Foreword

"LIFE" WITH PHOTONS: Universal Health Care.

As of March 2020, the estimated world population stands at >7.775 billion [1]. Of this, the 35 OECD (Organization of Economic Development and Cooperation) "developed" countries all together have a total ~1.291 billion (16.6 % of total), more than 80% of which live in urban areas, with only about 6% of the remaining, in remote areas [2]. The rest of more than 6.4 billion people in the world are mostly in the developing countries. Of these, India alone accounts for 1.38 billion (17.7%), only ~32% of them in urban areas, 68% in rural areas [1].

An idea of the humongous disparity in human development between the two groups- OECD and the Rest of the world- can be seen in the "Human Development Index-HDI-" [3]. All the OECD countries belong to the "Very High HDI" group (HDI > 0.8, except Mexico & Turkey 0.77 & 0.79, respectively) while the "Developing and Underdeveloped" countries (including India) all have medium or low HDI (< 0.7). India, 129th in a list of 189, has an HDI = 0.65 only. One of the important parameters, perhaps the most important, defining HDI is "Access to quality health" [3]. The difference at birth, in life expectancy between low and very high human development countries, is 19 years; more than a quarter of a lifespan! Lost just because of your place of birth, a choice not made by you! Article 25 of the Universal Declaration of Human Rights states: "Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family--" (www.un.org/en/universal-declaration-human-rights).

One of the great anomalies in health-care services in countries like India is the fact that, the small fraction of urban population consisting mostly of employees of Public and Private Sector enterprises, are given complete, almost free, health care by their employers, the Government and Industries. *In other words, the health-care financial burden on the country at present is mostly due to health care given to the few million Public and Private Sector regular employees who can afford it even otherwise, while people at the lower end of economic and social status*, *without any regular employment, who need it most and who cannot afford it, are very poorly served.* This highly biased distribution of health-care services, combined with the huge disparity in income between urban and rural populations, have led to a situation in which routine health care has become almost unavailable and unaffordable for the bulk of the country's population.

Though a host of illnesses contribute to the health-care burden, it is well recognized that a major part of it is due to the "killer" diseases which may require prolonged therapies (because they are detected at advanced stages), and costly medicines, and which also cause considerable loss of man-power, even before detection, because of physical and mental incapacities inflicted on the victims by the diseases even under dormant/indolent conditions. It is also well-known that the "Killer" diseases, both non-communicable (Cardiovascular diseases, various types of cancer, diabetes, child malnutrition), and communicable (TB, Malaria, Diarrhoea), are all amenable to successful therapy if detected in earlier stages. **Cost-effective methods for screening and early detection of these diseases or their causative factors, which can be made easily available for universal applications, can obviously contribute to a considerable extent to reduction of the health-care burden.**

For the 70% of the rural population in developing countries like India, regular screening facilities, available only at multi-speciality hospitals in big towns and cities, are almost always unavailable and un-affordable, not only because of their high cost, but also because of the difficulties for the subjects to leave their home/work-place, for repeated screening. In addition to this, most of the rural poor are **unaware of the need for regular screening**. Even those who are aware, are **highly reluctant to undergo the current personally invasive screening programs**, like mammography, Trans-Vaginal Sonography, colposcopy, sigmoidoscopy etc., for screening and early detection of diseases like cancers of breast, ovarian, cervical, and colo-rectal,

which constitute some of the major killers. Similar situations arise in screening for coronary diseases, since methods like cardiac CT, Coronary CT Angiography (CTA), Myocardial Perfusion Imaging (MPI), etc., are not easily accessible for the rural population. For diagnosis of pre-diabetic and diabetic conditions, currently a few markers like HbA1c and glucose are available, but not affordable for regular screening for the rural poor.

The outcome of such deficiencies is a humongous indirect health-care burden on the country in terms of manpower, economy, societal well-being, and human welfare index. In an analysis of global burden of disease study [4], out of 188 countries worldwide, India was ranked as 143rd in health-related sustainable development goals Index.

Since the urban/upper class is readily available for regular screening, even if we can minimize their requirement through advanced technology, we can then divert some of the corresponding financial gains to the rural population of self- or poorly- employed daily wagers, farmers,etc., providing better universal health care.

In general, life expectancy has increased almost two-fold even in the under-developed countries [1,5] and in many of the diseases mentioned above this has lead to serious concerns about health-care. The best method to reduce the health-care burden is "Early Diagnosis"; that is, detect, locate, evaluate, and understand the disease process down to the cellular/molecular level.

The solution for the problem is thus, **provide Nation-wide access, on a Point-of-Care (POC)/ Location basis through small hospitals, health-care centers, and other public avenues, cost-effective, non- or minimally- invasive** screening technology,. That is**, accessibility and affordability has to be ensured, awareness has to be created and reluctance for regular screening has to be eliminated.**

In many disease conditions, especially in the killer diseases mentioned above, the progression of the disease from the early stage of "Induction" to the final stages of catastrophic conditions is controlled by several bio-molecular processes, which in turn change the bio-molecular scenario in the living systems, including changes in usually present molecular species, production of entire arrays of new bio-molecular species not usually observed in normal state etc. It is to be emphasized that the structures and functions of such "Marker" molecules will also vary during the successive stages of induction, progression, regression or recurrence of the disease, allowing staging of the disease and resultant better therapy modes, if detected.

It follows that the best method for Screening, Early detection, Staging, Therapy- Planning etc. is thus detection of the bio-molecular markers as early as possible, that is, as soon as they start appearing. The markers include, Transcription factors, DNA Re-modelling Enzymes, RNA Binding Proteins, Cellular Receptors and Associated Proteins, Enzymes etc. These markers can be detected not only at the origin of their production(**Cells, Tissue** sites, and various organs) where the disease starts, but also in other samples since they will enter the blood as soon as they are produced, and will be transported around. The **blood** (similarly other body fluids like saliva and urine) also thus provides a convenient detection medium since it can be sampled in a **minimally invasive** way and can be handled and transported easily, by standard procedures. Many of the new molecular marker species will also be transported through blood, from the different locations where they are produced, to the lungs finally. The volatile species among them, called Volatile Organic Compounds-VOCs- thus end up in exhaled breath. Detection of these **BREATH** markers, Breath Analysis, also provides a powerful, **totally non-invasive** tool for screening and early detection of diseases like various cancers (which remain clinically silent over long periods), TB, and even viral diseases, and conditions like malnutrition, neurological disorders etc., which usually remain unobserved for long periods until overt symptoms appear.

Molecular systems are uniquely characterized by their optical spectra and spectroscopic observation can therefore provide a highly reliable technique for detecting any molecular species with very high sensitivity,

down to even single molecule levels [6]. In the last few decades, with the availability of various kinds of lasers and other radiation sources like LEDs, and versatile detectors like CCDs, spectroscopic instrumentation have advanced tremendously, providing the answer for many analytical problems. Spectroscopy-based diagnostic instruments are cost effective, can be operated by technicians, and at present can be made highly compact with miniature lasers, so as to be portable/hand-held. The techniques can be easily adapted for *in vivo/in situ* observations or remote analysis, using equipments and methods which are highly cost-effective, can be taken around or installed at several places even in rural areas, are non/minimally invasive so that reluctance for their use is eliminated. They are thus ideal for field deployment, or rapid use in emergency situations. Further, the results are obtained from observed spectral data by statistical pattern analysis methods, and are thus highly objective. The observations can be carried out by any trained technician, without the need for highly qualified professionals, and results are given by effective data analysis methods like Artificial Intellegence and Machine learning.

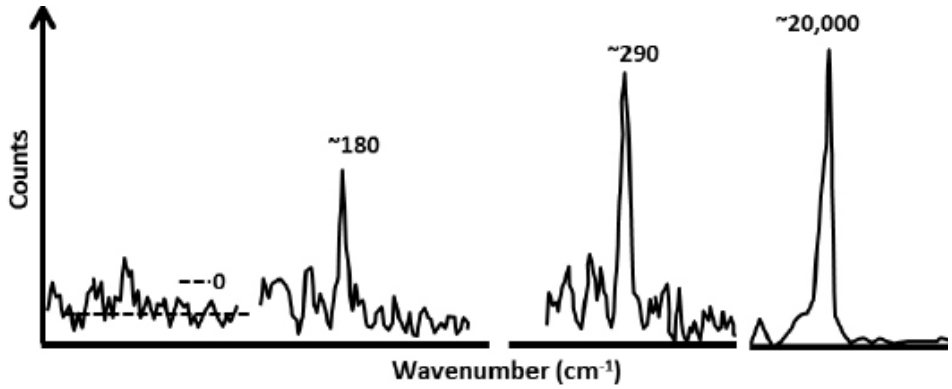


Fig 1. SERS Spectra Adenine: From left: Blank, 1, 2, and ~100 Molecules.The numbers on top of the 735 cm^{-1} band gives the signal in each case.

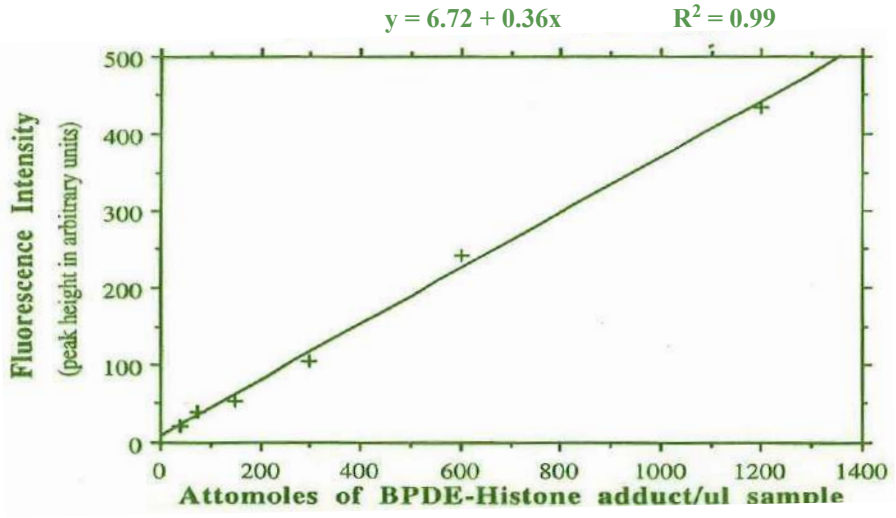
Biomedical spectroscopy can thus provide the answer to many of the Health-Care problems in developing countries, and light the path towards universal health care. There are several spectroscopic methods already well-established for various analytical applications. These include fluorescence, Raman scattering, absorption, reflection, and scattering [7]. Each of these spectral procedures have many variations. For example, in fluorescence we have multi-wavelength excitation, Fluorescence Life Time Spectroscopy, Super Resolution Radial Fluctuation (SRRF), Fluorescence Recovery After Photobleching (FRAP), Total Internal Reflection Fluorescence (TIRF) etc. Different Raman spectroscopy methods include conventional multi-wavelength Raman, Resonance Raman (RRS), Surface Enhanced Raman (SERS), Spatially Offset Raman (SORS), Tip Enhanced Raman (TERS); and in absorption, conventional absorption with tunable or super-radiant laser sources, Tunable Diode Laser Absorption (TDLAS), Photo thermal/Photo Acoustic (PAS) absorption, Cavity Ring Down Spectroscopy (CRDS) etc.

A few examples, described below, will illustrate the versatility and capabilities of various laser spectroscopic techniques. Conventional Raman is considered as a technique which can only be used with samples containing high concentrations of any given molecular species. But, as mentioned above SERS can increase the sensitivity several orders of magnitude. This is shown below for the biologically very important DNA component Adenine. The SERS spectra of Adenine –one, two and 100 molecules- are shown in Fig 1 [6].

It is seen that even a single molecule of a given species can be detected by this technique in a sample of few micro liters, making it ideal for samples like blood or breath. The Raman spectra can be recorded in a

few seconds, and examination of a large number of samples in a short time can be routine operation, making screening of many people at a single location in a day.

Similarly, Fluorescence, which is a million times stronger than Raman, can be easily used for ultra-trace detection. Current spectroscopy systems, including the laser radiation source, can be miniaturized and can provide a wide wavelength coverage for high selectivity for individual classes of molecules. They can be thus easily hyphenated with other high-efficiency separation methods, like HPLC (High Performance Liquid Chromatography) and GC (gas Chromatography) to analyse individual members in complex mixtures of bio-molecules like proteins (fluorescence) and nucleic acids (Raman), Hydrocarbon derivatives, etc. A typical result is shown in Fig 2, where a calibration curve for Benzo Pyrene adducts of histones in DNA is shown [8], for analysis of lung-brush biopsy samples, using HPLC-Laser Induced Fluorescence.



Benzopyrene-Histone Adduct-Attomoles

Fig 2. Calibration curve: HPLC-LIF Determination of Benzopyrene-Histone Adduct.

All these techniques can be easily adapted for observation of samples in "As is, Where is" manner:***in vivo*** diagnosis, endoscopic observations, environmental (for pathogens, pollutants) monitoring, pathology, and ***in situ-*** during surgical procedures. This is shown in Fig 3, where a portable system for screening in oral cancer (or diseases of organs accessible with an endoscopic procedure) is shown, together with a hand-held model of the same [9].

A **B** **C**

Fig 3. (A) Portable LIF/Raman System, (B). System in use; (C). Hand-held Model.

This issue of The *Asian Journal of Physics* contains Sixteen articles describing original research on applications of laser sources, like, Raman spectroscopy in therapy monitoring, photon transportation in tissue, dynamics of excited molecules, and other areas of lasers and laser applications, highly relevant to the role of **LIGHT for Universal Health-Care**.

Realising the potential of use of lasers and compact spectroscopic instrumentation in many medical applications, several international research groups had started research in this area from the early nineties. A few groups in India also had started investigations in this field around that time. Dr P K Gupta with his research group at RRCAT, Indore, was one of the pioneering groups in India, who started investigations in this area at that time.

Prior to starting his research on bio-medical applications of lasers, Dr. Gupta had worked extensively on development of new laser systems, dynamics of interaction of atoms and molecules with photons etc. [10,11]. With this background, he could develop path-breaking technologies in many areas of health-care, like early detection of various cancers by fluorescence and Raman spectroscopy, malaria diagnosis, optical imaging of organs by Optical Coherence Tomography etc. [12-18].

It is highly appropriate that, recognising the contributions of Dr P K. Gupta in the field of lasers and Bio-medical spectroscopy, The Asian J Phys, is dedicating this issue of the journal to him. I wish P K Gupta many more years of highly rewarding research in the field of lasers and their applications in universal health care.

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V Bhaskaran Kartha FNA;FNASc
bhasikartha@gmail.com

Dr V Bhaskaran Kartha took his M Sc (Chemisry) from Kerala University, Thiruvananthapuram in 1957 and joined the First Batch of The Atomic Energy Training School, Bombay. After graduating from the school he joined the Spectroscopy Section of the Analytical Chemistry Division, Atomic Energy Establishment, Trombay (AEET), now known as Bhabha Atomic Research Center –BARC. He started his research career with investigations on developing, standardizing, and validating spectroscopy techniques for trace and ultra-trace analysis of Nuclear materials. Following this he started research on molecular spectroscopy, using techniques like cryogenic spectroscopy, High-Pressure Raman, etc. He took his Ph D (Chemistry) from Bombay University in 1967.

In the years following, Dr Kartha worked on spectroscopy of supercooled atomic and molecular beams, electric discharges, laser excitation and relaxation in complex molecules, laser enhanced ionization, photo acoustic spectroscopy, optogalvanic spctroscopy, saturation spectroscopy, ultra-high resolution tunable diode laser spectroscopy etc. In the course of these studies he carried out the first molecular laser isotope separation in the country, demonstrating the feasibility of laser isotope separation. He also conceived, designed and initiated the installation of 3 spectroscopy beam lines at Indus I, India's first Synchrotron Radiation source.

During his tenure at BARC, Dr Kartha also worked as a Visiting Scintist at National Research Council of Canada, Ottawa, Chalmers University of Technology, Sweden, and NIST, Washington D C. In 1993, at the invitation of Prof M S Feld, Director, G R Harrison Spectroscopy Laboratory, MIT Cambridge, Dr Kartha joined MIT, where he worked for the next 4 years, in various areas of Biomedical spectroscopy. In 1997, at the invitation of Dr Ramdas Pai, President, Manipal Academy of Higher Education, Dr Kartha left MIT and joined MAHE, Manipal. Here he set up The Center for Laser Spectroscopy, for research in bio-medical applications of lasers and laser spectroscopy. Dr Kartha and his group at MAHE developed various spectroscopy methods (fluorescence, Raman, SERS, PAS, Protein Marker profiling) for screening and early detection, staging, therapy follow-up etc of various cancers (Breast, cervical, oral, bladder etc) and other diseases.

Dr Kartha is a recipient of "Prof Rangadhama Rao memorial Lecture Award" (INSA), "Prof S C Sirkar Memorial Lecture Award " (IACS),"Life-time Achievement Award" (Indian Society for Radiation and Photochemical. Sciences), "Prof Nandlal Singh Memorial Lecture Award" (Laser & Spectroscopy Society, India), and "Prof Sathyananadan Memorial Lecture Award" (Cochin University of Science & Technology). Dr Kartha is a Fellow of The Indian National Science Academy, The Indian Academy of Sciences, and Laser & Spectroscopy Society of India.