated. Therefore, clinicians have agreed upon certain distinct symptoms of dyslexia.

SYMPTOMS

- (a) Speech and language difficulties begin in childhood. Inadequate phonological awareness is most prominent. So dyslexics are deficient in the ability to recognize different sounds in spoken language. The knowledge about the relationship between written and spoken parts of speech is limited. Dyslexics do not realize that words consist of smaller units of sound which are denoted by printed letters.
- (b) Problems occur in recall of verbal materials (e.g. words, sentences, poems, stories, etc.) after short intervals of time.
- (c) Difficulties in proper ordering and sequencing of letters, numbers, words, etc², for instance, 450 may be read as 054. The sentence,

“Open your book” may be read as “Open book your”.

- (d) Clumsiness e.g. a dyslexic child may not be able to copy from the blackboard properly. He or she may start copying from the top portion of the blackboard, suddenly change his or her mind and start to copy from the bottom of the board. In the process, much of what is written on the board is missed out.
- (e) Lack of consistent hand-preference. Almost all of us either exclusively use our right or left hand for writing. But dyslexics usually do not have fixed hand-preferences. They sometimes use the right hand and sometimes the left for writing. The result is inefficiency. Their work is slow, untidy and the handwritings are mostly illegible.
- (f) Frequent reversal of letters of alphabet like b for d, p for q etc. while reading and writing.
- (g) Poor verbal fluency². Besides being poor readers, they suffer from halting speech, unclear pronunciations, etc.

If we consider the symptoms, we would realize that such behavior patterns are not uncommon among children from impoverished, educationally backward families. But such children are not necessarily dyslexics. They may be perfectly normal youngsters who just need remedial training to compensate for disadvantaged backgrounds. But this situation presents a curious problem-what if a few of them are actually dyslexics? It was found very difficult to diagnose dyslexia among disadvantaged children³. However, psychological tests have been devised to assess the disorder as accurately as possible.

ASSESSMENT

Two of the popular psychological tests are Dyslexia Early Screening Test and Dyslexia Screening Test. Both are published by the

Psychological Corporation. A computerized assessment program titled, "Cognitive Profiling System" produced by Chameleon Educational is also used.

Different assessment devices may vary superficially but essentially each assesses the skills considered important for the diagnosis of dyslexia viz., memory, phonological awareness, auditory discrimination and verbal fluency³.

CAUSES

Researches are on to unearth the causes of dyslexia so that effective remedies can be planned. There is some evidence that genetic components may be involved. This is because frequently the disorder runs in families. Most cases of dyslexia are thought to result from neurological defects in processing of speech sounds. Important systems for reading alphabetic scripts are located in the left hemisphere of the brain. In most individuals, the left hemisphere is larger in size than the right one. But this may not be the case for most dyslexics³. Besides, the organization of the right hemisphere is different for dyslexics⁴. These conditions may have damaging effects on reading and speech skills.

Investigations reveal that alphabetic processing is generally associated with Occipital, Temporal and Parietal areas of the brain⁵. Dyslexic children display lower than normal activation in Temporo-Occipital areas which may also explain their poor reading skills⁶. Such children with mathematics-difficulties may show neural anomalies in the activation of the Temporo-Occipital system (specializing in alphabetic-speech linkages necessary for reading) but not in the activation of the Parietal and Premotor number systems (specializing in understanding of mathematics)⁷. So it seems that these children actually have potentials to grasp mathematics but reading and language difficulties of dyslexia are preventing them from performing satisfactorily in mathematics.

Researchers have reported that persons with damage to the Angular gyrus (a region of the brain located at the border of the Parietal, Occipital and Temporal lobes) may be able to communicate and understand speech but can not read properly. As a result, they suffer from dyslexia⁸. So, currently it appears that biological factors play significant roles in the causation of dyslexia. The pattern of causes provide clinicians inklings about the kinds of remedies which would prove effective.

REMEDIES

Dyslexia does not fade away. Remedial training helps to manage it so that it does not interfere with academic performance. Such training is imparted individually or in small groups. The venue could be any school or a specialist centre for dyslexics⁹.

Multisensory learning is the most useful remedy wherein the child learns the names, sounds and shapes of letters by involving a number of sense modalities—hearing, vision, touch and movement. For example, the child may be shown the letter 'M' in print, taught its pronunciation, directed to trace its shape using his or her fingers, demonstrated the finger movements involved in writing it and made to practice the same. Spellings of words, sentence constructions and their pronunciations are taught painstakingly in a similar fashion. To increase children's awareness of basic speech sounds of languages, listening and rhyming games have been included more in school lessons⁹.

Dyslexics also benefit from computer programs such as "Texthelp !" It provides a host of facilities in several languages. As a person types, he or she receives speech feedback by letter, word, sentence or block of text. Speaking Spellchecker and Speaking Thesaurus facilities render necessary help. Even the internet pages can be read aloud⁹ while the dyslexic watches the text and listens carefully. All these activities have to be supervised by experts in remedial learning

so that dyslexics receive valuable phonological training from these programs.

Simultaneously, counselling of dyslexics have to continue. It can relieve them of feelings of anxiety and guilt, boost their confidence and enhance their self-esteem.

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DO YOU KNOW ?

- Q4. What is the name of the first test tube baby ?
- Q5. What length fo tunnel can a more dig in the earth per day ?
- Q6. Which reptile can live happily with one good meal a year ?

PHYSICO-CHEMICAL NATURE OF DRUG-NUCLEIC ACID BINDING

S. N. Upadhyay*

Drug-nucleic acid binding ushers a new area of research with therapeutic application. The different steps of drug action, principles of different techniques used earlier for monitoring drug-biopolymer interaction, mode of binding of the drugs with nucleic acids/oligonucleotides and their mechanism of action with special reference to different therapeutic application have been discussed.

INTRODUCTION

Life saving drugs of various categories (e.g. anti-cancer, anti-tumor, antiviral, anti-pyranosomal, anti-biotic, anti-angiogenesis, anti-inflammatory, anti-coagulating, etc) have proved useful in the treatment of a wide variety of human maladies and, therefore, have lengthened human life. In a mechanism based drug design effort, the most common targets for interrupting a disease process are enzymes, receptors, RNA, DNA and proteins. Interaction of different types of drugs with these biopolymers deserve special consideration for achieving the desired goals¹. The binding of drugs with RNA, DNA or specific proteins controlling gene expression is of primary importance in controlling the efficacy of the drug.

MODELLING DRUG-NUCLEIC ACID INTERACTION

A number of drugs are believed to mediate biological effects through specific interactions at membrane bound extra-cytosolic receptors or by disrupting membrane fluidity in a non-specific manner. Other drugs are known to enter the cytosol and the nucleus to exert their action by interacting with specific macromolecular targets. Nucleic acids and proteins are generally important targets for

such drugs. The overall action of drugs are dependent upon the following factors :

(i) interaction with macromolecular hosts, (ii) transport to the site of action, (iii) transport across the cellular plasma membrane, (iv) absorption into cytosol and metabolism and (v) passing through nucleolar membrane and interaction with genes, chromosomes and their constituents.

The different modes of binding with nucleic acids can be by intercalation, covalent and non-covalent groove binding, charge neutralization/interaction and non-specific interaction. The intercalators are 9-Amino-acridine, Proflavin, Ethidium bromide, etc. The covalent binders through minor groove are Netropsin, Mytomycin, Anthramycin, etc. Covalent and non-covalent groove binders exhibit DNA sequence specificity. Non-specific interactions of drugs with nucleic acids usually refer to electrostatic and hydrogen bonding interactions with the backbone phosphates and or counter-ion or solvation atmosphere surrounding them²⁻⁴.

MONITORING OF DRUG-BIOPOLYMER INTERACTION

The drug-biopolymer interaction can be detected by the following techniques :

(i) Gel electrophoresis, (ii) Electron microscopy, (iii) X-ray crystallography, (iv) NMR spectroscopy, (v) Quantitative foot

* Radiation Chemistry Department, Institute of Nuclear Medicine & Allied Sciences, Brig. S. K. Mazumdar Road, Delhi-110054

printing analysis and (vi) Spectro-photometry, Spectrophotofluorimetry, Conductometry, Infra-red spectroscopy, etc.

(i) **Gel electrophoresis** of different kinds and efficient procedures for labeling and sequencing DNA have been reported^{5,6}. Drug's specific binding generally begins by selecting a DNA restriction fragment and labeling it with radioactive ³²P, followed by incubation of restriction fragment with drug of interest.

(ii) **Electron microscopic** technique is used to detect the intercalation of drugs in the major and minor grooves of DNA. By this process DNA unwinds and hence its length increases. The drug-DNA complex is placed on an electron microscopic grid on which formvar film and carbon coatings are done to give support. The drug-DNA complex remains in a lengthwise straight fashion when adsorbed on a protein film. To enhance contrast, high atomic number elements like Cr, W, Pd, etc are used. The whole drug-biopolymer assembly is suitable shadowcasted and electron micrograph is taken⁷.

(iii) **X-ray crystallography** technique requires > 95% purity of final product which is possible to be achieved by HPLC or gel filtration columns (e.g.sephadex G 50). As crystal growth kinetics is influenced by pH, it should be meticulously monitored to get a good crystal. Many times minute concentration of salts of Na⁺, Ca⁺⁺, Zn⁺⁺, Co⁺⁺, Ni⁺⁺, Mn⁺⁺ etc. are used for facilitating crystallization. In this process drawing out of water from the crystal is normally done by vapour diffusion method.

Bragg equation i.e. $n\lambda = 2d \sin \alpha \dots (1)$ is used to determine the crystal structure. The X-ray beam (of wavelength λ) glances the miller planes at an angle of α , resulting in a reflected beam emitting at the same angle α due to constructive interference of the X-rays in the path. Presently, fully automated computer controlled four circle diffractometer, using rotating anode X-ray

generator, is utilized. Collected intensity data I_{hkl} is related to structure factor F_{hkl} by

$$I_{hkl} = K L_p \cdot F_{hkl}^2 \dots \dots \dots (2)$$

Where K = correction factor for absorption, crystal decay, etc.

L_p = Geometric physical correction factor i.e. Lorenz polarization factor. The crystallographic residual factor R is given by :

$$R = \frac{F_0 - F_C}{F_0} \dots \dots \dots (3)$$

Where F_0 = observed experimental structure factor.

F_C = theoretical structure factor.

For small molecules R-factor is below 5% and for macromolecules R-factor is between 15-20%. Thus drug-biopolymer crystal is assessed finally by X-ray crystallography⁸.

(iv) **By NMR spectroscopy**, structure determination involves sample preparation, data collection, 1D and 2D NMR spectra, resonance assignments, model building and structure refinement. It requires superconducting high field NMR spectroscopy equipment with state of the art electronics and computer. A magnetic field of 9-14T (resonance frequency 400-600 MHz for proton nucleus) is required. Fourier transformed technology is employed for rapid data collection.

For obtaining information regarding connectivity through bonds, multi-dimensional NMR spectroscopy uses a number of pulse sequences. This is given by 2-dimensional J-correlated spectroscopy (COSY) and corresponding starting point of connectivity pathway is shown by NOSEY spectrum. By both these spectra, all the proton resonances are identified. Then idealized DNA/RNA structures (models) are constructed. This helps in assigning structure refinement when monitoring by an NMR discrepancy factor (R-factor) becomes necessary.

$$R\text{-factor (NMR)} = [N_0 - N_c]/[N_0] \dots \dots (4)$$

where N_0 = observed off-diagonal NOE volumes of all the corss-peaks associated with a given proton.

A reasonable model should produce an R factor of lower than 20 percent. Thus NMR spectroscopy is an excellent method for structure assignment of drug-biopolymer binding^{9,10}.

(v) **Quantitative foot printing analysis** is essentially an auto-radiographic technique. Here a probe or cleavage agent is used which contains radio-isotopically lebeled bases (**A, T, G, C**).

The basic equation for foot printing plot is :-

$$i(\text{rate})i = Ki(\text{Probe } i) (1 - ui) \dots(5)$$

$i(\text{rate})i$ = cleavage rate at cleavage site

Ki = cleavage rate constant at the site .

$(\text{Probe } i)$ = concentration of cleavage agent or probe at the site.

$(1 - ui)$ = fraction of **site i** not blocked by drug binding at a site near cleavage **site i**. The drug binding site need not be identical to the cleavage site.

For single hit regime the auto-radiographic spot intensity is proportional to $(\text{rate})i$. This proportionality constant multiplied by Ki gives a new constant.

In case of an isolated drug binding site. the binding constant Kj at the **jth** drug site is given by :

$$Kj = Cj/(C - Cj)D_0 \dots\dots(6)$$

Where, Cj = Concentration of **sites j** at which drug is bound

C = Total concentration of **sites j**

D_0 = Free drug concentration.

As $u_i = (C - Cj)/C$,

$$1 - u_i = [1 + Kj D_0]^{-1} \dots\dots(7)$$

If two drug **sites j and k** are near one another, an enzyme cleavage **site i** may be blocked by drug binding at either **site j or site k**.

The $1 - u_i = (1 - Cj/C) (1 - Ck/C)$

$$= \frac{1}{(1 + Kj D_0)(1 + Kk D_0)} \dots\dots(8)$$

Then, by this thchnique, it is possible to follow the binding mode of drug with the biopolymer from experimentally determinable quantities¹¹.

(vi) **Spectrophotometry, Conductometry, Spectrophotofluorimetry, Infra-red spectroscopy.**

In vitro studies have been conducted in our laboratory by the above mentioned techniques, the active principles of which are well known. This was to find out interaction of **5-hydroxy L-tryptophan (5HTP)**, a radioprotector and a drug, **b-Aminoethylisothiuronium bromide hydromide (AET)**-a radioprotector and **Dilitiazem**-a cardiovascular therapeutic drug and a radioprotector with **DNA** and **Nucleohistone**. All three of these compounds have the property of binding with **DNA, Nucleohistone** and the bases of **DNA** (i.e. **A, T, G, C**) and some aminoacids¹²⁻¹⁵. Thus these drugs modify their course of action physiologically inside the body. **5HTP** has been recognized as a drug in treating depression, fibromyalgia, binge eating associated with obesity, chronic headache and insomnia¹⁶. All of these three compounds are capable of modifying radiation-induced damaged to different organs¹⁷⁻²⁰. So, potentially these are capable of mitigating radiation-induced carcinogenesis. Their radioprotecting property was tested as anti-tumor drugs to mitigate radiation carcinogenesis.

Table 1 enumerates in short some drugs, their modes of action, binding sites and techniques by which drug-biopolymer interactions have been detected. The binding characteristics of some of these drugs, modeling of such drugs and their designing for better efficacy have been reported in details²¹.

TABLE-1
DIFFERENT DRUGS, THEIR MODES OF ACTION, BINDING SITES
AND TECHNIQUES FOR DETECTION OF BIDDING SITES

| Drugs | Mode of action | Binding site | Techniques |
|--|--|---|---|
| Mytomycin | Antitumor agent | Binds covalently to DNA in minor groove and alkylate the exocyclic group of guanines. | X-ray crystallography |
| Anthracycline | Antitumor agent | Binds covalently to DNA in minor groove and alkylate the exocyclic group of guanines | X-ray crystallography |
| CC1065 | Antitumor agent | Binds covalently to DNA | NMR spectroscopy |
| Bleomycin | Antitumor, Antibiotic agent for treatment of squamous cell tumours & malignant lymphomas | DNA cleavage agent at G-T Dinucleotide | Electrophoresis |
| Neocarzinostatin | Antitumor, Antibiotic agent | Binds to minor groove of B form of DNA | Spectrophotometry, Circular dichroism |
| Methyl nitrosourea | Anticancer agent | Alkylation of DNA through N-7 position of guanine at the major groove | NMR spectroscopy |
| Cisplatin | Anticancer agent | Binds to DNA in N-7 position of guanine | Electrophoresis |
| Netropsin | Antibiotic, Antiviral and Antitumor agent | Binds to double stranded B form of DNA at A-T rich site | X-ray crystallography |
| Distamycin | Antibiotic, Antiviral and Antitumor agent | Binds to minor groove at A-T rich regions of DNA in the O-2 position of thymine and N-3 position of adenine | X-ray crystallography |
| Berenil | Antipyranosomal agent | Binds to minor groove of DNA through A-T rich regions | X-ray crystallography |
| Adriamycin | Anticancer drug | Intercalates with DNA via the minor groove. Adjacent G-C pair are recognized | Foot printing technique |
| Chromomycin | Antibiotic, Antiviral agent | Binds to double helical DNA | Foot printing technique |
| Mithramycin | Antibiotic, Antiviral agent | Binds to double helical DNA by two contiguous G-C pairs | Foot printing technique |
| Daunomycin | Anticancer agent | Intercalates in the major groove of DNA | Spectrophotometry & X-ray crystallography |
| Olivomycin | Antibiotic, Antiviral agent | Binds to double helical DNA by two contiguous G-C pairs | Foot printing technique |
| Nogalamycin | Antibiotic agent | Binds to regions of alternative purine-pyrimidine sequence | Foot printing technique |
| Actinomycin | Antibiotic agent | Binds to DNA through hydrogen bonding and intercalation | Spectrophotometry |
| D-Aminoethylisothio-uronium bromide hydrobromide | Radioprotector | Binds DNA by charge neutralization | Spectrophotometry & Spectrofluorometry |
| 5-Hydroxy-L Tryptophan | Radioprotector & drug | Binds to DNA and Nucleohistone by charge interaction and intercalation | Spectrophotometry & Spectrofluorometry |
| Diltiazem | Radioprotector & drug | Binds to DNA by charge neutralisation | Spectrophotometry & IR Spectroscopy |

MECHANISM OF ACTION OF DRUGS BOUND TO OLIGONUCLEOTIDES

It was suggested in 1980 that RNA ligands might be useful for therapeutic ends. These were named 'Aptamers' by Ellington and Szostak²². In 1990, it was demonstrated²³ that large libraries of RNAs could be screened in vitro for RNA ligands that bind T₄ DNA polymerase and a variety of organic dyes. This 'systematic evolution of ligands by exponential enrichment (SELEX) starts by generating a large library of randomized RNA sequences. This library containing 10¹⁴ to 10¹⁵ different RNA species fold into different structures depending on their particular sequence. The library is incubated with the target protein of interest and those RNAs present in the library, that bind with the protein, are separated from those that do not. Different analytical techniques like affinity chromatography, immuno-precipitation, electrophoretic mobility shift or filter binding techniques are used for separating the highest affinity molecules from the pools. The retained RNAs are then amplified by RT-PCR and in vitro transcribed to generate a pool of RNAs that have been enriched for those that bind the target of interest. This process is repeated 8 to 12 times to get the RNA ligands with the highest affinity for the target protein isolated. The winning 'Aptamers' are then cloned and sequenced.

'Aptamers' act as attractive therapeutic agents by folding into a three-dimensional structure based on their nucleic acid sequence to find to their targets. Binding of an 'Aptamer' is a highly specific interaction with the ability to discriminate between related proteins that share common sets of structural domains²⁴⁻²⁷. Some of the important properties of 'Aptamers' are :

(i) Binding affinity in nanomolar to picomolar range ; (ii) Entire selection is a chemical process and can therefore target any protein ; (iii) It can select for ligands under a variety of conditions for *in-vitro* diagnostics ; (iv) Uniform activity regardless of batch synthesis ; (v) It returns to

original conformation after temperature insult ; (vi) Unlimited shelf life ; (vii) No evidence of immuno-genicity ; (viii) Cross reactive compounds can be isolated to facilitate preclinical studies and (ix) 'Aptamer' specific antidote can be developed to reverse the inhibitory activity of the drug²⁸.

Pharmacokinetic manipulation of 'Aptamers' rely on the efficacy of the clearance mechanism. To render 'Aptamer' activity independent of biological clearance, base pairing between the 'Aptamer' and the oligonucleotide antidote occurs. This alters the shape of the 'Aptamer' thereby preventing it from binding to its target. The ability to develop 'Aptamers' that retain activity in multiple organisms facilitates preclinical development. Antidote control of 'Aptamer' activity enables safe, tightly controlled therapeutics.

'Aptamers' may prove useful in the treatment of infectious diseases, cancer and cardiovascular disease. Optimally stabilized and formulated 'Aptamers' are now available as intravenous or subcutaneous injectables with blood half-lives in the 6 to 12 hour range^{29, 30}. New oligonucleotide stabilization chemistries continue, thereby producing injectable 'Aptamer' formulations with longer blood half-lives (e.g. > 24 hours) seems feasible in future. Immune-modulated aptamers as adjuvants to cancer and other vaccine strategies are being developed³¹. So, 'Aptamers' may prove useful to a large extent in the clinics.

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TERMINATOR TECHNOLOGY : AN ECOLOGICAL DISASTER

B.L. Jagetiya, M.J. Kaur, Tina Choudhary, Pankaj Purohit,
Khushbu Bhatt and Neelam Acharya*

The paper deals with terminator seeds and the technology to produce them as well as their hazardous effects on farmers, food security, agricultural biodiversity and ineffectiveness for preventing gene flow.

INTRODUCTION

In 1998, for the first time the Delta and Pine Land Company, working with the U.S. Department of Agriculture [USDA] acquired U.S. patent for Technology Protection System [TPS]. Within days the rest of world knew TPS as terminator technology. In Terminator Technology certain genes are inserted into seeds that ensure that resulting plants will produce self terminating offspring 'Suicide seeds'. This genetic technology is designated to prevent unauthorized seed saving by farmers. The utility of this technology to an agrobiotech company, marketing these crops would be to prevent farmers from cheating by breaking their agreement and saving seeds anyway. For this reason the seed killing strategy was later named "Genetic Use Restriction Technology" [GURT]. GURT is a system, which has the purpose to protect the financial interest of the developers that means the multinational companies. In this case there is absolutely no agronomic benefit for farmers. The sole purpose is to facilitate monopoly control and the sole beneficiary in this case is agribusiness community.

The terminator technology is used to control the plant gene expression in two major ways. The terminator consists of a set of three novel genes inserted into one plant. In another technique, two or three genes are present on two different plants, which are later to be cross-pollinated. The end result is always a dead seed in the following generation. The

three genes required are : a 'terminator gene' that stops seed development, a 'repressor gene' that represses the terminator gene and an 'activator gene' that activates the terminator gene by preventing the repressor gene from working. Controlled expression of these genes results, sterile offspring of an engineered plant.

These genetically modified crops have some agronomic advantages like increased yield, nutritional quality, flavour, disease and drought resistance and processing characteristics, but these seeds hold farmers back from their traditional saving of seeds for future generations and utilization of breeding technique. The terminator technology with its terminator seeds force farmers back to the market every season. They also scuttle community conservation of agricultural biodiversity. This technology, therefore, is called "Neutron Bomb" of agriculture. Civil society and many governments have called for a ban on the technology².

THE HISTORY

In the history of plant breeding, Mendel published his work on the genetics of pea in 1865. He laid down genetical rules of plant crossing for the first time. He is known as "Father of Genetics". In 1860, Major Hallett discovered a modern plant breeding concept "Pedigree method", for cereals.³ In this method farmers brought seeds, sowed them, selected the best seeds for the next season and bred their own varieties. The advantage of this method was that the varieties uniquely adapted themselves to local soil, weather and environment.

In 1908 George Shull introduced 'hybridization',

* Laboratory of Plant Physiology and Biotechnology, Department of Botany, M.L.V. Government College, Bhilwara (Rajasthan)-311001

a wonderful euphemistic term. These discoveries led farmers to save and develop their own seeds for generations. In hybridization, two distant plant relatives were crossed, that create a 'hybrid vigour'.

Dr. Melvin Oliver, a scientist at the USDA laboratory, developed a strategy to allow a plant to develop from a seed but produces non-viable offsprings. His approach was to utilize normal growth process in all plant and place it under a different genetic control switch. The normal process is called 'programmed cell death' and is used by plants to fight off pathogens. For example, when a plant leaf is damaged or infected, the cells around the affected region immediately go for self destruction by making a protein that arrests their cell machinery for producing proteins. Genes control the production of proteins and Dr. Oliver put the gene responsible for this process under the control of another gene which is active only as a seed reaches full maturity. The presence of the active inhibitor gene prevents the seed from germinating.

The terminator crops have been field tested in Europe since 1990 and in United States since 1992, where several have already been released commercially. There are more than 150 US patents listing for the terminator technology.⁴ The first terminator patents to catch public attention were those jointly owned by USDA and Delta and Pine Land Company, which they acquired in March 1998. The novelty of those patents lies in the fact that the company gained complete control over the hybrids as well as proprietary chemicals that control gene expression. These patents, being contrary to basic human rights, met with universal condemnation world wide.

THE TECHNOLOGY

There are three key components of terminator technology :

(i) Terminator or Barnase gene, (ii) Blocking Sequence or Repressor gene and (iii) Activator or Recombinase gene.

Terminator gene : This gene halts seed development and produces Barnase enzyme, which breaks down RNA. RNA is an intermediate in the expression of all genes. So barnase gene is lethal to all the cells, in which it expresses. When barstar is present (specific inhibitor of barnase), it forms one to one complex with barnase, in this way barstar blocks the lethality of barnase gene. Both barnase and barstar are the products, of bacterium *Bacillus amyloliquefaciens*, In the bacterium cell both of these bind with each other and show no harmful effects. When barnase is secreted outside, it is harmful to other cells.

Repressor gene : It is DNA sequence that keeps the terminator gene 'turned off' until the seeds are sold to farmers, This gene would be programmed to stay 'on' all the time to keep terminator gene 'turned off'.

Activator gene : This is a recombinase gene that produces recombinase enzyme. This enzyme is responsible to splice out the blocking sequence so that the terminator or barnase gene can express itself. The recombinase gene is placed under the control of a promoter that responds to an external chemical, say the antibiotic tetracycline. Cre recombinase and RAG recombinase are some examples of recombination system. Cre/lox P system was originally isolated from bacteriophage P1. Cre catalyses recombination between two lox P sites, splicing out any stretch of DNA in between. This system is useful both in plants and animals. RAG recombinase is useful only in animals.

There are many ways to engineer sterility but little is published for field trials. Two systems are discussed below :

(A) Barnase Recombinase system and (B) Barnase Barstar system.

Barnase Recombinase system : In this system, to engineer pollen/ovule sterility barnase is placed under the anther/ovule specific promoter that allows the gene to be expressed only during anther/ovule

development. A blocking sequence (repressor gene) is also engineered between promoter and barnase gene.

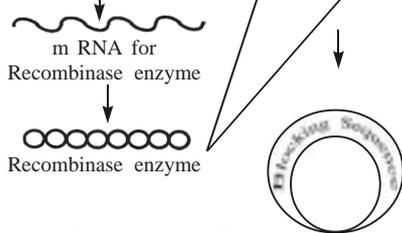
| | | |
|--------------------------------|-------------------|--------------|
| Anther/ovule specific promoter | Blocking sequence | Barnase gene |
|--------------------------------|-------------------|--------------|

Recombinase gene with its tetracycline specific promoter, is engineered first to barnase gene or it can be introduced by crossing the GM line containing recombinase with another, that contains barnase to give a hybrid.

| | | | | |
|--------------------------------|------------------|--------------------------------|-------------------|--------------|
| Tetracycline specific promoter | Recombinase gene | Anther—ovule specific promoter | Blocking sequence | Barnase gene |
|--------------------------------|------------------|--------------------------------|-------------------|--------------|

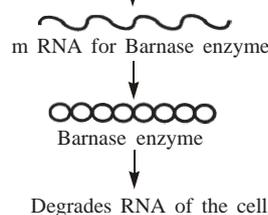
Transgene of interest (like as in herbicide tolerance) with its own promoter is stitched next to barnase.

| | | | | | |
|--------------------------------|------------------|--------------------------|-------------------|--------------------------------|--------------------------|
| Tetracycline specific promoter | Recombinase Gene | Anther specific promoter | Blocking Sequence | Terminator Gene (Barnase Gene) | Foreign Gene of Interest |
|--------------------------------|------------------|--------------------------|-------------------|--------------------------------|--------------------------|



| | | | | |
|--------------------------------|------------------|--------------------------|--------------------------------|--------------------------|
| Tetracycline specific promoter | Recombinase Gene | Anther specific promoter | Terminator Gene (Barnase Gene) | Foreign Gene of Interest |
|--------------------------------|------------------|--------------------------|--------------------------------|--------------------------|

| | | | | |
|--------------------------------|------------------|--------------------------|--------------------------------|--------------------------|
| Tetracycline specific promoter | Recombinase Gene | Anther specific promoter | Terminator Gene (Barnase Gene) | Foreign Gene of Interest |
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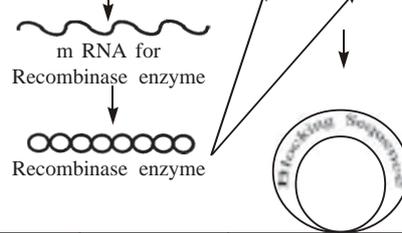


| | | | | | |
|--------------------------------|------------------|--------------------------------|-------------------|--------------|-----------------------|
| Tetracycline specific promoter | Recombinase gene | Anther—ovule specific promoter | Blocking sequence | Barnase gene | Transgene of interest |
|--------------------------------|------------------|--------------------------------|-------------------|--------------|-----------------------|

In the absence of external chemical, the tetracycline, the activator gene or recombinase gene does not produce the recombinase enzyme. At this time the blocking sequence is programmed to stay 'on' to keep the terminator gene turned 'off'. In the presence of tetracycline the recombinase gene is expressed and produces recombinase enzyme which splices out blocking sequence in the barnase promoter and barnase gene is expressed in male/female part of the plant. Theoretically, there will be no fertile pollen/ovule from this transgenic crop.

When the seed company is ready to sell seeds to growers, it first treats the seeds with tetracycline,

| | | | | | |
|--------------------------------|------------------|-------------------------|-------------------|--------------------------------|--------------------------|
| Tetracycline specific promoter | Recombinase Gene | Ovule specific promoter | Blocking Sequence | Terminator Gene (Barnase Gene) | Foreign Gene of Interest |
|--------------------------------|------------------|-------------------------|-------------------|--------------------------------|--------------------------|



| | | | | |
|--------------------------------|------------------|-------------------------|--------------------------------|--------------------------|
| Tetracycline specific promoter | Recombinase Gene | Ovule specific promoter | Terminator Gene (Barnase Gene) | Foreign Gene of Interest |
|--------------------------------|------------------|-------------------------|--------------------------------|--------------------------|

| | | | | |
|--------------------------------|------------------|-------------------------|--------------------------------|--------------------------|
| Tetracycline specific promoter | Recombinase Gene | Ovule specific promoter | Terminator Gene (Barnase Gene) | Foreign Gene of Interest |
|--------------------------------|------------------|-------------------------|--------------------------------|--------------------------|

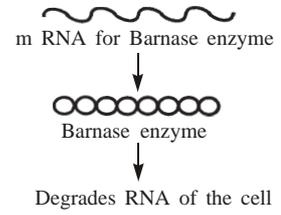


Fig. 1A and 1B : Terminator Technology to produce male / female sterility

which turns 'on' the recombinase gene. This recombinase gene produces recombinase enzyme. This enzyme binds to the blocking sequence and splices out this blocking sequence so that terminator

gene becomes active and produces barnase, which breaks down the mRNA, and becomes lethal to the cells. In self fertilized crops, there will be no seed set (Figures 1A and 1B).

In other cases, a recombinase gene may be engineered in to a GM line with a barstar gene. This line, when crossed to a GM line (male sterile) containing barnase gene, will give a hybrid which, when treated with tetracycline will produce plants that will set seed at least theoretically because barstar neutralizes barnase. If the harvested seeds are grown again, only 7/16 of the seeds will be fertile with same characteristics as those of original and 3/16 seeds will be sterile. Two seeds out of sixteen will be partially sterile.

Barnase Barstar system (Male sterility system of Bayers Crop Sciences) :-In AgEvo's (now Bayer Crop Science) application for field trials, only two lines are mentioned. These are :

Male sterile oil seed rape line : This line is maintained in a hemizygone state. i.e. with only one copy of the male sterility gene barnase under the anther specific promotor and a gene for phosphinothricin tolerance (glufosinate tolerance gene, H).

Male restorer oil seed rape line : This line is maintained in homozygous state i.e. with two copies of the restorer gene barstar under the control of anther specific promotor linked to glufosinate tolerance gene H.

Barstar and barnase genes are on different chromosomes and each is linked to a glufosinate tolerance gen H. Cross of Male sterile and Male restorer lines produces F₁ hybrid containing two kinds of plants. (a) Plants with H-barnase & H-barstar transgene in hemizygous state. Barnase in such plants is neutralised by barstar, so, plants are male fertile and produce pollen and are glufosinate tolerant. (b) Plants with H-barstar in hemizygous state which are male fertile as well as glufosinate tolerant.

As H-barnase and H-barstar are on different chromosomes, they assort independently of each other. Two kinds of F₁ hybrid plants produce different kinds of pollen. The plants with H-barnase and H-barstar (both in a hemizygous state) produce four kinds of pollen in equal proportions, three of

which carry the glufosinate-tolerance gene. The plants with only H-barstar in hemizygous state produce two kinds of pollen in equal proportions, those with the glufosinate-tolerance gene and those without. Thus, 5/8 of the pollen produced by the F₁ hybrid plants will spread the glufosinate-tolerance gene and 2/8 of the pollen will spread the male-sterility gene barnase, half of them carrying the male-sterility restorer gene barstar, and half without (Figure 2)

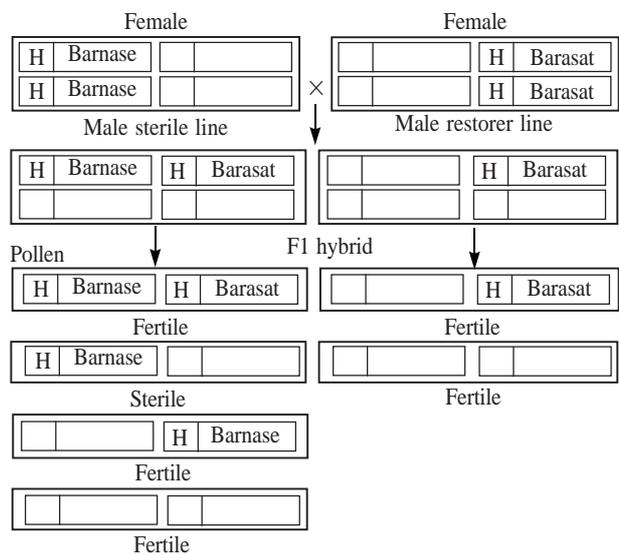


Fig. 2 : Reconstruction of the male sterile system (devised by Bayer Crop Science)

HAZARDOUS EFFECT OF TERMINATOR TECHNOLOGY

The terminator technology is supposed to give the plant higher yields, drought and insect resistance ability etc., but the results are disappointing. Some of hazards are as follows :

Misfortune of farmers : The 12,000 years old practice in which farm families save their best seed from one year's harvest for the next season's planting, may be coming to an end if terminator technology will be approved all over the world. Critics say that it could spell disaster for world's food supply, since more than one billion farmers, primarily small farmers in Africa, Asia and Latin America depend on saved farmed seeds.

Threat to food security : The second reason for

criticizing the terminator technology is the absence of adequate biosafety legislation. Countries might be induced to accept the terminator on the assumption that the technology is safe and the transgenic traits can not survive to a second generation, even by cross pollination. This assumption is ill founded. As with all genetic engineering, its direct effect and its side effects are unpredictable and carry all the risks inherent in this technology. The gene cocktail of the terminator increases the risks that new toxins and allergens will show up in our food and animal fodder. So it should be banned unless "it is too late to lock the stable door when the steed is stolen".

Destruction of agricultural biodiversity : The terminator genes themselves could infect the agricultural gene pool of the neighbouring crops and of wild and weedy relatives, placing a time bomb. Temporary gene silencing of the poison gene or failed activation of this countdown enable such infection. Molecular biologists have mixed views on the potential ecological hazards of the sterility trait. From first generation seed might spread via pollen to neighbouring crops or wild relatives growing nearby. The danger is that neighbouring crops could be rendered sterile due to cross pollination wreaking havoc on the surrounding ecosystem. So biosafety issues remain an important concern.

Ineffectivity for preventing gene flow : Terminator crop system is ineffective for preventing gene flow, because this gene control system is leaky, in the sense of not being 100% accurate as some fertile pollen/seeds are likely to be produced. Male sterile terminator plants can still be fertilized by non terminator pollen, just as terminated pollen from ovule sterile plants can cross with non terminated plants, thus enabling gene escape. Horizontal gene transfer is also possible in this system. It is the process whereby the GM DNA is taken up directly in to cells of unrelated species and incorporated into the cell's genome. Bacteria viruses, plant residues, dust pollen, insect pollinator act as vector of horizontal gene transfer.⁵

Lethal effects of barnase gene and recombinase gene : The gene involved in terminator crops is potentially fatal.⁶ Barnase is an universal poison. It is a potent RNase that breaks down RNA indiscriminately and is known to be harmful to animals and humans. When perfused into rat kidney's, barnase causes kidney damage.⁷ The site specific recombinase is not specific. There is already evidence suggesting that genome can be scrambled by the recombinase. Transfer of both the terminator gene barnase and the recombinase will have drastic, potentially fatal effects on health.

Both the patent and the technology should be rejected on the basis of common sense, food security and agricultural biodiversity. The terminator technology has absolutely zero agronomic benefit, there is no reason to jeopardize the food security of the poor by gambling with genetic engineering in the field. Whether the terminator works immediately or later, in either instance it is biological warfare on farmers and food security. So these killing crops must be stopped once and for all.

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PRESENT SCENARIO OF ULTRASONIC APPLICATIONS

Kailash and K. M. Raju*

In this article, some recent developments and applications of ultrasonics are presented. It includes laser ultrasonics, acoustic microscopy, ultrasonic stimulated vibro-acoustography, acoustic emission, saser and medical ultrasonics.

INTRODUCTION

Research and development in the field of ultrasonics is growing steadily. Some latest topics and applications such as laser ultrasonics, acoustic microscopy, ultrasonic-stimulated vibro-acoustography, acoustic emission, saser and medical ultrasonics are discussed in this paper.

Ultrasound is playing an important role in our daily life. It is finding applications in various branches of science, engineering and medicine. As late as in 1900, only the ultrasound whistle was used. The interesting observation of the relaxation phenomena in gases and liquids towards the late twenties and the observation of diffraction of light by ultrasonic waves in the mid thirties greatly increased the interest in physical ultrasonic waves. By 1930, it had become an interesting but small research area of physics. In the 1960s and 70s, however, it became an important research tool in physics, a far ranging instrument for flaw detection in engineering, in medicine and a reliable method of underwater signalling. One could for example, study phonons using ultrasonic techniques. Other applications in solid-state studies and in materials science phenomena have made the subject an active one.

The range of frequencies available has been extended to mega hertz (MHz) and even giga hertz (GHz). Ultrasonics is a powerful technique for

inspecting and characterizing materials. It can be used not only to detect bulk and surface flaws but obtain information of material microstructure also which determines the engineering properties such as elastic moduli and ultimate strength. Ultrasound techniques use the interaction of high frequency sound waves with matter, in order to generate information about the physico-chemical properties. Such measurements have been established in numerous areas like medicine, oceanography and material sciences. All these developments have increased the range of ultrasonic applications manifold. There appears to be no area today where ultrasonics does not find an application. There are numerous applications such as fluid flow measurement, liquid level measurement, gas sensors etc. In fact, the uses of ultrasonics are increasing every day with research and development work keeping right pace with each other.

LASER ULTRASONICS

The method of generation, detection and coupling of ultrasound may be called conventional ultrasonics. Such a technique cannot obviously be applied at elevated temperatures, because it requires fluid coupling and most fluids vaporize above a few hundred degrees Celsius. Also, if the temperature exceeds the limit of the transducer material, the transducer ceases to be piezoelectric and to be operational. On the other hand, being able to use ultrasound at elevated temperatures could be of far-reaching importance, since all metals and ceramics are processed at elevated temperatures.

* Dept. of Physics, B. N. V. P. G. College, Rath, Hamirpur-210 431, U. P.

In this case, ultrasound could not only provide information on the thickness of the part being processed but also on its microstructure, which determine many engineering properties. Such a limitation could be circumvented by using lasers for generation and detection of ultrasound. This technique is called laser ultrasonics^{1, 2}. Laser techniques use one laser for generation and another for detection. In this case, there is no need of fluid contact and transduction can even be performed in vacuum. Laser ultrasonics also provides a solution to limitation of conventional ultrasonics which is less obvious and prevents its use in so many cases of industrial interest. Conventional ultrasonics requires a manipulator to make the transducer to follow the curved surface and eventually, especially for small radius pipes, the addition to the transducer of an acoustic lens for acoustic wave-front matching. In the case of laser ultrasonics there is no need of such added gel and the beams are simply scanned over the surface. The experimental studies show that Laser ultrasonics is, in general, less sensitive than piezoelectric transduction and considerable research and technological development was needed to provide useful signals.

An important application of laser ultrasonics is to measure the strength and flexibility of paper without touching it and even when it is moving at 30 meters per second. Paul Ridgway and Rick Russo are developing a laser-based ultrasonic technique to measure paper's mechanical properties non-destructively while it is on the paper-making machine or 'Web'. Laser ultrasonic is a non-contact and non-destructive method to analyze paper's mechanical properties. A short pulse of laser light less than micro second generates ultrasonic waves by either a thermal expansion or an ablation shockwave or both. The ultrasonic wave propagates along the paper sheet and is detected at known distance (several millimeters) using a non-contact interferometric technique. The time of flight of the

wave over the known distance gives the propagation velocity of the wave. The wave velocity is theoretically related to elastic properties, which is empirically related to strength properties.

ACOUSTIC MICROSCOPY

For imaging the variations of the mechanical properties of materials, acoustic microscopy is maturing into a very useful technology. Quantitative measurements are possible in the field of biological applications, material characterization and diagnostic medicines. There are several types of acoustic microscopy, which are as follows :

- (a) Scanning acoustic microscopy.
- (b) Scanning electron acoustic microscopy.
- (c) Scanning laser acoustic microscopy.
- (d) Near-field scanning acoustic microscopy.
- (e) Line focus beam acoustic microscopy.

Scanning acoustic microscopy is a reflection-imaging instrument, which images the surface and near surface variation of the mechanical properties of the sample. The major applications of scanning acoustic microscopy are in the examination of structural materials³. In scanning electron acoustic microscopy (SEAM), the focused electron beam generates acoustic signals by periodic or pulsed heating of a solid and acoustic signals are detected by piezoelectric transducers in contact with the solid, as shown in **Fig. 1**. The electron beam scans the surface of the solid and the transducer output is used to form a magnified scanned image. The sensitivity to semiconductor doping and its subsurface imaging capabilities make the technique useful in microelectronics. Resolution and depth probing on the micron scale are well suited to many integrated circuit devices. The other useful applications of SEAM are imaging grain structure in polycrystalline solids, imaging acoustic vibrational modes in plates, foils and wires imaging near surface and subsurface cracks. Scanning laser acoustic microscopy is a transmission-imaging

instrument which images the interior of samples by visualizing the shadow cast by material property variations in the path of the acoustic beam. This

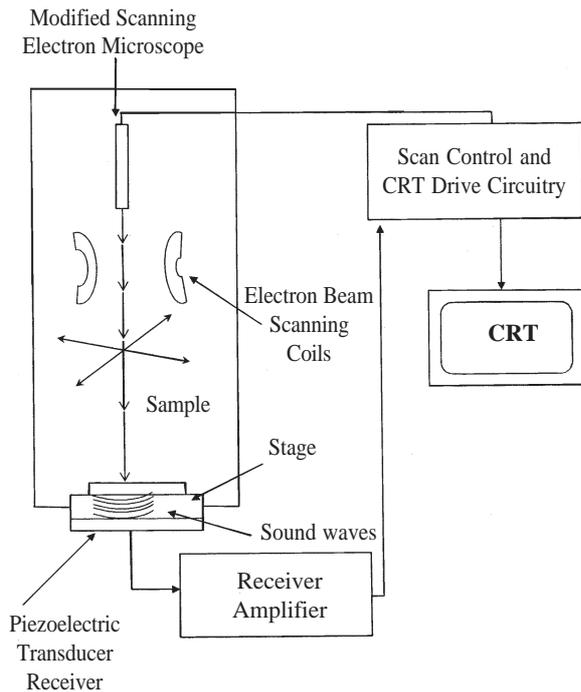


Fig. 1 : Scanning Electron Acoustic Microscope

provides a new capability for visualizing the structural characteristics of living tissues. The most popular industrial application of the scanning laser acoustic microscopy is bond evaluation. The scanning laser acoustic microscopy can distinguish between bonded and unbonded ribs and can measure the percentage of bond for partially bonded ribs as well. Scanning laser acoustic microscopy provides the means to visualize the grain structure, grain boundaries and impurities in the metal specimens. Photo-acoustic microscopy, scanning electron acoustic microscopy and scanning laser acoustic microscopy technique, theory of acoustic imaging, schematic diagram and their industrial application have been reviewed by few workers⁴. Some investigators⁵ have reported line focus beam acoustic microscopy and found these measurements be very accurate non-destructive. Near-field scanning acoustic microscopy can be either a reflection or a transmission-mode instrument. Transmission near-

field scanning acoustic microscopy is similar to scanning laser acoustic microscopy except that the sound field on the surface of a sample is detected with a tip or a pin hole that is much smaller than the wave length. The images obtained by the near-field scanning acoustic microscopy represent variations in the mechanical properties of the sample with a spatial resolution equal to the size of the pinhole or tip. Line focus beam acoustic microscopy is useful to study a material's propagation characteristics and these measurements have been found to be very speedy and accurate.

ULTRASONIC STIMULATED VIBRO-ACOUSTOGRAPHY

Palpation is routinely used for the evaluation of the mechanical properties of tissues in regions that are accessible to touch. These means of detecting pathology using the stiffness of the tissues are more than two millenia old. Even today, it is common for surgeons to feel lesions during surgery that have been missed by advanced imaging methods. Palpation is subjective and limited to individual experience and to the accessibility of the tissues to touch. It appears that some means of non-invasively imaging elastic modules may be useful to distinguish the tissues and pathologic processes based on a mechanical property such as elastic modulus. To this end, many approaches have been developed over the years. These have been used in conventional imaging methods to measure the mechanical response and mechanical stress of tissues. Static, quasi-static or cyclic stresses have been applied. The resulting stress has been measured using ultrasound and the related elastic moduli has been computed from visco-elastic models of tissue mechanics. A new ultrasonic technique has been developed that produces speckle-free images related to both tissues stiffness and reflectivity. The method, ultrasound stimulated vibro-acoustography^{6,7} uses ultrasound radiation pressure to produce sound vibration from a small region of the tissue that depends on the elastic

characteristics of the tissue. With this method, one can detect micro-calcification within breasts and this technique promises to provide high quality images of calcification within the arteries. This method may also be used in non-destructive evaluation and for underwater communication.

ACOUSTIC EMISSION

The emission of elastic waves, as a result of rapid release of strain energy caused by a structural alteration in solids, is called acoustic emission. In conventional engineering materials, acoustic emission has been correlated with various types of dislocation motions such as crack-growth, moving dislocations, slip, twinning, grain boundary sliding and fracture. Acoustic emission sources range from atomic size lattice defects to macroscopic size earth-quakes and rock burst in mines. Generally, an acoustic emission source behaves like a point source and radiates energy in the shape of spherical wavefront. Acoustic emission studies are extremely interesting and have great potential in the understanding of mechanical properties of solids. Practical applications of acoustic emission technique are in determining the approach to failure in large pressure vessels in the nuclear, aerospace, bridges, cranes, chemical industry, etc. The acoustic emission method has many distinct advantages over other non-destructing testing methods⁸.

SASER

The abbreviation of "Sound Amplification by Stimulated Emission of Radiation" is SASER. There are many types of laser devices generating coherent electromagnetic waves, but creation of an 'acoustic laser' *i.e.* SASER is of great interest because of a variety of potential applications of such devices. Some researches⁹ have reported about a SASER, which is made from a 5mm long rectangular crystal of ruby. The ruby block is kept into liquid helium bath to cool it to 3.8K to freeze out unwanted sound waves. When a laser beam is focused on the crystal, electrons on the chromium ions absorb the

light energy, jump to a higher energy level and then drop back to a lower level, giving out their excess energy as light. To create phonons rather than photons, a strong magnetic field is applied. When the field is switched on, the electrons absorb light but lose their energy in small steps rather than a single leap. These steps are too small to give a photon but just enough to create vibrations in the crystal lattice. These phonons travel the length of the crystal and reflect from the walls, making five or six passes in all. Each time, they whiz through the region where the laser light is focused, they stimulate excited electrons on the chromium ions to lose their energy and give out more phonons. This process is known as stimulated emission, which is the basic ingredient of the SASER. Some investigators¹⁰ have studied phonon emission due to transition in a two-level system well known in glasses. This SASER has a pair of tiny piezoelectric transducers mounted on opposite ends of a small block of glass just 2 cm. long. Recently some workers¹¹ have reported a resonant tendency in a double layer heterostructure designed in order to produce intense terahertz coherent phonons. This SASER is based on a quantum well, an artificial atom made from layers of semiconductors such as GaAs that can trap an electron in quantized energy levels. When an electron is injected into the well with a small voltage, it jumps between these energy levels, blasting out a stream of phonons at ultra high frequencies. Some¹² have reported the theory of sound SASER with consideration for coagulation. Their device is based on a cylindrical vessel filled with water containing thousands of tiny gas bubbles, which are produced by electrolysis. If these bubbles are squeezed by varying electric field, they will resonate. If a sound pulse is injected now, it will gather energy from the vibrating bubbles. Thus, finally a powerful, highly directional narrow beam of low frequency sound waves emerges from the end of the container, as shown in **Fig. 2**.

The applications of the SASER are many with immediate use in acoustic microscopes and sensors.

A tunable SASER could discover exactly how electrons vary their energy when a material heats up or cools down. This could reveal the inside story of things like heat dissipation, electrical

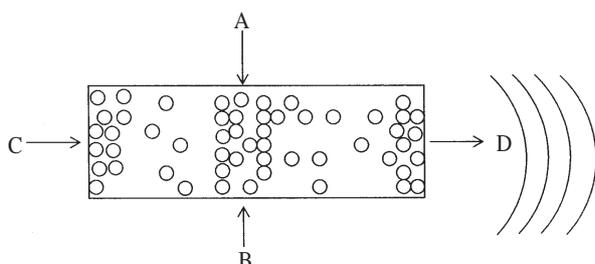


Fig. 2 : SASER (A. suspended tiny bubbles of gas, B. set of bubbles ringing, C. pass sound waves & D. sound waves emerge)

resistance and conductivity. The powerful and directional sources of sound could be used for tasks such as detonating explosives from afar, or as a weapon, to immobilize terrorists by stunning them with a blast of sound. The amplitude of the phonon beam can be easily modified.

MEDICAL ULTRASONICS

Ultrasound finds extensive applications in the medical field¹³⁻¹⁶. It has made an outstanding contribution in imaging and has become an indispensable tool in various specialities such as obstetrics, cardiology and internal medicine. At present, ultrasonics has brought about a revolution in the medical sciences.

The use of ultrasound in the medical field can be divided in two major areas—the therapeutic and the diagnostic. The major difference between the two applications is in the ultrasonic power level at which the equipment operates. In therapeutic applications, the system operates at ultrasonic power levels of up to several watts/cm² while diagnostic equipment operates at power levels below 100 mW/cm². Therapeutic equipment is designed to agitate the tissue to the level where thermal heating occurs and has been found to be quite successful in its effects for the treatment of muscular ailments such as lumbago. Ultrasound has taken its

place along with X-rays and nuclear medicine as a diagnostic tool. Its main attraction in imaging lies in its non-invasive character and ability to distinguish interfaces between soft tissues. In contrast, X-rays only respond to atomic weight differences and often require injection of a denser contrast medium for visualization of non-bony tissues. Similarly, nuclear medicine techniques measure the selective uptake of radioactive isotopes in specific organs to produce information concerning organ function. Radioactive isotopes and X-rays are clearly invasive. Ultrasound is not only non-invasive, externally applied and non-traumatic but also apparently safe at the acoustical intensities and duty cycles presently used in diagnostic equipment. The main limitation of ultrasound, however, is that it is almost completely reflected at boundaries with a gas which is a serious restriction in investigation of and through gas-containing structures. The frequency shift caused by the reflection of sound from moving objects (Acoustic Doppler effect) is used to image flow in medicine. Blood flow in vessels can be imaged within the body in real time without the use of radioactive tracers.¹⁷

Ultrasound through tissue medium :

Density and compressibility fluctuations in a tissue medium act as the scattering centers for an incoming ultrasound wave. As a result of this scattering, the scattered wave carries a significant amount of information about the tissue medium. Thus, in principle, it is possible to characterize the tissue medium by analyzing the scattered component of the wave, in particular the back scattering component¹⁸. Due to the non-invasive nature, ultrasonic medical imaging currently draws attention from scientific community worldwide, although it suffers inherently from poor resolution. However, with the developments in transducer technology, it is possible today to investigate the velocity and attenuation of ultrasound propagating through tissue media with greater details useful for pathological

interpretation. It is, generally, observed that the pressure amplitude as launched by transducer falls off exponentially with distance and attenuation becomes frequency dependent¹⁹.

Ultrasonic lithotripsy :

An acoustic lithotripter is a device for destroying stones in the kidney or gallbladder by focused ultrasound of very high amplitude. Extra-corporeal shock lithotripters²⁰ generate pulses in water in which peak positive pressures extend up about 100 MPa and peak negative pressures to 10 MPa. These pulses are less than a microsecond in duration. In clinical practices, they are delivered at pulse repetition frequencies up to 40 Hz. A single pulse may contain only a half cycle, or several cycles ; taking the frequency to be the rate at which zero crossing occurs, this varies from 150 kHz to 700 kHz. In a surgical procedure for destroying kidney stones, it is typical to apply 1000 shocks or more. This has become a very popular method of treatment. A special advantage of focused high intensity ultrasound signals is that deep-seated diseased tissues like tumours can be accurately destroyed in the body without damaging the surrounding tissues between the surface and the lesion²¹.

Medical diagnosis :

Acoustic sonograms have become an important medical diagnostic tool, which is widely used now a days^{22, 23}. An acoustic wave propagates easily through biological tissues. The scatterings from the discontinuities in the system are detected by the receiver as in SONAR. Knowledge of the velocities and attenuation in the various tissues then enable one to have an acoustical image inside of the human body, for instance, the abdomen. Several imaging processes are used to get additional information. It is becoming a common practice for pregnant women to have a sonogram of the baby to be sure that all is well. The eye and the heart are also studied under some conditions using these techniques. Tumours, cysts, abscesses and

any other disorders can be recognized in many organs.

With the increasing demand for rapid and more accurate ultrasound diagnosis, it is important that the ultrasound systems deliver high quality and reliable images and with minimal effort. For high quality imaging, transducers with multi-directional focusing allow unparalleled image resolution and clarity. These transducers enable us to achieve exceptional special resolution throughout the depth of the field with fine control of the beam pattern. Also, as compared to the conventional ultrasound systems using multiplexing techniques in array transducers, each transducer element has its own dedicated channel, thus contributing to the formation of an individual pixel in the image, and, therefore, providing a high signal to noise ratio. Digital technology has greatly helped to improve the image quality. With the availability of high-speed data converters, analog processing of the signals is minimized. With the development of high frequency transducers and electronics, an era of micron imaging has opened up²⁴.

Ultrasonic imaging and therapy :

Ultrasonic imaging and therapy of the brain using concepts derived from time reversal mirrors, a technique is developed for focusing ultrasonic waves through the cranial wall, permitting to obtain focal spots as delicate as in the absence of the skull. This research aims to develop ultrasonic imaging of the brain and a system, which will destroy brain tumours by 'hyperthermia'. This technique takes an ultra fast ultrasonic imaging system which captures several thousand ultrasonic speckle images per second. An 'Ultrasonic Pistol', which will measure the rheologic properties of soft materials, is under development.²⁵

CONCLUSIONS

From the above discussion, one can, undoubtedly, say that ultrasound finds extensive

applications in different aspects of modern life. The latest developments have greatly increased the interest in ultrasonics and have made the subject to be an active one. The study of ultrasonics, at present, extends an unlimited field of activity for investigators and it opens up immense opportunities for their applications.

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TWINNING AND TWINS

A. B. Das Chaudhuri*

Methodologically twins render valuable service to the science of human genetics. Researches on twins in India done by the scientists of different disciplines appear to be still in a formative period. In this paper the biology of twins is briefly described along with relevant twin researches in India ; moreover, researches in our laboratory conducted in the area of twins specially related to human genetics are presented. Interdisciplinary researches on various problems of twins are required and the knowledge thus achieved could be used for the development of human genetics and biomedical sciences.

INTRODUCTION

Although research investigations have continued in different branches of biological sciences in the area of twin studies, the issue is yet to be resolved convincingly so that it may open new vistas in development of human genetics and biomedical sciences in India. An attempt has been made in this paper to assess the extent of researches on twins in India including works in our laboratory.

OCCURRENCE OF TWIN BIRTHS, ETIOLOGY, ESTIMATION AND ETHNIC DIFFERENCE OF TWINNING AND ZYGOSITY DIAGNOSIS OF TWINS

The interest and curiosity involving twins may be found in ancient mythology where twins were considered to be supernatural. The commoner has the notion that the twin birth is an accidental and rare phenomenon. In reality it follows a quantitative rhythm which recurs worldwide among all groups of populations. It is, therefore, not an accidental phenomenon but is determined by certain laws governing generation in human species. The use of twins as a research tool in service of man was first proposed by Sir Francis Galton with a great

foresight in the second half of the nineteenth century.

Regarding occurrence of multiple births in human species Hellin put forward a mathematical proposition which is now known as Hellin's Law. According to this law in human species an average number of one twin birth is found in every 89 single births, one triplet birth in every 89² single births and so on. Thus, within the limits of probability, one X multiple birth would be seen in every 89^(x-1) single births.

It is now known and generally accepted that identical/monozygotic (MZ) twins are derived from a single fertilized egg whereas non-identical/dizygotic (DZ) twins developed from fertilization of double eggs by double sperms separately. The two members of MZ twin pair will be always of same sex i.e., male-male or female-female. On the other hand, two members of DZ twin pair may be male-male, female-female or male-female.

For estimation of proportion of MZ and DZ twins in a population a statistical method was developed by Weinberg¹. In a population in which secondary sex ratio is 1 : 1, DZ twins of ♂♂; ♂♀ and ♀♀... types should occur according to

♂ = Male, ♀ = Female

* Human Genetics Laboratory, Department of Anthropology, University of Calcutta. 35 Ballygunge Circular Road, Kolkata-700019. e-mail : adcanthro@caluniv.ac.in

the chance frequencies $\frac{1}{4} : \frac{1}{2} : \frac{1}{4}$. This means that the number of same-sex DZ male and female twin pair $\frac{1}{4} + \frac{1}{4}$ would be same as that of opposite-sex twins, $\frac{1}{2}$ or the total number of DZ twins would be twice that of the observed number of opposite-sex twins. Therefore, the number of MZ twins is obtained simply by subtracting the number of dizygotics from the total number of all twins.

On a racial basis the declining rate of twinning from highest to lowest is found among Negroes, Caucasians (Whites) and Mongolians. The African tribe, Yorubas from Nigeria is reported to be having the highest average of one twin pair in 22 pregnancies. On the other extreme, the Japanese average only one pair in about 160 births and even lower rates have been reported for other Mongoloid groups.

The most important aspect of use of twin method of study in human genetics is to diagnose the zygosity of twins, i.e., whether they are MZ or DZ twins. Therefore, classifying a set of twins according to zygosity is a prior task before using them in human genetical research work. The uniqueness of twin study in human genetics is that it offers to determine the relative role of heredity and environment and their interactions in respect of qualitative and quantitative traits of man which may be morpho-metrical, physiological, biochemical and behavioural in nature. The identical or MZ twins with the vital function of their genotypes remain similar or concordant throughout their lives, even in widely different environments. Methodologically, therefore, twins render valuable service to the science of human genetics.

The reliability of determination of zygosity of twins improved gradually by using efficient methods viz. :

1. Fetal membrane method
2. Similarity method
3. Weinberg's differential rule

4. Mailed questionnaire
5. Genetic markers, and
6. DNA finger printing.

In fetal membrane method, the physicians have frequently tried to judge whether a twin birth is MZ or DZ by means of analysis of the *afterbirth of twins* i.e., amnion, chorion (germinal discs of the fetus) and placenta (germinal disc attached to the uterus by placenta). All twins enclosed in a single chorion are indeed sure test of monozygosity.

Earlier, in most twin studies the similarity method of diagnosis was based on a multitude of traits. Concordance or similarity and discordance or dissimilarity of hair and facial traits were usually considered in similarity method for zygosity diagnosis of a member of a twin pair.

The Weinberg's differential rule is already described in the text earlier. In this method individual twin pair is not subjected to zygosity diagnosis but MZ and DZ twin pairs are statistically estimated from total twin population.

Psychologists developed this twin zygosity method by mailed questionnaire. In this method a set of well designed seventeen questions (approximately) are mailed to parents of twins or adult twin pairs and are asked to fill up the questionnaire. By scoring the rating of concordance or discordance of question answers the pairs were diagnosed as MZ or DZ twins.

In the method of twin zygosity by genetic markers, single locus traits such as blood groups, red-cell enzyme systems, serum proteins, etc. which follow Mendelian inheritance are taken into consideration. Concordance in respect to number of genetic markers increases the probability of twin pair being monozygotic whereas single difference in any system immediately recorded the pair under study as dizygotic twins.

In the method of twin zygosity by DNA finger printing, DNA analysis with multilocus minisatellite DNA probes has been used for zygosity

determination of twins. The international status of research in use of microsatellites in zygosity diagnosis of a twin pair is most reliable and dependable since its efficiency is claimed to be at 99.97% level of probability.

BRIEF DESCRIPTION OF TWIN RESEARCH IN INDIA

A recent exhaustive review on Twin Research in India², covering most of the works available from the existing literature, clearly showed that scientific workers explored twin study in India mainly on the following lines (a) twinning rate, (b) maternal age and twinning, (c) mortality rate in twins and (d) zygosity determination of twins and estimation of role of heredity and environment in respect of particular trait.

On the basis of an arbitrary sample size of 3000 births covering various regions of India, the reported rates fluctuate between 2.7 per thousand in Ludhiana (Punjab) and 21.8 per thousand in Srinagar (Jammu and Kashmir). The MZ twinning rate varies between 1.42 per thousand in Mysore (Karnataka) and 7.90 per thousand in Lucknow (Uttar Pradesh) whereas DZ twinning rate varies between 2.94 per thousand in Howrah (West Bengal) and 13.8 per thousand in Nagpur (Maharashtra).

The effect of maternal age on twinning was investigated by a number of workers. The maximum incidence of twinning in the age groups 35-44, 25-34 and 15-24 years was found to be 62.4%, 59.9% and 37.5% respectively. Guha observed higher trend of twinning rate with advancing age of the mother. The gradual increase of twinning rate from the age group 30-34 years and upwards is due to increase of DZ twinning whereas MZ twinning rate did not show a clear trend of increase or decrease.

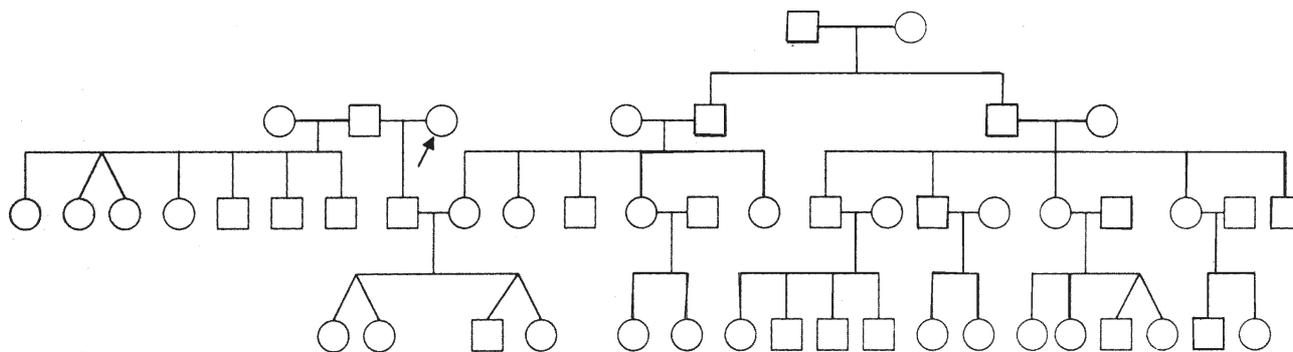
The literature on perinatal mortality rate of twins available in India show a wide variation ranging from 0.104 to 0.344 (Trivedi and Matashaw⁴ and Srivastava et al.⁵).

The first attempt to estimate twin zygosity using Weinberg's differential rule was made by Sarkar⁶ in the All India Survey. The proportion of MZ and DZ twins in percentages in differential racial and genetic heterogeneity of Indian populations was found to be 34.5 : 63.6. Further works with same method were done by Goswami and Wagh⁷ in Madhya Pradesh and Guha³ in West Bengal. Srivastava et al.⁵ and Sharma⁸ made efforts to determine zygosity of twins in precise way with the help of both morphological traits such as somatoscopy, somatometry, dermatoglyphics, pattern of placentation etc. and genetic traits such as PTC taste sensitivity, secretor factors, blood grouping, colour blindness, G6PD etc. It was Sharma⁹ who for the first time used adequate number of standard genetic markers such as A₁A₂BO, CcDEe, MN, Kell, Duffy, ABH secretor factor etc. for proper diagnosis of 48 pairs of Punjabi twins in Chandigarh. The relative contributions of genetic and environmental components in the variability of lung function variables were determined based on 54 pairs of zygosity diagnosed Bengalee twins with blood types (ABO, Rh, MN), finger prints, physical appearances and parental history¹⁰.

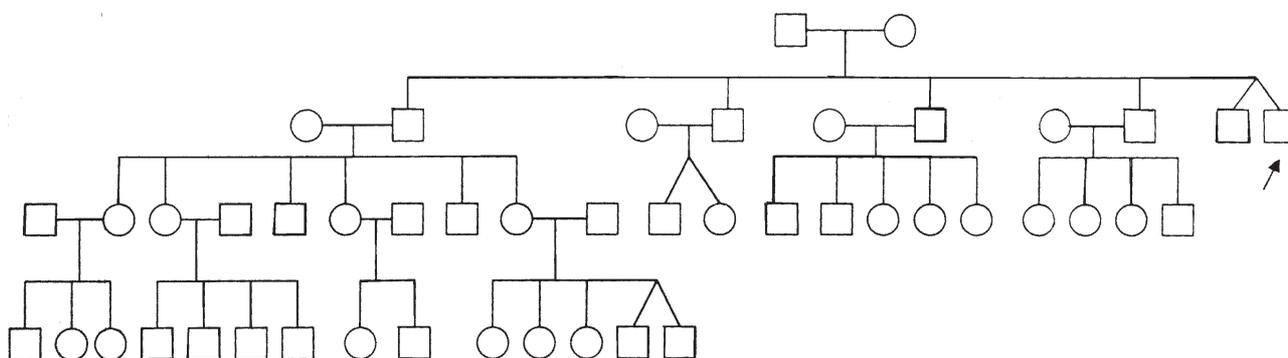
TWIN RESEARCH CONDUCTED BY THE AUTHOR AND COWORKERS ; ITS IMPLICATION IN HUMAN GENETICS

An attempt has been made to throw some light on the question of hereditary nature of twinning with Bengalee twin materials. For the purpose 77 pedigrees, each with four generations, were collected from rural Bengalee population inhabiting villages surrounding Habra township in North 24 Parganas district, West Bengal. The incidence of occurrence of twins was first detected in a particular family and then considering twins as proband the pedigree was constructed upto four generations. Two important pedigrees are presented in Appendix-1. The occurrence of twins in the generations of pedigrees is due to genetic factors.

APPENDIX-I



Pedigree 1. (i) With one pair of twins both females.
 (ii) With another wife, son has two pairs of twins one same sexed females and the other unlike sex.
 (iii) Two pairs of twins in a family.
 [NB : □ = Male, ○ = Female, ↗ = Proband]



Pedigree 7. Twinning in families in successive generations.
 (i) With one pair of twins both females.
 (ii) With another wife, son has two pairs of twins one same sexed females and the other unlike sex.
 (iii) Two pairs of twins in a family.
 [NB : □ = Male, ○ = Female, ↗ = Proband]

It can be deduced that twinning is familial trait which fits the hypothesis of genetic control¹¹.

In our laboratory data on hair variables such as incidence of medulla, diameter, area of cross-section and weight were collected from 48 pairs of zygosity diagnosed German twins with 11 genetic markers. With some limitations heritability or h^2 statistic has been estimated using formula $h^2 = \frac{bDZ^2 - \sigma Mz^2}{\sigma Dz^2}$. Here h^2 is the proportion of variability in twins attributable to

genetic variation and σDz^2 and σMz^2 are the intrapair variances of the DZ and MZ twin pairs respectively. The incidence of medullary structure, diameter, area of cross-section and weight of hair heritabilities have been found to be 0.96, 0.92, 0.87 and 0.59 respectively¹². Further, heritabilities of some important parameters of antioxidant defense system like glucose-6-phosphate dehydrogenase (0.93), catalase (0.72), glutathione peroxidase (0.60) and lipid peroxidation (0.50) are estimated in red blood cells by twin study.

As mentioned earlier, in human genetics zygosity diagnosis of MZ and DZ twins using blood groups and other genetic markers is prior task in order to determine the relative role of heredity and environment and their interactions with respect to any trait in man. Significant contribution has been made on the methodology for diagnosis of twin zygosity by pointing out that the indiscriminate use of several conventional genetic markers in determination of zygosity of twins from a particular population should be discontinued. This is because efficient sequential search procedure for twin diagnosis utilizing frequency of genetic markers in a population has been developed in our laboratory and demonstrated in the German population. Efficient genetic markers have to be selected considering the gene frequencies in the population concerned. Moreover, large number of genetic markers must usually be investigated because of low mean heterozygosity of proteins and antigen. It is hoped that this method will be helpful in the efficient application of genetic markers to zygosity determination in any population. The formulae developed are quite general and procedure explained can easily be generalized to other situation¹³.

Assuming twinning as a recessive trait the higher incidence of twinning rate in the Bengalee Muslim population than in the Bengalee Hindu population is attributed to inbreeding¹⁴. The Bengalee Muslim population practise consanguineous marriage leading to inbreeding where the triat concerning recessive genes escalates.

Zygosity of 15 pairs of Bengalee twins was diagnosed using genetic markers like ABO, Rh, MN, Hp and PTC in our laboratory. Of these MZ and DZ twins were found to be 7 and 8 pairs respectively. The zygosity diagnosed set of twins were utilized to investigate the genetic influence in determining the effect of cadmium on glutathione content of red blood corpuscles. The results clearly show that genetic endowment is an important determinant of reduction in glutathione content of

human red blood corpuscles after treatment with toxic element, cadmium¹⁵.

CONCLUSION

Noting the absence of any nationwide Register for twin birth, it appears that accurate assessing of rates in the diversity of social and biological background in populations in India is nearly impossible and attempts to estimate them might lead to confusion. On the other hand, the variation in twinning frequencies in different populations of India offers a unique opportunity to investigate factors responsible for this variation. In Indian population, besides considering well known factors such as birth order, maternal age, etc. affecting multiple births specially of twins, the role of socio-economic, rural-urban differences and inbreeding effect (like in Muslim community) affecting twinning rates may well be examined. It appears that an active centre involving twin research is a dire need in a country like India. In the last decade the development of molcular technique and its applications in biology have opened new avenues of research previously unavailable. Emphasis should be given on molecular technique specially use of microsattellites for determination of twin zygosity. These diagnosed sets of twins could be utilized for multiple purpose in researches on human genetical problems.

It appears that research on twins is not considered seriously as it ought to be among the scientific workers of different disciplines in India. Fortunately, importance of twin research is now realized. What is needed most in the Indian context is interdisciplinary work on various problems of twin study so that knowledge achieved therefrom can be utilized not only for benefit and welfare of twins but also for development of human genetics and biomedical science in general.

ACKNOWLEDGEMENT

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DO YOU KNOW ?

- Q7. Which thing lives for 17 years but is active only for 5 weeks, spending the rest of its life sleeping ?
- Q8. A normal human needs about 3300 cal/day for his daily survival. How much does a full grown crocodile need ?

SOMETHING TO THINK ABOUT

STORING EXCESS CO₂ UNDERGROUND

Prof. H.S. Ray

Nuclear wastes need to be stored in special containers to avoid contamination of the environment which will be lethal. It may be time to seriously devise CO₂ storage schemes too because vast amounts of CO₂ coming out of gasoline driven vehicles and thermal power plants are now well beyond the assimilative capacity of nature.

CO₂ level is rising in the atmosphere at a rate of about 2 molecules per million. A recent article published in Scientific American, (July 2005, p 49) says that when William Shakespeare took a breath, his lungs received 280 molecules of CO₂ per million molecules of atmosphere. Now he would breath in 380 molecules.

CO₂ emitted by vehicles is scattered and therefore, it posed difficulties of collection and storage but that from thermal power plants through chimneys should be more amenable for storage. A medium size car going 10,000 miles consuming 1 ton of gasoline will release about 3 ton of CO₂ out of the tail pipes. A large (1000 mega watt) coal fired thermal power plant would produce some 6 million tones of CO₂ annually, roughly equivalent to 2 million cars. Today some 25 percent of total world wide CO₂ emission is due to thermal power plants equivalent to 1000 big plants. The number is expected to double in the next decade. India and China will be main contributors to enhanced CO₂ emission.

The consequences of this CO₂ in the atmosphere will be global warming, gradual increase of sea level, CO₂ absorption in the sea acidifying the water etc. Consequences of these changes may be

devastating. In the past there was an equilibrium in the CO₂ cycle where CO₂ was absorbed in sea, where it went in skeletons of sea animals, and by plants on land which produced CO₂ absorbing carbon to grow. However, there is not enough green cover now and photosynthesis being a slow process, there is just not enough land mass to grow all the excess CO₂ in the atmosphere. One theory says that global warming will bring in climate change and melting of polar ice and warming of the northern areas of the globe will create new green cover to restore ecological balance. This, however will destroy the civilization that we have now. There will be catastrophic changes unless we develop new technologies with priority to store the excess CO₂ being emitted to air.

At the same time mankind has to concentrate on energy more efficiently and substituting noncarbon, renewable or nuclear energy sources rather than fossil fuels (coal, oil and natural gas) which are primary sources of man made atmospheric CO₂.

The strategy that is recommended for battling the CO₂ menace in the first phase envisages capture of CO₂ emissions from power plants and subsequent injection into geological underground formations for long term storage. This is contributing significantly towards slowing down the rise of CO₂ concentrations in the atmosphere.

There are essentially three kinds of power plants. The traditional plants burn coal fully in one step in air, converts water to system at high pressure that turns a turbine to generate electricity. In the improved process, coal gasification is done in

steps, the first, burns coal partially in presence of oxygen to produce a synthetic gas, 'syngas' containing hydrogen and CO₂. It then removes sulphur and burns Syngas in air in gas turbine. In the third kind under development, only oxygen is used.

The CO₂ emission from these plants first needs a treatment for sulphur removal after which the gas can be injected into a solution of brine in sand in a geological formation deep down in a way that this will not affect the aquifer. The layer targeted is salt-water formation more that 2 km below the surface in sedimentary rock. At such depth, because of the pressure that is many times the atmospheric

pressure, CO₂ will go into a 'super critical-phase' one that is nearly as dense as the brine it replaces in the geological formation.

Other schemes envisaged include storage in depleted oil and gas reservoirs, in coal seams, in minerals (e.g. serpentine) that form stable carbonates and, of course, will be more controversial because nobody is sure whether this CO₂ will go into the bodies of animals more efficiently or whether it will be counter productive.

What is no longer debatable is that something needs to be done on a massive scale when mankind is still fit enough to think, plan and act.

ANSWERS TO "DO YOU KNOW?"

- A1. In planet Neptune.
- A2. 21 years.
- A3. Ante Meridiem.
- A4. Louise Brown.
- A5. About 220 feet.
- A6. The python.
- A7. A type of Grasshopper called Cicada.
- A8. Only about 200 cal/day.

SHORT COMMUNICATION

HIGH SPEED KNOCKOUT IN THE BRAIN

D. Balasubramanian*

Every time we think of the brain we are filled with wonder. It is an exquisitely made organ, neatly packed and protected by a sturdy and robust skull within which it sits packaged in a skin that allows things to enter and exit in a selective and planned manner. The more we learn about it, the more it defies easy categorisation. It is also the bugbear of reductionists, people who like to say things like “the heart is nothing but a pump”, “the kidney is nothing but a filter” or, more to the point, “the brain is nothing but a computer”. The answer, of course, is that it is and it is not. The mechanisms of operation can turn out to be fundamentally different. The acquisition of information, addressing and storing it and recall are only formally similar but the way some of these are handled by the brain and by the computer are different indeed.

Yet, what draws people to make such “nothing but” statements ? I believe it is this formal similarity, or a study of only a part of the whole, which leads to this—quite like the famous case of the six blindfolded people where, each in his own way, was describing the elephant by feeling but one part of it. The brain operates on the basis of measured transport of specific chemical substances across cells and the consequent triggering of electrical signals. Basic perception in the brain and in the central nervous system itself, uses both these modes. When you feel something, it is a

consequence of these primary events. Neurophysiology describes the actual way the nerve cells are arranged and connected for their function. Neurochemistry discusses the chemical aspects of the matter while electrophysiology attempts to provide the details of the electrical activities of these cells and tissues.

Here too, an understanding to the brain is attempted at two levels ; one at the molecular, cellular and tissue level which is what much of today's molecular and cell biologists do. The other level is to approach it as a whole system in its complexity and analyze it, the way a systems engineer or a computer hardware person does.

The molecular and cellular level approach is the bottom-up approach while the systems approach is top-down. It is clear that the two approaches complement one another and that a total understanding will come about only when we combine the two. Today, we are yet to understand in detail individual processes and responses in the brain, such as what causes pleasure, what causes pain, or what the detailed steps are when we react or respond to a stimulus. The molecular biologist would say that since many of these are hardwired and genetically determined through genes and the DNA molecule, it is worthwhile to identify the actual chemical molecules involved and the biological steps that lead to some of these aspects of brain function.

We seem to be doing a lot of things by instinct, many through experience and quite a few by learning from examples. Some of the tastes that we

* L. V. Prasad Eye Institute, LV Prasad Marg, Banjara Hills, Hyderabad 500034, e-mail : dbala@lubly:itph.net. Article published earlier in The Hindu, Reproduced with permission.

acquire or experiences that we enjoy are really that—acquired, meaning that we learn to derive pleasure or enjoyment even from substance or stimuli that are not necessarily immediately acceptable. The use of mood-altering drugs for enjoyment is one such. Likewise, to enjoy alcohol is to acquire a taste for it, by first overcoming the initial negative response. Tobacco chewing or smoking is another such example. The first reaction is of distaste or even pain. It is the aftertaste when the nicotine hits the brain cells that the tobacco user starts to enjoy.

PLEASURE CENTRES

What are these pleasure centres or pain centres in the brain? On the anatomical or large-scale level physiologists have identified zones, regions or parts of the brain which are largely concerned with feeling, response, activity or the other. Hence, it is said that one hemisphere is the intellectual part while the other hemisphere is the aesthetic part. The processing of signals that reaches from the eye to the brain occurs in the visual cortex and the final result is the perceiving of the object.

One can go further down into the cell and molecular level. Specific molecules and substances are used to tickle the pleasure centres in our brain. This is something that mankind has known since the dawn of civilization. Hemp or *bhang*, *charas* or *cannabis*, as they are called, have been known in Hindu mythology. Persian and Arabic scholars have written about it. Shaik Tafar Shirazi of Iran talks at length about them. The Maratha king Shivaji went a step further and used the tinctured hemp leaf in wine for his enjoyment. The betelnut is hallowed in Hindu, Parsi and Jain scriptures, Social grace demanded that the host offers his guests a few betel leaves and a couple of betel nuts. Likewise is a third narcotic substance which comes from calatropis, called akra or mandara (or *madar* as the Hindu physician Susruta called it). Legend has it that Emperor Akbar was so named as he was born under an Ak bush.

Then there was this wily custom recorded in colonial books about Indian Ayahs or nannies, who would feed a crying infant a bit of opium so that the child is comforted and goes to sleep. Cocaine comes from Latin America and is perhaps one of the most sought after drugs that soothes the tense mind and dulls one into a sense of relaxation, peace and satisfaction. Modern chemistry and medicine have given us molecules such as amphetamine which acts even faster than cocaine (hence the slang “speed” for this drug).

How do these psychoactive drugs act? We are learning more about it now and an important advance has been made by two groups of scientists working at the Duke University Medical Centre and in North Carolina University, both in the state of North Carolina in the US. Mark Wightman of the University of North Carolina and Marc Caron of the Duke University Medical Centre, along with three other associates, have published an interesting paper in the 15th February 1996 issue of *Nature* on this subject.

DAT'S THE WAY IT WORKS !

This group built on the already known fact that the cocaine-amphetamine class of antidepressants and drugs of abuse cross the blood-brain barrier and interact in the brain with a protein called the dopamine transporter or DAT. Dopamine is an important molecule that acts as a neurotransmitter; it is a chemical in the brain that modulates interaction between neurons or nerve cells. Its accumulation and transport across neurons is important, both in the control of limb movement and in the response to stimuli that offer pleasure or aversion. You can neither have too much of dopamine in a neuron nor too little of it; the level has to be regulated so that neuronal activity and brain response are appropriately controlled. This protein called DAT does precisely that. It is able to bind to dopamine and control the amount of available or free dopamine over a function of time and across the tissue. Too much of dopamine can

make you hyperactive while too little of it can result in uncoordinated movement of limbs. The North Carolina scientists argued that if we were to remove the dopamine transporter protein completely from the brain cells—would the brain then become hyperactive forever? The argument is that control in the level of dopamine would then be gone; this neurotransmitter would then not be carted off but would be available all the time and the individual would be on a constant “high”. To test this idea, they chose to work with the mouse as an experimental animal and resorted to a technology that is referred to as *gene knockout*. It was possible for them to breed mice which lack DAT by artificially disrupting the gene that produces DAT in the mouse. Lo and behold, these mutant mice which lacked the DAT protein were hyperactive, as if they were under the influence of cocaine or amphetamine all the time. In addition even when these mice were given doses of cocaine they showed no further response.

HELP FOR PARKINSON'S PATIENTS ?

There is an important corollary to this work; if one were to block DAT by specific chemicals and inhibitors, that could become an important pharmaceutical way to handle illnesses such as Parkinson's disease. In this illness, the effective levels of the neurotransmitter dopamine are significantly reduced compared to the normal individual. It is this lack of dopamine that lends a Parkinsonian to suffer from motor disability. Hence, this is why the patient is given the drug L-Dopa, which increases the levels of dopamine in the brain and CNS. The present research suggests the alternative, namely blocking the pathway by which dopamine is carried away from the neurons, or inhibiting DAT. The use of DAT inhibitors would thus have beneficial effects on Parkinson's patients.

Not only does this research point to specific regions of activity in the brain, namely where and how pleasure centres are activated, but it also has an immediate end use. Interestingly such an

experiment could not have been done with such elegance and ease until about ten years ago. It has been made possible thanks to *gene knockout* technology. What one does here is knock out or disrupt one particular gene and then study the effect or what happens in the whole animal. This is not a random or shotgun approach but a precise, molecular surgical one, addressing itself to a particular gene in the cells. In principle, a simple way to know the function of a single gene is to breed an animal lacking that particular gene and then look for the effects of this change on the anatomy or the physiology of the animal. In *gene knock-out* technology what one does is to choose not the adult animal cells but those from the early embryo of the animal, called the embryonic stem cells or the ES cells. One knocks out a gene in two steps. First, one makes a functionally disabled or a damaged copy of the gene under study and introduces it physically into the ES cells. What this defective gene would do when it is introduced into the ES is look for and home in on its healthy cousin, namely, the same gene inside the cell which is not disabled. This process of pairing-up of the two similar genes is referred to as *gene targeting*. The result of this doubling up is to also transfer the disability of the introduced gene into the “native” gene, which also gets disrupted. Note the surgical precision and specificity of this process. The knock-out gene looks for, recombines and disables this partner gene and none else. All the other genes in the cells remain unaltered.

Now comes the next step. Here, we pick up the genetically modified ES cells where the gene is disrupted, put them in the womb of a fertile mother animal and generate a live animal. The novel offspring thus born will be different from its parents only in a single gene. All other genes are identical. Thus, we have a specifically disabled gene and an animal with a precisely disabled trait. A sort of bottom-up approach, wherein the effect of a molecular change on the whole grown animal is studied.

KNOW THY INSTITUTIONS



INDIAN LAC RESEARCH INSTITUTE, NAMKUM, RANCHI

Lac, a natural resin, is a minor forest produce, cultivated and collected by tribals inhabiting the sub-hilly tracts of Jharkhand, Chattisgarh, West Bengal, Madhya Pradesh, Maharashtra, Orissa and Uttar Pradesh. Before the advent of synthetic plastics and resins, lac was invaluable in moulding and insulating industries. India, then under British rule, had an unparalleled global monopoly over the lac trade. Lac is used in paints and varnishes, adhesives, food and pharmaceuticals, cosmetics and ethnic jewellery, electrical and leather industries, besides lac dye.

Realising the strategic importance of this commodity, the then Imperial Govt. of India constituted the Lindsay-Harlow Committee in 1920,

to look into all aspects of the country's lac trade and its development. On the suggestions of this Committee, lac merchants organised the Indian Lac Association for Research, under the aegis of which, the foundation stone of the India Lac Research Institute (ILRI) was laid on 20 September, 1924, at Ranchi. It started functioning under the founder Director Mrs. Dorothy Noris. Subsequently, on the recommendations of the Royal Commission of Agriculture, the Indian Lac Cess Committee (ILCC) was constituted, which took over the reigns of the ILRI in 1931. The ILCC also organised and maintained liaison with London Shellac Research Bureau, UK and Shellac Research Bureau, Polytechnique Institute of Brooklyn, USA. As a result of reorganisation of

agricultural research and education within the country, the ICAR took over the administrative control of the ILRI from 1st April 1966. This Institute is thus, one of the oldest, within the ICAR system, having completed 80 years of fruitful service to the nation.

A Unique Institute

The ILRI is unique and only one of its kind in the world, being devoted exclusively to all aspects of lac cultivation, processing and utilisation. It follows a multidisciplinary approach in carrying out researches on beneficial insects (lac insects and predators / parasites of lac insect pests), forest based lac host trees as well as bushy / shrub hosts, for a wide range of target beneficiaries- from tribal farmers, craftsmen / artisans to high-tech industrial houses, for applications in surface coatings, fine chemicals, electrical insulation, etc. ILRI has the world's richest and oldest books and literature on lac, a well organised lac museum depicting all aspects of lac and a collection of a wide range of lac host plants.

Location and Agro-Climate

The Institute is located 9 km. South-east of Ranchi city, on the Ranchi-Jamshedpur highway (NH 33), at an altitude of 650m above mean sea level, 23°23' N latitude and 85°23' E longitude. The soil status of the Institute indicates advance weathering on granitic gneiss. The soil of the experimental farm is of lateritic type. The area experiences mild, salubrious climate, with a rather heavy rainfall pattern of about 1,400 mm average, of which, about 1,250 mm is during the monsoon.

Mandate

ILRI is a nodal Institute at national level, for research and development on all aspects of lac production, processing, product development, training, information repository, technology dissemination and national/international

cooperation. It is mandated to :

- Develop lac culture technologies, adopting existing or genetically improved lac insects and hosts.
- Develop lac processing techniques for the industry.
- Conduct research for diversification of lac utilisation, leading to pilot plant demonstration.
- Act as a repository of information on lac production, processing and utilisation.
- Transfer technologies to farmers and entrepreneurs.

Organisational Structure

Headed by a Director, the Institute has three Research Divisions viz. (i) Lac Production, (ii) Lac Processing and Product Development and (iii) Transfer of Technology. The Divisions address their identified mandates through core programmes. Presently, the entire research programme of the Institute is divided into 6 thematic areas, called Core Programme, listed below :

Core Programmes

1. Productivity and Quality Improvement
2. Production Improvement and Crop Management
3. Processing and Value Addition
4. Product Development and Use Diversification
5. Technology Assessment, Refinement and Dissemination
6. HRD for Capacity Building in Lac Production, Processing and Value Addition.

Infrastructure

Manned by a strong band of dedicated scientists

from various disciplines including entomology, organic chemistry, physics, engineering, biotechnology, etc., the Institute has about 207 staff in scientific, technical, administrative and supporting categories. There are several well-organised and equipped service sections to support research management of the Institute. Some of these Sections are : Administration, Audits & Accounts, Library, Farm, Estate, Dispensary, ARIS, Product Demonstration Unit, Guest House etc. The Institute is responsible for the collection and maintenance of germplasm of lac insect lines as well as lac host trees. Presently, the ILRI is maintaining 7 distinct strains of the lac insect, one cross, one in-bred line, as well as 9 insect stocks, collected from various parts of the country. The experimental farm area spread over 36 hectares has all conventional and cultivated lac host plants and the farm has 1,540 nos. host trees of *Schleichera oleosa* (*kusum*), 2,480 nos. trees of *Butea monosperma* (*palas*), 1,351 nos. *Zizyphus mauritiana* (*ber*) and 8,695 nos. of minor host trees. The field gene bank of the Institute has the following genotypes in stock : *palas* (13), *kusum* (4), *ber* (7), *Dalbergia szemaoensis* (2), *Eriolaena spectabilis* (1) and *Albizia saman* (2). The Institute has several prestigious laboratories, viz. High Voltage Laboratory, Bio-technology and Bio-control Laboratories, Quality Evaluation Laboratory etc. Besides these, the DTP and publication facilities are also available. A number of modern and sophisticated laboratory equipment, including DSC, FT-IR etc. are available for research on all aspects of lac production, processing and product development. The ILRI Library has holding of more than 50,000 volumes of scientific journals, 2,000 rare books, including back volumes of research periodicals in the field of lac and surface coatings. Since the holdings of back volumes of certain journals date back to *circa* 1760, the library has been catering to the documentary supply services of INSDOC, New Delhi. Besides catering

to the scientists and staff of the Institute, the library also attracts researchers of neighboring educational and research institutional, including BIT, RU, BAU and HARP, Ranchi, IIT, Kharagpur, RAU, Samastipur, PU, Patna, NIT, Jamshedpur etc. The Institute website, available at www.icar.org.in/ilri/default.htm, developed and maintained in-house, is a valuable source of information on ILRI as well as lac. The Quality Evaluation Laboratory of the Institute caters to the quality control needs of lac processing / lac product industries as well as exporters of lac / lac products. This QE lab analyses about 150 samples, on an average, per annum. The lab has facilities for carrying out testing of lac / lac products as per BIS requirements. Over the years, the Institute has consistently maintained close collaboration with other ICAR Institutes, State Agricultural and other Universities, and national agencies like Shellac Export Promotion Council (SEPC), Indian Council of Forestry Research and Education (ICFRE), Bureau of Indian Standards (BIS), Tribal Cooperative Marketing Development Federation (TRIFED), etc. A number of external projects, funded by agencies such as Department of Biotechnology, Technology Mission on Cotton, AP Cess Fund and Jharkhand State Government are concurrently operational at the Institute. The ILRI has responded to the globalization of lac industries and agricultural enterprises of the country as well as structural and functional reorganization of ICAR. The Institute also has undergone structural changes and the priorities redefined in the past to suit R & D needs of the times.

The Institute is confident of addressing challenging research needs on lac during 21st century.

Contact :

Indian Lac Research Institute, Namkum,
Ranchi-834010

Website : www.icar.org.in/ilri/default.htm

Conferences/Meetings/Symposia/Seminars

| Date | Topic | Contact |
|------------------------------------|--|---|
| 8-9 August 2006 | National Seminar on Organic Farming for Alleviation of Rural Poverty , Bangalore. | Kantharaja Secretary Association for Promotion of Organic Farming (APOF) APOF, UAS Alumni Association Building, Bellary Road Hebbal, Bangalore-24 Email : aproganic@yahoo.com |
| 18-19 August 2006 | Emerging Principles & Practices of Computer Information Technology Ludhiana | Dr. S.B. Singh Guru Nanak Dev Science and Engineering College, Gill Park Ludhiana 141006 Email : principal@gndec.ac.in |
| 23-25 September 2006 | Algal Biodiversity and its Role in Bioremediation Chennai | Dr. Sivasubramanian Krishnamurthy Institute of Algology 9, Lady Madhavan I cross street Mahalingapuram, Chennai-600034 Email : vsivasubramanian@gmail.com |
| 9-11 October 2006 | International Conference on Toxicology, Toxicogenomics and Occupational health & 26th Annual meeting of Society of Toxicology, (STOX) Gwalior | Sangeeta Shukla School of Studies in Zoology Jiwaji University, Gwalior-474011 Email : rblstox26@rediffmail.com |
| 25-27 November 2006 | International Conference on Natural Hazards and Disasters : Local to Global Perspectives , Anantapur | Dr. Ravindra Reddy Department of Geography Sri Krishnadevaraya University Anantapur, Andhra Pradesh-515003 Email : ravikadati@yahoo.co.in |
| 30 November- 2 December 2006 | International Conference on Lasers and Nanomaterials Kolkata | Dr. Debnarayan Jana Convener (ICLAN) Department of Physics University of Calcutta 92, A P C Road, Kolkata-700009 Email : djphy@caluniv.ac.in |

S & T ACROSS THE WORLD

IDENTIFYING MICROBES

Scientists at the US Department of Energy's Brookhaven National Laboratory have developed a new method for identifying different species of microorganisms living in an unknown "microbial community."

The method has many applications ranging from assessing the microbes present in environmental samples and identifying species useful for cleaning up contamination, to identifying pathogens and distinguishing harmless bacteria from potential bioterror weapons.

The technique which is called "single point genome signature tagging" uses enzymes that recognize specific sequences in the genetic code. These enzymes chop the, microbial genomes into small segments that contain identifier genes common to all microbial species, plus enough genetic information to tell the microbes apart. As growing cultures of microbes to identify species is slow and error prone, scientists have been searching for a way to identify key segments in the genetic code that are short enough to be sequenced rapidly and they hit upon this method.

(www.bnl.gov, Mar 8, 2006)

ANTI-MALARIA DRUG DEVELOPS RESISTANCE

Malaria which used to decimate entire populations in the tropics, largely came to be controlled in the 1950's with the use of chloroquine till people began to develop resistance to it. It was replaced by artemisinin, which had been developed from a chinese herb and for the last few decades it has been widely in use. Studies now indicate that it might meet the same fate as chloroquine, unless its use is strictly regulated.

Scientists from the Pasteur Institute took blood samples from hundreds of patients in South-East Asia, and treated the samples containing the parasite *Plasmodium falsiparum* to a variety of anti malaria drugs, including artemisinin. The results were then compared with a similar exercise carried out in respect of malaria patients in French Guiana. It was found that the patients of French Guiana, where the use of artemisinin was not regulated, had developed resistance to the drug unlike those in Cambodia and other South-eastern countries where there was no resistance to the treatment, because the use of the drug was regulated.

These findings underscore a warning by WHO on the need for extreme all round vigilance while prescribing artemisinin-based drugs and for its use to be carefully regulated.

(PTI Science Service, Dec. 16-31, 2005)

ARTEMIS TECHNOLOGY

Many objects today have computers or microprocessors embedded in them that cannot be modified by the consumer. For instance, in the automobile industry embedded systems operate in the car engine to improve efficiency, operate satellite navigation, air conditioning etc. A whole industry has grown around these embedded systems and now the Advanced Research and Technology for Embedded Intelligence and Systems (ARTEMIS) provides a platform which brings together the major companies in this industry.

There are believed to be more objects containing embedded systems than there are human beings on the earth and by 2020 the capability exists for such embedded systems to occupy much of our natural environment and react to our preferences automatically. To make this a reality the gulf between architecture and physics will have to be bridged speedily and while ARTEMIS is seeking

to do this from the software side, the nano-technology platform ENIAC is trying to do the same thing from the nano-architecture side.

The embedded systems industry is growing at the rate of 10% annually, and ARTEMIS which is a public-private partnership that is open for any organisation to join has ambitious plans for the future.

(CORDIS Tech. Marketplace, March 8, 2006)

IMPROVED WHEAT STRAINS

Australian scientists are developing strains of wheat that contain a higher proportion of amylose, a particular form of resistant starch for incorporation into breads, cereals, and other foods to meet the deficiency caused by the excessive intake of processed and refined food by a majority of Australians.

Nowadays one of the most serious health issues in the developed world is the rise of diet-related

non-infectious diseases, such as cardiac heart disease, obesity, diabetes, and colorectal cancers. The resistant starch which contains high levels of amylose, is not digested in the small intestine and passes into the colon where it is broken down by the resident bacteria, releasing short chains of fatty acids which is believed to promote bowel health and reduce the risk of colon cancer.

The inclusion of additional fibre in breads is now a routine practice, but scientists say that the benefit of using high amylose wheat in products, such as bread, avoids the need to add supplementary fibre.

Trials on animals have shown that wheat with high amylose levels had significant health benefits, owing to the presence of short chain fatty acids in their bowels.

In this connection, gene technology has proved particularly useful in pinpointing the genetic changes in wheat that are required to create this new type of wheat.

(National Academy of Sciences, Feb 27, 2006)

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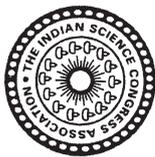
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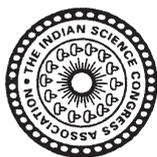
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1. All papers to be submitted for presentation at the 94th Science Congress must be sent to the **Concerned Sectional Presidents**. Each paper must be accompanied by *three copies* of abstracts (within 100 words, without any sketches, tables, etc.) and a copy of the full paper. The name of the Section where the paper is to be presented should be indicated. The model format for abstract is given below. The addresses of Sectional Presidents are given in the website : <http://www.sciencecongress.nic.in>
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