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Editorial



Ageing — Sunset Sign ?

Prof. (Dr.) Jyotirmoy Pal
MD, FRCP, FRCP, FICP, FACP,
WHO Fellow, Hon. Editor, JIMA

The world's population is rapidly ageing with a projection of proportion of aged people above 60 years doubling from 11% to 22% during the duration of 2000 to 2050. India is also in the phase of a demographic transition with the gradual increase in the elderly population from 20 million in 1951 to a staggering 57 million in 1991. It has been projected that by the year 2050, the number of elderly people will rise to about 324 million. India can thus be called "an ageing nation" with more than 7.7 percentage of its population being constituted by people more than 60 years of age.

Decrease in mortality rates more than the fertility rates due to availability of better healthcare has been attributed for this demographic transition.

Over the past few decades, India's health program and policies have focused more on issues like maternal and child health, disease control and population stabilisation without much emphasis on the elderly population. But, with the current trend of rising elderly population initiatives for the neglected population involving their social, medical and economic problems is in dire need.

Social and demographic profile of the elderly :

In India, most of the Elderly population is illiterate and dependent on physical labour- consisting mostly of men indicating increased mortality in females. The elderly female are mostly widowed and completely dependent on their families for their day to day needs.

Medical and social economic problems faced by the Elderly :

The elderly people in India suffer from both communicable as well as noncommunicable diseases, which is further complicated by the presence of impairment of special sensory functions like vision and hearing. They are also highly prone to mental disorders like dementia, due to ageing of the brain, problems due to ailing physical health, cerebral pathology, socio-economic factors such as breakdown of family support systems, and decrease in economic independence.

In the recent years, rapid evolution and societal modernisation has led to a further increase in the breakdown of family values and framework of family support, economic insecurity, social isolation and elderly abuse. Unavailability of social security and inadequate facilities of healthcare, rehabilitation and re-creations or the elderly population further aggravates the socio-economic problems.

Although the Centre and the State governments have formulated multiple policies to curb the problems of economic insecurity in the Elderly, the benefits of such policies have been questionable.

Ageing in Medieval Europe :

Throughout most of the middle ages, ageing and old age were conceptualised as a natural part of life, with distinct rules of how every individual were to cope with their problems. There was no collective provision for the aged as they were not considered as a distinct class or stratum but remained as a matter of personal concern.

The transformation of old age was gradually considered as a social phenomenon rather than an individual

event during the transition from the Medieval to modern times. This change arose as the transformation of the cultural, economic and social aspects in the European society occurred.

As the European society started being governed by the secular authority of the state instead of the agriculture based economy which was mainly governed by the local law- there was a shift away from the church to a much more democratic form of government. This change gave way to more critical appraisal of social relationships.

According to the Greek and Roman beliefs, the various divisions of life were not linked to specific ages. Thus, old age was not distinguished based on a specific age. The lifespan was traditionally divided into *Infans, puer, adolescens, iuvenis, senex* - with very less emphasis on the chronology.

Michael Gooch commented on this Medieval Christian Terminology as :

"Infans might refer to a newborn child, a neophyte Christian, an oblate or anyone still under the legal care of parents . . . at whatever age. A puer may be a servant, young soldier, oblate, student or someone of a lower ecclesiastical rank . . . while a senior may be simply a married man, an abbot or lord.

Isidore of Seville rather linked the six ages of the world to six distinct moral qualities (*Infans- speechlessness/innocence, puer-pureness, adolescens-licentiousness, iuvenis- helpfulness, gravitas-seriousness, senex- wisdom*)

As commented by Rosenthal, on the position of the elderly in the Medieval Period-

"It is hard to think of the elderly as coming anywhere near a special position in regards to treatment, privilege or public concern"

In the Mediaeval period, the church was supposed to protect the '*miserabiles personae*' (unfortunate people) which included the widows and orphans but did not include the old people- which may be due to the equal representation of the elderly among both the rich and poor community, where the elderly from the richer part of the society did not face the same social

issues like those from a relatively poorer section.

Ageing in India :

The Indian tradition is well known for the close-knit family relationship which includes of respecting the elders and the aged. One can find concrete references with special considerations to Geriatric Care in the ancient Indian Scriptures like Vedas and Dharmashastras.

मातृदेवो भव। पतिदेवो भव।

(Be one to whom a mother is as god, be one to whom a father is as god..)

— Taittiriya Upanishad, I.11.2[41][42]

Concept of ageing :

According to the Hindu Scriptures there are four *Ashramas* or stages of individual life- *Brahmacharya*- student life for 25 years, *Grihasta*- household life after marriage for another 25 years, *Vanaprastha*- age of retirement for another 25 years and finally *Sannyasa*- permanent seclusion from all human activities for rest of the life.

The *Manu Smriti* is the oldest of the nineteen *Dharmashastra*, which contains the words of Sage *Manu* as told to the *Rishis* while enlightening them regarding the laws of society towards the elderly. He pays his respects to the elderly for their profound knowledge and advises the rest of the population to never insult or debate with them under any circumstances. They are to be worshipped like the Gods themselves.

Ayurveda, which literally means the "Science of life" also gives top priority to geriatrics. It is a branch of medicine concerned with the care, treatment and rehabilitation of the diseases associated with the elderly population.

Ageing in modern times :

As an unprecedented rapid increase in the ageing population has been noted all over the world, concerns regarding the well being of this population has also

increased. The elderly population in the less developed countries are facing much more difficulties than their counterparts from the more developed countries due to the prevalence of poverty, poor hygiene and inadequate health care services in these developing countries.

Due to physical and mental ailments, the elderly are unable to participate in the labor force as the younger population- leading to negative impact on the country's economy. It has also been noted that in developing countries, poverty and ill health is closely associated. The elderly, who are more prone to illness, have greater healthcare needs and are more likely to succumb under poorer hygienic conditions due to spread of communicable diseases.

Strategies to improve the quality of life of the elderly: the Role of Healthcare System:

At present most of the geriatric out patient departments (OPDs), day care centres, old age residential homes, counselling or recreational facilities are situated in the cities-catering to the needs of the urban elderly population only.

As majority of the elderly population resides in the rural areas, geriatric health care should be made a part of the primary health care services also. The community health volunteers should be trained to identify the specific problems of the elderly patients and help them to be transferred to their nearest Geriatric Care Centre hassle free.

The optimal utilisation of available geriatric health care is also required, which requires a comprehensive survey. Until now, only the Secondary Prevention of diseases were taken care of in the tertiary care centres. Gradually, with inclusion of the primary healthcare centres, focus can be shifted to primary prevention of diseases in elderly. "Comprehensive care" should be aimed in this population which should expand from psychological to all physical health treatment, targeting from preventive care to rehabilitation. Only and only then, can the upliftment of the current socio-economic condition of a developing nation like ours be ensured.

In 73rd World Health assembly on 3rd August, 2020 WHO declared 2020-2032 as 'Decade of Healthy Ageing'.

Decade of Healthy ageing is an opportunity to bring together Governments, Civil Society, International Agencies, Professionals, Media for ten years of Concerted, Catalytic, Collaborative action to improve the lives of older people, their families and communities in which they live.

So clouds on setting sun never obstruct, rather give new colour & dimension. We can not roll back Chronological ageing, but can retard biological ageing. That should be our slogan in "**Decade of Healthy Ageing**".

"We don't stop playing because we grow old. We grow old because we stop playing".

— George Bernard Shaw

Sir Nilratan Sircar — *A Life Sketch*

Dr. Sanjoy Banerjee

Hony. Secretary, JIMA

Born of a poor family he rose to heights which can be reached by very few. He was born in a humble family in the village of Netra near Diamond Harbour in 1861. His father's name was Nanda Lal Sircar. After passing his Entrance examination from the Jaynagar H. E. School he qualified as a sub-assistant surgeon from the Campbell Medical School. The scope of a Sub-Assistant Surgeon could not satisfy his ambitious nature. He went up for University examination and took the B.A. degree of the Calcutta University. He served as the Head-master of the Chatra H. E. School for some time, but his burning ambition could not be satisfied with this small post.

He came back to Calcutta and joined the staff of the University School founded by Dr. Aghore Chatterjee (father of Mrs. Sarojini Naidu). He was in the school for about a year and then took his admission into the Medical College in 1885. In the Medical College he was noted both for industry and brilliance. He was the Goodeve Scholar and obtained honours in Midwifery and Medical Jurisprudence. While still a student, he read a paper on the Etiology of Infantile Liver (Biliary Cirrhosis) before the Calcutta Medical Society, which was published in the Indian Medical Gazette in 1887. He obtained his M.B. degree in 1888, and joined the Mayo Hospital as House Surgeon in the same year. His thirst for knowledge, however, could not be satiated with so little. He went in for the M.A. degree which he followed up by obtaining the M.D. degree of the Calcutta University.



Sir Nilratan started private practice in 1890 and soon his reputation spread far and wide. In those days consultation practice was almost a reserve for the European professors of the Medical College. Since the time he boldly started consultation practice, the ring has been broken and to-day it may be said that the Indian medical men are not looked down upon as mere assistant Surgeons. The public has also learnt to recognise the virtues and qualities of their own countrymen. His labours have borne fruit and his memory will be cherished as one of the pioneers who had the courage to set up private practice on equal terms with the members of the Indian Medical Service. For the first time in the history of the medical profession in this country he, along with his friend, Dr. Suresh Prosad Sarbadhikary, began to charge the same amount of fees as the highest European practitioners, Sir Nilratan held that they should establish this principle that, given equal opportunities, an Indian could rise to the level of a European in every sphere of life. Thus he was instrumental in raising the status of the Indian doctors.

A man of many sided activities, Sir Nilratan found time to devote his attention and energy to questions of public welfare. Sir Nilratan believed that Indian young men studying medicine should be taught by Indians and with that end in view, he together with the Late Drs. R. G. Kar and Suresh Prosad Sarbadhikary, started an institution in Calcutta, the first non Official institution of its kind in the whole of India. This institution was later amalgamated with the Calcutta Medical School and came to be known as the Calcutta Medical School and College of Physicians and Surgeons of Bengal. This was the nucleus around which the present Carmichael Medical College was built. He was also the President of Carmichael Medical College. In recognition of the distinguished services to this institution, a Research Institute named after him was created in 1942 for carrying on research in various problems peculiar to this country. He was the President of the Chittaranjan Seva Sadan and the Jadavpur Tuberculosis Hospital. He was the President of Calcutta Medical Club till 1940. Then he was made a Patron of the Club. His connection with the Indian

Medical Association was intimate for a long time. He was elected President of the Association once in 1918 and again in 1932. He was also one of the founders of the Journal of the Association, which made its appearance in 1930 under his editorship. It was then named as "Indian Medical World." The name was changed to the present title from 1931 but he continued to act as the Editor and served the Journal for over a decade. It was due to his untiring zeal and energy and his never-failing guidance that the Journal gradually took the present shape.

Besides devoting his energies to the spread of medical education, Sir Nilratan was also deeply interested in the progress of general education. He was an elected Fellow of the Calcutta University since 1893 and was its Vice-Chancellor from 1919 to 1921. He was Dean of the Faculty of Science as well as Faculty of Medicine of the University and was President of the Post-graduate Teaching in both Arts and Science. In 1920, he went as a delegate of the Calcutta University to the Congress of Universities of the Empire in London.

While there, he received the honorary degrees of D.C.L. of Oxford University and of L.L.D. of Edinburgh University. As an educationist, he realised that the salvation of his country lay in training young men to manufacture articles and receiving training in tanning, dyeing, bleaching and industrial chemistry, mechanical and electrical engineering and sheet metal work and he was found 'working day and night as Secretary to the National Council of Education and then conducting the Bengal Technical School and afterwards, in running the Jadavpur College of Engineering and Technology. He went to Baroda and Bombay for receiving practical training in industrial subjects in 1905 and 1907. He took an active part in the Student's Welfare Movement and in the introduction of the Science Course in the University Curriculum. In fact, he might be said to be the corner-stone of the big edifice of the Science College, Calcutta, which we see today."

He was also intimately connected with the Science Congress and delivered lectures there. He was also invited by the Andhra University to deliver a Convocation address. He took keen interest in the industrial development of Bengal and he encouraged, patronised and sponsored several industrial enterprises. His was an idealistic outlook and financial entanglement could not curb his zeal. The great possibility of Indian hide industry attracted his attention and he saw what a great drain it was on the wealth of the country.

Sir Nilratan took the bold step of founding an Indian-owned tannery, the first of its kind, in the face of tremendous opposition from vested interests. Then he undertook manufacture of soap and the soap works founded by him was a pioneer work in India.

Throughout his life Sir Nilratan took an active interest in politics and had been a delegate of the Indian National Congress since 1890. For several years he was secretary to the several sections of the Congress. Though he seceded from the Congress in 1919 along with other Moderate leaders, he could not belong to the Liberal party either. He felt and made no secret of it that its political outlook and programme lacked idealism and vigour. He was a great admirer of Gandhiji, and Gandhiji also held him in high esteem. Sir Nilratan's statesmanship of high order; there was nothing personal about it. He never had his own axe to grind and it was in the spirit of service and sacrifice for the motherland that he worked. He never had desire to be in the limelight and scrupulously shunned publicity.

He was in the Bengal Legislative Council from 1912-1927. He did his work in the Council in his usual thorough way and devoted much time. A Knighthood was conferred on him in 1918.

Sir Nilratan was a deeply religious man, a Brahmo of the old order. To him religion was a living force, a matter of practice and not only of theory. Presiding over the All India Theistic Conference some years ago he declared: "No form of religion has any life-value today which fails to yield a living inspiration and social service, more specially the service of the lowly and the over-burdened, the afflicted, the downcast, the oppressed and the fallen: and devotional religion in our Samajes, if it be not a mere luxurious sensation, must go out among the depressed classes in loving humility and patient life-giving sacrifice." His religion was firmly rooted in the 'Fatherhood of God and Brotherhood of Man', and he made Service and Sacrifice the motto of his life.

His relation with his colleagues had always been most cordial and most honourable. He always upheld the banner of truth and righteousness, honesty and integrity till the last days of his career as a physician.

Review Article

Tuberculin Therapy — Echo from the Past

M S Valiathan¹

Tuberculin, developed by Robert Koch, is a general name for the toxic products of Tubercle bacilli grown in culture. The products consist of soluble components and endotoxins of the cell body of the bacterium. Their selective affinity for tuberculous lesions indicated diagnostic potential which Koch utilized in designing the tuberculin test which continues to be in use. However its application in therapy, also introduced by Koch, underwent clinical trials in the first decade of 20th century and showed less than satisfactory results. Trials not with standing, general physicians used tuberculin in therapy extensively and many tuberculins appeared especially in Europe. Koch and the German School gave a scientific underpinning of active immunisation to tuberculin therapy and made efforts to standardise treatment protocols and dosage schedules. Meanwhile Wright introduced opsonic index as a guide and facilitator for tuberculin therapy though its essentiality remained doubtful.

The questions which attracted the keenest attention of investigators in tuberculosis in that period were the prime route of entry of tubercle bacilli in the body; Interrelation between bacilli of human and bovine origin; and active immunisation induced by tuberculin.

A few illustrative cases of tuberculosis who underwent tuberculin therapy in a District hospital in Travancore (merged in Kerala) during 1913-14 are also reported.

[J Indian Med Assoc 2020; 118(10): 15-9]

Key words : Robert Koch: Tuberculin therapy, Tuberculin test, Opsonic index, Clinical trial.

Tuberculin was developed by Robert Koch to destroy tubercle bacilli after his momentous discovery of the bacillus in 1882. Initially employed for treatment and diagnosis of tuberculosis by Koch, its therapeutic usefulness was seriously questioned in the first decade of the 20th century in Europe and Britain while its diagnostic role steadily gained recognition and "tuberculin test" became universally used to this day.

In the first decade of 20th century, Dr V Sankara Valiathan from Travancore, India studied medicine in the University of Edinburgh (MB ChB 1905; MD 1915) and wrote a thesis on "The present position of tuberculin therapy" in partial fulfilment of his MD requirements. This article retells the contents of his thesis in an abridged form with no deviation or alteration from the original. Sectional headings 1 to 8 comply with those in the original thesis. They hold a mirror to the status of tuberculin therapy in Europe and a Government hospital in Travancore (now part of Kerala) in early 20th Century.

Introduction :

Tuberculosis was known from the time of Hippocrates, but it was reserved for Robert Koch to

Editor's Comment :

- Tuberculin is the name for 'toxic products' of tubercle bacillus grown upon artificial media.
- Tuberculin treatment is an immunological procedure which induces the body to produce antibodies.
- Koch & German school suggested active immunisation by tuberculin therapy & tried to standardise treatment.
- Wright & English school, on the other hand, introduced opsonic index as guide for tuberculin therapy.
- Studies in Travancore showed that tuberculin treatment was unsuccessful in full-fledged Pulmonary tuberculosis.

make the epoch-making discovery of the tubercle bacilli grown in pure culture as its cause. He announced his brilliant discovery in March 1882, heralding a new era in the history of medicine. Koch next began the search for a remedy that would destroy the pathogenic bacteria in the living tissues. Years of search turned fruitless because the agents which destroyed the bacteria did not spare the healthy tissues either. He therefore took an untrodden path and made an important observation. When guinea pigs were inoculated with incremental dose of dead tubercle bacilli, the wound healed, but in 10-14 days a hard nodule appeared on the site, which broke down, ulcerated and refused to heal until the animal's death. If, on the other hand, the animal had

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already been infected with tubercle bacilli, the wound would heal first but show no tendency to nodule formation: it would however develop ulceration followed by healing. Koch also observed that the same phenomena which appear after reinjection of living and dead bacteria could be reproduced by administering their extracts called tuberculin. In 1890, he claimed that he was "able to render animals immune against tubercle bacilli and to bring a standstill to the tuberculous process in animals" The extract consisted of a glycerine extract of tubercle bacilli evaporated to 1/10th of the volume in a water bath and then filtered through a porcelain filter.

Historical Outline :

Tuberculin : Is the general name for the toxic products of the tubercle bacillus grown upon artificial media. The toxic products are diffusible and soluble extractives and endotoxins of the cell body of bacteria. In man tuberculous lesions tend to be localised and dormant for months or years. Tuberculin has a selective action on these lesions, which it lacks against normal tissues. The selective action of tuberculin is both general and local; general action includes fever, rigor, and malaise, and local is typically seen in lupus where tuberculin picks out diseased tissues and spares the healed parts. This highlights the diagnostic potential of tuberculin. One could, for example, make a diagnosis of tuberculosis when tubercle bacilli are not detectable in incipient tuberculosis of the lung. The inflammatory response is a manifestation of an antigen – antigen body reaction where tuberculin is the antigen and anti- tuberculin is the antibody. Koch emphasised that tuberculin does not kill bacilli present in the tissues but affects only tissues harbouring the bacteria. The tissue response may be disintegration or sloughing.

Koch was encouraged by the early results of treatment of tuberculosis of skin, glands, bone and joints with tuberculin. Soon patients with pulmonary tuberculosis were also recruited and different dosage regimes proposed. From initial results Koch concluded that in early stages pulmonary tuberculosis was curable; in advanced stages, improvement was possible.

The rosy view of tuberculin for treatment led to several clinical trials and the dramatic cure of lupus heightened the belief in the curative power of tuberculin. Before long, misguided enthusiasm led to the use of too large doses in the treatment of advanced cases, resulting in severe reactions. The Brompton hospital report (1892) declared that tuberculin did not favourably influence the course of disease in the majority of cases. Tuberculin was practically abandoned as a therapeutic

agent but survived as a diagnostic tool thanks to the febrile reaction it produced in a tuberculous individual. Osler's text book of Medicine (1901) stated "During the past few years, it (tuberculin test) has been employed extensively in the Johns Hopkins Hospital, both on the Medical and Surgical sides, with the most satisfactory results, and so far as I know, without any harmful results. In obscure internal lesions, joint cases, and in suspected tuberculosis of kidneys the use of tuberculin gives most valuable information".² In veterinary practice it found a permanent place for recognising concealed tuberculosis. It is a sobering thought that Koch had warned against the use of tuberculin for treatment of tuberculosis in the presence of other infections and emphasised that tuberculin acted solely by the process of active immunisation, radically differing from the passive administration of man-made antiserum. It was felt that the failure of tuberculin in 1891 was due to a disregard of the limitations and restrictions laid down by Koch and to a general ignorance of the role of mixed infections in pulmonary tuberculosis. By a coincidence, tuberculin was tried as a remedy when influenza pandemic (Spanish influenza) raged in Europe. This further eroded the validity of the clinical trial of tuberculin.

The Various Kinds of Tuberculin :

Following the original tuberculin of Koch, he introduced modified versions in response to feedback from the experience of earlier versions; other investigators brought out their tuberculins. Most of these modifications were related to process control or improvement.

A few tuberculins in regular use are listed

i. Old Tuberculin (TO): This was the first tuberculin developed by Koch from a glycerine broth of tubercle bacilli 6 – 12 months old. It was evaporated 1/10th of its volume and then filtered through a porcelain filter. It is practically a solution in glycerine of the extra cellular toxins produced by the organism.

ii. Koch's Original Tuberculin (TOA): Prepared exactly like TO but not concentrated to 1/10th volume.

iii. Albumose-Free Tuberculin: This was introduced by Koch to avoid the fever caused by albumoses. It is prepared by growing bacilli on media free from albumoses.

iv. New Tuberculin (TR): TO was believed to provide immunity against bacterial toxin only, not against the bacilli themselves, just like anti- tetanus serum. Koch's aim was to combine both forms of immunity and he therefore prepared a new form of tuberculin by breaking up bacilli by a mechanical process which contained the curative and immunising

substances of bacilli in a form suitable for injection. It produced no ill effects and could be used as a preliminary to a course of TO. It had immunising properties unquestionably.

v. New Tuberculin Bacillary-Emulsion (BE):

This is new tuberculin by eliminating centrifugation in its making, which was expected to enhance durability.

vi. Sanitized Bacillary Emulsion (SBE):

As suggested by Meyer, dried human bacilli mixed with tubercular serum and kept in incubators at 37°C for several days. Further processing to be carried out.

vii. Beranek's Tuberculin (TBK):

Contains all substances having immunising properties whether in culture fluid or in bacteria themselves.

viii. Carl Spengler's Immunising Substances

Koch and the German School :

In the first decade of twentieth century, Koch's discoveries of tubercle bacilli and the twin role of tuberculin in diagnosis and treatment dominated the practice of medicine in Europe. The foregoing discussion shows the dominance of tuberculin in theory and practice of tuberculosis and its impact on the emerging science of immunology. The German School led by Koch was identified with certain views outlined below:

- Absence of reaction to tuberculin test indicates successful immunisation against bacterial toxins, which favours survival. The detoxifying effect is signalled by signs such as disappearance of fever and headache, drop in rapid pulse rate, gain in weight and increased appetite.

- Tuberculin treatment is an immunological procedure in so far as it induces the body to produce antibodies and boosts body's natural production of antibodies.

- Opinions are divided on tuberculin therapy employing high and low dosage regimes. Experience in practice does not support the claim that larger doses of tuberculin have a necessary correlation with severe reactions. At the same time, use of small or tiny doses at long intervals has proved ineffective and has raised the spectre of hyper-susceptibility. It would seem in the present state of knowledge and experience that the majority of cases can be managed successfully through tuberculin treatment without appreciable rise of temperature and without damage to general health. It is essential that tuberculin therapy is regularly monitored and regulated by attention to patient's temperature (limit 37°C), loss of body weight and increase in pulse rate, which represent increased level of toxins.

- Too rapid increase of dosage of tuberculin may cause hyper susceptibility. This is harmful and indicates toxæmia requiring corrective treatment.

- A school of thought (Petruschky) has advocated a system of interrupted treatment for two years when tuberculin treatment is given for periods of 2–3 months when injections are given, alternating with pauses of 3–4 months. Disappearance of skin reaction to tuberculin test, absence of fever, return of normal pulse and gain in weight could be regarded as an indication for the cessation of tuberculin treatment.

- About twenty European clinicians and medical scientists are on record in support of tuberculin therapy and even for establishing "tuberculin dispensaries".

Wright and the English School :

Wright's development of opsonic index in England is not an essential part of the therapeutic application of tuberculin. The earlier practice of using clinical signs including pulse, temperature, weight gain, local signs and long experience justify the claim that they are sufficient to regulate tuberculin therapy apart from opsonic index determinations. It should also be borne in mind that the complexity of Wright's method and the consequent high margin of error do detract from its general utility in medical practice. However Wright's work has brought into focus the active immunisation method in the treatment of tuberculosis.

By the first decade of the 20th century, the bactericidal action of blood serum outside the human body was established in the laboratory. Apart from direct bacteriolytic action, destruction also took place by agglutination of bacteria, which was believed to be caused by a specific substance called agglutinin. Wright believed that still another substance called opsonin prepares bacteria for ingestion by phagocytes. The exact relationship of opsonin to other antibodies such as agglutinin and antitoxin is not known. Wright had experimental evidence to show that there was a substance in serum which greatly increased phagocytosis. However it had not been isolated or characterised and its physico-chemical properties were debated. The opsonic theory holds that vaccines act by stimulating the immune system to produce more opsonin. It was believed that opsonic index would enable one to track the immunisation process and facilitate the injection schedule on the basis of the amount of opsonin present. Wright's elaboration of opsonic index involving positive and negative phases, auto-inoculation etc., became highly complicated, and very frequent estimations of the index – subject to frequent fluctuations – cast doubt on whether it could be used widely as a reliable guide to immunisation.

Opsonic index lacked practical value for a large percentage of practitioners.

Modern Experimental Work :

Modern studies on the nature of tubercle bacilli have focussed on three questions:

(1) How tubercle bacilli gain entry into the human body?

(2) Do human and bovine tubercle bacilli intercommunicate? interact?

(3) How does the induction of active immunity work for the patient with or without opsonic index?

i) Originally Koch had shown in experiments that lungs always became infected by direct inhalation of bacilli in dust. There was rethinking when it was urged by Von Behring that infant's bowel is the main portal of entry of tubercle bacilli, and adult tuberculosis is an activation of tubercular foci which were quiescent from infancy. In Calmette's laboratory it was found that lungs of rabbits made to breath smoke did not become blackened if their gullet had been ligated. These observations are supported by other experimental studies, which suggest that tubercle bacilli gain entry into the body through the bowel. They may be arrested at the level of mesenteric glands or may enter blood via thoracic duct. It should also be kept in mind that inhaled bacilli could be arrested in the mouth or upper respiratory passages and subsequently swallowed.

These discussions would clarify why non-pulmonary tuberculosis is dominant in children who have pulmonary infection rarely. The oral route of entry is of practical importance thanks to the consumption of milk obtained from tubercular cow especially when unboiled. In England 30% of milch cows are shown by tuberculin test to be tuberculous.

ii) Koch surprised the world when he declared that tubercle bacilli of human and bovine origins were two different organisms. However subsequent investigations confirmed his observation that humans are vulnerable to attack by both organisms. The infectivity of human and bovine tubercle bacillus for either or both species is so important an issue for public health that numerous research studies were carried out to unravel the inter relationship between the two organisms. Generalisations such as tuberculosis affecting the respiratory system is caused by human bacillus and that of the abdominal, bone and joint, military and children's is bovine are misplaced. However a few facts are known at this time:

- Calves can be infected by subcutaneous injection of human bacillus.

- Monkeys are infected by feeding tuberculous cow's milk.

- Enough evidence that tubercular cow's milk should never be used for human consumption.

- Direct evidence of the infection of human beings by tubercular cow's milk is scanty.

- Humans do not inherit tubercular infection.

- Milk must always be boiled before consumption to 95°C for 1 minute or 70°C for 30 minutes.

iii) Active immunisation occurs when an organism undergoes a change following the assimilation of bacterium or its products and produces specific protective antibodies (such as antitoxins). This form of immunisation is called active immunisation (Ehrlich) as the organism has to do work of its own to produce the antibodies. Passive immunisation occurs when specific antibodies made by one organism is injected into another who gets it free.

Behring injected a culture of human tubercle bacilli into calves whose antibody response is mild to the human bacillus. When calves mature, the cows supply pure milk, but its administration to patients in the hope that anti-tuberculous antibodies may be present in the milk and may protect the patients was futile. Many other attempts to induce passive immunity to tuberculosis were equally unsuccessful.

The chief hope of fighting established tuberculosis currently is centred on tuberculin, Koch's original tuberculin (TO) and new tuberculin (TR) being generally used. For therapeutic purposes, TR is the candidate of choice. Wright's method is also employed for treatment using minute doses where the dosage and intervals between injections are determined by their effect on opsonic index. Alternately, tuberculin is administered on the same schedule without employing opsonic index. A detailed debate on the need and efficacy of using opsonic index in tuberculin therapeutics is superfluous in the present context. Suffice to say, the "opsonic doctrine is assailed by an increasing number of investigators whose attack combined with much practical shortcomings have tended to produce widespread distrust in the practical value of the opsonic index".

Clinical Trial :

A clinical trial of tuberculin therapy was conducted in the Quilon District Hospital of Travancore from 1913 – 1914. The local conditions conformed to the Edinburgh System in terms of open air, sunshine, good food and friendly attendants during hospitalisation. Effort was made to provide "conditions, as little artificial in these respects as possible, and as nearly alike as practicable to the conditions under which he will afterwards have to live and work". Ten illustrative cases among those treated at the hospital were analysed to

provide an overall picture of tuberculin therapy in a public hospital which had no radiologic facility but did boast of a laboratory for bacteriological tests.

Patient profile —

Age : Seven adults and three children below 10 years.

Gender : Male – 6, Female – 2, Not indicated - 2

Diagnosis —

■ Pulmonary Tuberculosis	5
■ Pulmonary Tuberculosis – Abscess elbow	1
■ Tuberculous peritonitis	1
■ Abscess hip	1
■ Intestinal tuberculosis	1
■ Pleurisy with effusion	1

Treatment and results —

■ Tuberculin injection weekly after admission when patient settles down; weekly injections of TR with increasing dosage; dosage/frequency determined by clinical signs

– fever, pulse, weight gain, return of appetite. Discharge when fever settles, pulse becomes normal, substantial gain in weight occurs and appetite returns. This happens in weeks or months.

■ Thoracentesis used for pleural effusion in a child.

■ A child 8 years with tuberculous peritonitis, severe wasting and fever showed no improvement and was taken away by parents.

■ A man aged 18 years with pulmonary tuberculosis and tuberculous abscess in the left elbow deteriorated (probably due to mixed infection of the elbow) and had to have the left arm amputated. He was discharged on request.

During the period of clinical trial, Travancore had no Sanatoria for tuberculosis treatment.

Summary and Conclusions :

Though tuberculin treatment does much good in the early stage of phthisis its results in treating full-fledged tuberculosis of the lung are disappointing. It must also be noted that success of tuberculin treatment demands favourable conditions such as fresh air, sunshine, and good food. No wonder the best results of treatment are believed to be obtained by a combination of the sanatorium treatment and tuberculin. At the present time, a standard method of tuberculin treatment is hard to recommend for various categories of patients because the use of tiny doses (1/5000th to 1/1000) of TR at one or two weeks'

intervals, with or without opsonic index, gives differing results in the hands of practitioners. This applies to other methods such as the administration of TR by mouth. A few generalisations are however possible such as the large dose method of tuberculin treatment on the continent for many years has improved the curability of pulmonary tuberculosis. Whatever the method of treatment, success depends on early diagnosis. Hence the importance of tuberculin test which can detect the presence of tubercular infection long before the signs of the infection become detectable by physical examination.

The role of exercise in the recovery phase of pulmonary tuberculosis has not received adequate appreciation. In a convalescent patient of tuberculosis, Paterson and Inman at Frimley noticed that physical exercise would cause the release of body's own tuberculin or toxin (autoinoculation) as indicated by fever and fall in opsonic index. If the exercise level is gradually raised, the patient would become accustomed to autoinoculation and increased body resistance to tubercle. This is tuberculin treatment, but the patient makes his own tuberculin. It is clear that the possibility of preventive medicine is therefore substantial in this disease. If it turns out that tuberculous cow's milk is the main source of infection and the inhalation of bacilli is of small account, vaccinating every calf against tubercle or killing every milch cow that tests positive on tuberculin would be a major step for prevention. A non-tubercular milk supply would enormously diminish the prevalence of disease in children. A simpler measure would be to boil milk before consumption as is being done in India.

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Review Article

Healthy Ageing

O P Sharma¹, Kaushik Ranjan Das²

World Health Organization defines Healthy Ageing "as the process of developing and maintaining the functional ability that enables wellbeing in older age". Presently we are in a state of developing the infrastructure for our senior citizens to enjoy their life in a healthy way. Several factors come in the way of healthy ageing. These comprises all the mental and physical capacities that a person can draw on and includes their ability to walk, think, see, hear and remember. The level of intrinsic capacity is influenced by several factors such as the presence of diseases, injuries and age-related changes. These also include the home, community and broader society, and all the factors within them. Based on some basic principles of public health policy, healthy ageing could be ensured through different levels of healthcare. Healthy ageing in India should not be a connotation but an achievable goal.

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Key words : Healthy ageing, components of healthy ageing, Quality of life, Components of healthy lifestyle, Basic principles of public health, Health care facilities in India.

World Health Organization defines health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity¹.

Ageing is a physiological process during which structural and functional changes occur in an organism because of the passage of time. The changes manifest as a decline from the organism's peak fertility and physiological functions until death².

HEALTHY AGEING :

WHO defines Healthy Ageing "as the process of developing and maintaining the functional ability that enables wellbeing in older age"? Functional ability is about having the capabilities that enable all people to be and do what they have reason to value³.

Functional Ability

It is about having the capabilities that enable all people to be and do what they have reason to value. Functional ability includes a person's ability to meet their basic needs; to learn, grow and make decisions; to be mobile; to build and maintain relationships; and to contribute to society⁴.

Functional ability is made up of the intrinsic capacity of the individual, relevant environmental

Editor's Comment :

- Promotion of healthy ageing through government infrastructure, specially through community health worker (CHW) and primary health centers under the leadership of geriatric physician is the most prominent tool.
- Barriers of healthy ageing could be removed/ resolved through a promotional activity targeting family and society to achieve community participation.
- Enhancing elderly friendly environment through intersectoral cooperation and using technology appropriate for our socioeconomic status.
- Policy formulation and enactment of laws by Central Government.
- Promotion of healthy ageing increases quality of life of senior citizens, increases productivity of concerned elderly and his working family members as well thereby by increasing GDP and reduces both direct & indirect health care burden of the nation in terms of GDP.

characteristics and the interaction between them. Being able to live in environments that support and maintain one's intrinsic capacity and functional ability is key to healthy ageing.

Intrinsic Capacity

It comprises all the mental and physical capacities that a person can draw on and includes their ability to walk, think, see, hear and remember.

The level of intrinsic capacity is influenced by several factors such as the presence of diseases, injuries and age-related changes.

Environments

It includes the home, community and broader

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society, and all the factors within them such as the built environment, people and their relationships, attitudes and values, health and social policies, the systems that support them and the services that they implement.

Wellness

Wellness may be described as our ability to understand, accept and act upon our capacity to lead aengaged life with a purpose. Here, we can use our potential (physical, emotional, spiritual, intellectual, social, environmental, vocational) to bring out and optimize possibilities in life⁵.

PRINCIPLES OF ACTIVE AGEING :

International Council on Active Aging (ICAA) has defined its principles of active ageing to guide governments, product and service providers, employers, and the healthcare industry in how they respond to population ageing. By implementing these principles, organizations and agencies will be able to build a foundation for their efforts and encourage active, engaged living for people of all ages⁶ (Fig 1).

LIFESTYLE :

The term was introduced by Austrian psychologist Alfred Adler with the meaning of a person's basic character as established early in childhood.

Life style of an individual, group or culture is their interests, opinions, behaviours and behavioural orientations. It differs from urban to rural ; even different in urban scope also. Life style affects a person due nature of his /her neighbour, degree of affluence and proximity to nature and culture.

Healthy Lifestyle

Healthy lifestyle includes nutritious diet, work, appropriate physical exercise, strategy for preventive healthcare, the interaction with the environment, and social connectivity⁹.

QUALITY OF LIFE :

WHO defines quality of life (QOL) as individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns? It is a broad ranging concept affected in a complex way by the person's physical health,

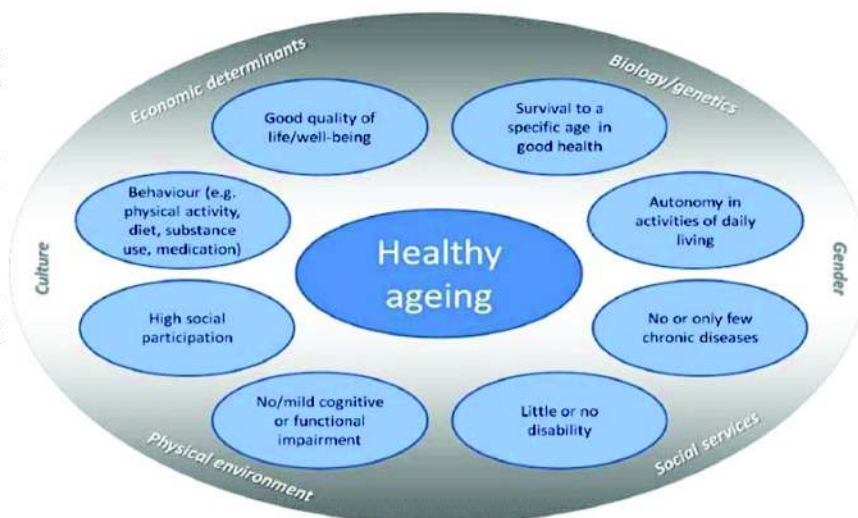


Fig 1 — Components of Healthy Ageing⁷

psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment¹⁰.

Quality of life includes everything from physical health, family, education, employment, wealth, safety, security to freedom, religious beliefs, and the environment. QOL has a wide range of contexts, including the fields of international development, healthcare, politics and employment. Health related QOL (HRQOL) is an evaluation of QOL and its relationship with health. Quality of life should not be confused with the concept of standard of living, which is based primarily on income¹¹.

Relation between QOL and Healthy Lifestyle

Quality of life is related to the following aspects

- Satisfied in one's daily activities
- Satisfied with individuals needs
- Reaching of goals in life
- Personal image and view towards life
- Connectedness with personal and socio-environmental factors¹²

Benefits of Living a Healthy Lifestyle for Elderly

■ Following healthy life style practices elderly will feel better! Their body and mind will have more freedom and ability for doing work that they could not before.

■ Since they will gain strength , their fatigue will be reduced when doing any physical activity,

■ As elderly feel good about themselves, they will express it on to others, and those closest to, will feel it too. As a consequence their social relationships will improve.

- Proper rest will be there, that will make them full of energy in the morning.

- Due to mental balance, elderly will be able to take decisions properly. Mental balance will help elderly to avoid going into the consumption of toxic substances.

- Senior citizens will be active, the risk of injury will be minimized.

- Due to taking a varied and balanced diet, body and mind of elderly will stay strong and healthy¹³.

Benefits of Living a Healthy Lifestyle for Society

- Senior citizens after getting benefited will help others to get started with their healthy habit's routine.

- They will also share all the benefits with others, they have received from following their changed healthy routine.

- There will be reduced expenses to the health system, due to strengthening of their immune system elderly will fall sick less often.

- Elderly will be respectful with the environment that surrounds them and therefore elderly will contribute to keeping the earth in good condition for future generations¹⁴.

Lifestyle Diseases

Many diseases in seniors may be prevented or at least slowed down because of a healthy lifestyle. Diabetes Mellitus, heart disease, High blood pressure, arthritis, Osteoporosis, Dyslipidaemia, depression, dementia, and certain cancers are some of the common conditions that can be positively modified in seniors through diet, exercise, and other simple lifestyle changes¹⁵.

Components of a Healthy Lifestyle

- Physical exercise
- Balanced diet
- Social activity
- Mental balance
- Enjoying free time
- Exercising the mind
- Enjoying healthy sex
- Getting good quality sleep¹⁶

Lifestyle Modifications to Lead a Healthier Life in Seniors include-

- Proper Diet and Nutrition
- Exercises
- Limiting alcohol intake to one drink daily
- Smoking cessation
- Using skin moisturizers and sun protection
- Brushing and flossing teeth once or twice a day
- Staying proactive in own healthcare and

participating in decision making

- Going to the primary care doctor routinely
- Reviewing list of medications with their doctor
- Following recommended instructions for health screening, preventive tests, and vaccinations
- Visiting a dentist annually or biannually
- Following up with eye doctor and foot doctor, especially for people with diabetes
- To remain aware of potential medication side effects and drug interactions including over-the-counter drugs, herbals, and alternative medicine.
- Vaccination¹⁷

HEALTHY AGEING STRATEGIES :

Based on some basic principles of public health policy, healthy ageing could be ensured through different levels of healthcare.

Basic Principles of Public Health include

- Human centered health care
- Human rights.
- Effective policy and good governance.
- Participation
- Solidarity
- Health in all policies.
- Equal rights and opportunities for all¹⁸

HEALTH CARE FACILITIES IN INDIA :

Primary level

Sub Centers

- Two workers are needed, one male & one female
- About 5000 people being served (in a remote, dangerous location population is 3000).
- National Government covers the expenses (but salary of male staff to be borne by State)
- Tasks relating to interpersonal communication to bring about behavioral change and referral of cases to PHCs are the role of subcentres¹⁹.
- More than 1, 50,000 Sub Centers functioning in the country as on 31st March, 2017²⁰.

Primary Health Centers

- One such centre is situated in more developed rural areas for 30,000 or more (in remote areas one for 20,000 population)
- Staffed with doctors and paramedics, a PHC undertakes its activities.
- State governments fund PHCs, not the national government. This is its difference with subcentre.
- The first contact point between village community and the medical officer is the PHC.
- They also function to improve health education with a larger emphasis on preventative measures²¹.

■ About 25,000 PHCs functioning in the country as on 31st March, 2017²².

Secondary Level :

At the secondary level there are Community Health Centers (CHCs) and smaller Sub-District hospitals.

Community Health Centers

■ CHCs are funded by state governments and accepts patients referred from PHCs

■ About 120,000 people being served in urban areas or 80,000 people in remote areas.

■ Patients from these CHCs can be transferred to general hospitals for further treatments. CHC's also works as first referral units.

■ CHCs are being established and maintained by the State government under MNP/BMS programme²³

■ As a norm, a CHC is required to be staffed by four medical specialists i.e. surgeon, physician, gynecologist and pediatrician, supported by paramedical²¹ and other staff. There are 30 in-door beds with one OT, X-ray, labor room and laboratory facilities.

■ CHCs serves as a referral center for 4 PHCs and also provides serves for obstetric care and specialist consultations.

■ As on 31st March 2017, there were about 5,600 CHCs functioning in the country²⁴

Tertiary Level

Government provides top level public care through the tertiary level, which consists of Medical Colleges and District/General Hospitals.

There is increase in number of PHCs, CHCs, Sub Centers, and District Hospitals has increased in the last years, but all of them are not up to the standards set by Indian Public Health Standards.

Community Health Worker

There has been more than 08 (Eight) lakhs CHW with the designation ASHA (accredited social health activist) worker appointed in India (one for a Village), who are regularized as group C worker and for health promotional activities at village level. Total villages in India are 6,49,481.

Primary Health Care Strategies

Healthy ageing Activities

At Primary Level

Four Pillars of Primary Health Care

- Community participation
- Inter-sectoral coordination
- Appropriate technology.
- Support mechanism made available²⁵

At Village Level, by Community Health Worker/ Asha Worker

■ Assessment of senior citizens status – biological functions, activities of daily life (ADL), instrumental activities of daily living, socioeconomic status, social connections, mental status, matter of abuses, comorbidities, history of medication, stigmas, in home environment, environmental sanitation etc.

■ Impart health education to elderly and family members about – prevention of malnutrition, falls & abuses; healthy life style including exercises, enabling elderly friendly environment in home, use of assisting devices, family and social relation, recreation, insurance & Medclaim, risk factors, hidden diseases in elderly, environmental sanitation etc.

■ Treatment of simple diseases, elderly vaccination, and referral to PHC's.

■ Follow up, Liaison and Companionship.

■ Finding barriers of healthy living of elderly in family & society.

■ Data collection and record keeping.

■ Reporting to higher authority including PHC and Gram panchayat.

All these activities should also be undertaken at Health Sub-centers in India.

At PHC

Under the leadership of Geriatrician/Family Physicians

■ Geriatric assessment

■ Providing health advocacy including healthy lifestyle, prevention of diseases and conditions through behavioral modification technique at individual or group level, family members need to be included. Use of appropriate technology should be a part of education.

■ Screening for diseases at individual and elderly community level with primary preventive measures.

■ Diagnosis and treatment of diseases; secondary and tertiary level of preventions.

■ Follow up and referral

■ Intersectoral coordination for resolving elderly issues including their societal functionality.

■ Geriatric Vaccination

■ Data collection and record keeping.

■ Reporting

Other Govt. Infrastructure

At CHC, Sub district and state hospital, district hospital, Medical College Hospitals, other govt. hospitals: Provide treatment, advocate preventive measures, follow up and feed back to PHC's. Data collection and research activities, record keeping etc.

Private Initiative & other Service Facilities

■ Corporate hospital by creating a chain of communication can provide health promotion activities for elderly. One such system is "In Home care for Elderly".

■ Corporates and organizations: Should render service to elderly keeping matters of healthy ageing at top priority.

■ Geriatrician: They can provide health promotion activities through one stop geriatric care that encompasses "In Home Care" also.

■ Other care facilities for elderly: Authorities running old age homes, respite care centers, day care centers for elderly, long term care centers etc. should promote geriatric care through their service areas.

Barriers of Healthy Ageing

- Individual factor
- Family factors
- Culture & beliefs
- Misconception
- Social factors
- Environmental factors
- Financial issues including Medicaide
- Trained workforce and their commitment
- Scarcity of geriatric physician
- Insufficient service facility both govt. & private.
- Non-inclusion of geriatric health promotion as primary health care component.

■ Lack of coordination, specially intersectoral coordination

■ Absence of data collection, record keeping and reporting of geriatric health issues.

Way Forward

■ There should be policies to include healthy ageing in primary health care and to enact and amend laws that will enhance healthy ageing (that also include legalization of in-home care with use of devices).

■ ASHA workers or community health workers are required to be trained with working knowledge of geriatric care immediately.

■ Urgent endeavor must be undertaken to bring out more geriatric physician for fulfilling the tremendous demand.

■ Meaningful intersectoral coordination must be ensured for enhancing elderly friendly in-built environment.

■ Assisting devices should be made available at subsidized cost with.

■ Financial constraints and insurance & Medicaide issues related to healthy ageing should immediately be looked in to.

■ Doctors initiatives regarding healthy ageing should be encouraged.

■ WHO required include healthy ageing as primary health care priority.

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Voice of the Expert

Herd Immunity

1. What is Herd Immunity?

Herd immunity refers to the indirect protection from infection conferred to susceptible individuals when a sufficiently large proportion of immune individuals exist in a population. Herd immunity can be achieved by two ways

- I. Vaccination
- II. Natural infection

The term "Herd immunity" was probably first coined by American veterinarians. In the first decade of the twentieth century, there was an epidemic of spontaneous abortion among cattle in the USA due to some infection. The then veterinarians like Adolph Eichhorn then envisioned a concept of "herd immunity" among cattle to protect farmers from livestock destruction. Thus, this was a term related to animal health, which was later incorporated into human public health.

2. What are the Elements contributing to Herd Immunity ?

Herd immunity is an important element in the balance between the host population and the micro-organism, and represents the degree to which the community is susceptible or not to an infectious agent. Herd immunity depends on the Basic Reproduction Number (R_0). R_0 is the average number of secondary infections caused by a single infectious individual when introduced into a completely susceptible population. R_0 for any infectious agent depends on population density, population structure, human behavior, and biological characteristics of the infectious agent.

Herd immunity can be measured either indirectly or directly.

I. Indirectly from the age distribution and incidence pattern of the disease if it is clinically distinct and reasonably common. Although it's not a very sensitive method.

II. Directly from assessments of immunity in defined population groups by antibody surveys (sero-survey) or by some other tests; these may show 'immunity gaps' and provide an early warning of

susceptibility in the population.

These measurements can also provide an estimate of burden and trend of disease, needs of vaccine, and impact of other preventive strategies within very short time frame.



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3. What is the difference between Herd Immunity and Herd Effect ?

Herd effect is the reduction of infection or disease in the unimmunised segment as a result of immunising a proportion of the population. Herd effect is determined by herd immunity as well as the force of transmission of the corresponding infection ie, Effective Reproduction rate.

4. What is R_0 value? What does it signify? How can we reduce the value of R_0 for a specific disease?

Pronounced "*R naught*", the Basic reproduction number also called the basic reproduction ratio or rate (R_0) is an epidemiological tool used to describe the contagiousness of transmissibility of infectious agents. It signifies the average number of secondary infections caused by a single infectious individual when introduced into a completely susceptible population. R_0 is affected by various biological, socioeconomic and environmental factors that govern the transmission. It depends on population density, population structure, and differences in contact rates and hence can be reduced by reducing any of these.

The estimation of R_0 involves a complex procedure and is usually calculated based on three primary parameters viz. duration of contagiousness, likelihood of contact between infectious and susceptible person and contact rates. The value of R_0 is usually constant for a given situation. It cannot be reduced. With various pharmaceuticals and non-pharmaceutical measures we can reduce the effective reproduction number (R). The effective R depends on the population's current susceptibility and changes over time. For example, for COVID-19 we do not have any effective treatment

or vaccine till date. The only way to reduce effective R is through non-pharmaceutical measures.

5. What is Herd Immunity Threshold ?

The point at which the proportion of susceptible population falls below the threshold for transmission of infection is known as herd immunity threshold. Herd immunity threshold can be achieved by natural infection or vaccination. This could be calculated by the given formula:

$$\text{Herd immunity threshold} = 1 - 1/R_0$$

6. What are the advantages of Herd Immunity ?

Herd immunity can protect people who have not been infected or vaccinated. It is relevant in case of immunization in most of the diseases as it protects individuals who cannot be vaccinated as well, like immunocompromised individuals from getting infected.

The concept of applying herd immunity to human population was probably first done by British doctors like WWC Topley and Sheldon Dudley in the 1920s. At that time in Britain, there was a lot of mortality among school-age children from infectious diseases like measles, diphtheria and scarlet fever. These British doctors wondered whether the same principle of acquired immunity as seen in the livestock, can be applied to human children.

7. What are the disadvantages of Herd Immunity?

There is no disadvantage of herd immunity. It is the ultimate goal in control of many of the infectious diseases.

8. Herd immunity against other common infectious disease. Comment on it.

Many of the infectious diseases exhibit herd immunity. Once a proportion of population is infected, the rest of the people are indirectly protected. For example, the herd immunity for measles can be achieved when 90% of the population are infected. This value depends on the basic reproduction number (R_0) of the infectious agent.

Dudley was a medical administrator who vigorously pushed forward with the concept. As such, the British had already a significant history of animal symbolism for human conditions. Dudley considered human society to be divided into herds like animals. He wrote, "we can contrast the shoregoing herd with the sailor herd, or herds dwelling in hospitals can be compared with those who live in mental hospitals." Later, he even published a picture of school going boys and captioned it the "human herd".

9. What will be the Role of Herd Immunity to overcome COVID-19 and how will we achieve it ?

COVID-19 is a highly contagious disease where transmission occurs from one person to another. As mentioned earlier, herd immunity can be achieved either through natural infection or through vaccination. As we do not have an efficacious vaccine yet, currently the herd immunity can be achieved by natural infection.

Editorial note: The concept of allowing a slow steady infection in the "human herd" to achieve herd immunity is naturally a controversial concept. People are justifiably anxious about being guinea pigs for such social experiment. When some spokesperson of the English government uttered the name early this year, there was severe public backlash and the British government had to withdraw their comment soon. Even if the mortality of COVID-19 is 1%, in order to infect 60% of the population of India (1.4 billion), we need to allow infection of 840 million, with estimated mortality of 8.4 million!! Can we allow this for "greater good"? NEVER

10. When will we achieve Herd Immunity against COVID-19?

This is a very difficult question to answer. The herd immunity will not be achieved everywhere at once. It will differ for all the places. The sero prevalence is higher in urban slums than the non-slum areas and rural areas. This is due to the higher population density in urban slums. These areas will achieve herd immunity faster. In the rural areas the herd effect will take longer. Factors determining the spread of infection will help in achieving herd immunity like overcrowding, higher mobility, increase in human to human interaction, etc.

11. Is it a good plan to be infected by COVID-19 just to "get over with it"? If no, why not?

COVID-19 is a mild disease in majority of cases. In few the disease may be severe and death may occur. The evidence from worldwide shows that we cannot prevent this disease, we can only delay the progression of disease for some time. The risk of infection to all including the vulnerable falls, as immunity builds in the population.

The best way to achieve herd immunity is focussed protection. Best approach that balances the risks and benefits of reaching herd immunity, is to allow those who are at lower risk of morbidity and death to live their lives normally so that immunity to the virus can be build through natural infection. This will protect those who are at highest risk.

With Covid-19, we are facing the same problem faced by the European doctors in the 1920s with Diphtheria. A highly contagious droplet infection with no vaccine or drug. How far should social distancing be enforced and is it feasible to allow some infection in the community?

12. We must slow down the disease process and check these preventable deaths. What should be the strategy ?

The various sero surveillance in parts of India show that the infection is widespread in the community. The

time to slow down the disease process successfully has already passed. Now the emphasis should be to provide best possible care to those who are in need. This way we can check many preventable deaths. Nonetheless continuing preventive control measures like face masks, physical distancing, hand washing, etc will slow down the disease progress.

There are a lot of controversies regarding herd immunity. we encourage the readers to go through other international publications like the excellent review of the topic in The Lancet by Jones et al on September 19, 2020. However, at this point, the editors of this journal do not recommend any strategy for herd immunity through natural infection. This is unethical and probably, would not be successful. India have had dengue and Chikungunya for at least the last 50 years. There is no drug or vaccine. Have Indians achieved herd immunity against these infections?

Also, India have had tuberculosis for thousands of years. There was no vaccine or drug till 1950s. There was hardly any social distancing. Did Indians get herd immunity? NO. India is still the country with highest number of new TB cases.

Thank you Dr. Sanjay K. Rai, for giving the invaluable insight regarding Herd Immunity.

View of the Expert

Pandemic, Casedemic and Infodemic : COVID-19

CCOVID-19 the disease due to novel RNA SARS CoV2 has seen a spectrum of wide clinical variance from silent, asymptomatic disease in large majority to severe, symptomatic disease in a small minority particularly in elderly and vulnerable population¹. Global pandemics in the last few centuries are rare but have had devastating consequences both medically and economically. Covid-19 has halted planet earth virtually making every one live in their own homes and a new world order is evolving with a so called "New Normal". India and Indians have responded optimistically with collective cohesion from all sectors. Covid-19 policies to care have seen excellent coordination and collaboration from all stakeholders including those from government to private sector. Every pandemic leads to panic, confusion and controversies and Covid-19 is no exception. Uncertainty, Unpredictability as well as fear of the unknown is not unique to covid 19 alone but every pandemic planet earth has faced². As we enter in the next season of the pandemic several common threads have emerged in India. Indians have done well with a large proportion being asymptomatic and recovering well with a very low case fatality rate (below 2 %). India has a large burden of hypertension and diabetes as well as heart disease and other chronic diseases including COPD as well as kidney disorders still the case fatality rate is low 3. India in a unique country with paradoxes. Indians have a poor "hygiene quotient" but paradoxically that lead to a better "immune quotient". The innate immunity and dense Indian population clusters in poor ventilated spaces makes Indians uniquely susceptible to SARS CoV2 exposure. Paradoxically despite of high exposure as evidenced by high antibody rates in serosurvey in dense urban slum clusters like Dharavi. Indian may be the first country in the world to develop the elusive often controversial "herd immunity" not Sweden. The link between hygiene hypothesis to autoimmunity is well known but covid will unravel another interesting immune spectrum in the Indians as we enter in the third season of covid pandemic India after summer and monsoon. Impending winter comes with fears of respiratory illness including flu like viruses especially in extreme harsh

climatic zones in Indian geography as well as dense air pollution from farm fires and vehicles. In temperate climates winter peak is expected in North America and Europe but in tropical India where covid peaked in monsoon will it flatten out in winter is an unanswered question. Winter possibly may pose problems only to those parts of India which will see extreme temperatures. ICMR and health department is gearing up to face unlocking, festive season and winter

together and the challenges faced to health care ecosystem is compelling and India will rise to the occasion. The positive direction of public policy to research as well as to treat and care has been seen across India in all states and needs to be complemented. Indians have a unique disadvantage of a large economically vulnerable population which had to battle adversities of health and livelihood both. Again paradoxically Indians have the best "adversity quotient" to battle any adversity from pandemic to cyclones as well as economic hardships. The Indian resilience and its leadership needs to be complemented for sustained struggle battling all odds. Health care workers have been at the forefront and have to protect themselves with care. Indians cannot lose focus on Noncovid health care despite of the covid pandemic and it poses a huge challenge as a tsunami of non covid mini epidemics should not peak up during covid times. Cardio metabolic risk as well as renal, respiratory illness apart from cancer need Special attention and focus should be on these vulnerable groups. During unlocking 'Reverse isolation' of the elderly as well as vulnerable groups will be a strategy to save lives.

"Casedemic" is a new term which has evolved and has been engulfed with a lot of criticism. Often the number of cases in covid don't tell the ground reality. Cases are a function of testing and exposure is far more than those tested. All mathematical models have been proven wrong by the predictably unpredictable corona virus and therefore the so called less testing to more testing debate is an interesting



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science concept. Merely testing and adding numbers do they really matter when most will recover and large proportion will be asymptomatic. It is impossible to test the whole country or whole cities like they have done on some parts of China or Korea. Casedemic term becomes relevant here. The virus is transmissible when usually the cycle threshold (CT) is below 24 (by a well established molecular laboratory) and this the threshold of 40 may need a strong relook by our planners. India was the first country on planet earth to start antigen testing which clearly picks up the CT below 24 which means the infective population. The value of aggressive testing, tracing to the point we screen whole India possibly is not practical. Public health policy makers will have to evolve pragmatic practices which can be realistic and clinically meaningful for care. India may have to adopt in future a symptom based testing policy as well as strategy driven tracing policy to close the tap. The use of digital technology will be the key. Essentially if we can achieve a zero fatality covid rate which may not be possible but a low below 0.5 to 1 percent case fatality rate we can avoid the "Casedemic". A significant number of Indians in some geographies already have had asymptomatic exposures and excellent recovery. The lasting T cell immunity needs systematic research and is more relevant even when we are undergoing Vaccine trials. Mere case numbers and India being number two should not lead to either panic or fear because this is more a "Casedemic" metric not a disability or mortality metric which is the real key in the pandemic.

COVID-19 has arrived via Internet in digitalised world so has lead to a proper "Infodemic" full of myths, changing facts, misconceptions, rumours mediated by social media across the world⁴. In times of uncertainty we need to rely on peer reviewed scientific

literature which had also local relevance. There is a huge bias in top global journals to publish what they want built as a narrative. India needs to build a strong publication network of high impact journals which impact Indians including JIMA and other indian medical journals. We need to generate India specific data for India by Indians in an evidence based matrix. Despite of resource limitations we have excellent repository of made in India compounds as well as test kits which will need validation within our own country. India has capabilities to develop best in class repurposed drugs, monoclonal antibodies/ immunologicals as well vaccines. India is the world's capital of generic medicines with a rich heritage. Indian ancient systems of medicines should also undergo the same scientific research rigor and validation so that they will get the recognition they deserve in an evidence based way. Indian respiratory techniques like Yoga, Pranayams as well as meditation have a role in respiratory physiotherapy both in care and recovery of covidCare. In controlling the Covid 19 pandemic we need to contain both "Casedemic" with a fine balance of "infodemic" and generate india specific data.

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Original Article

Prediction of Cardiovascular Events in Patients with Chronic Kidney Disease by Serial B-Type Natriuretic Peptide Levels

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Background : Patients with CKD and ESRD are at a high risk for cardiovascular complications and it accounts for about 50% of mortality. Echocardiography is recommended by current guidelines as a fundamental tool for profiling cardiovascular disease in these patients but operator skill, and lack of availability of this technique at point of care are barriers. A rapidly assayed biomarker like B-type natriuretic peptide (BNP) with advantages of ease, low cost, availability and objectivity in measurement could be ideal for cardiovascular profiling in ambulatory care settings. High levels of BNP are related to adverse outcomes but it is difficult to interpret one-time BNP measurement. It is likely that serial BNP levels may be more informative.

Objectives : (a) To perform serial B-type natriuretic peptide (BNP) testing at point of care (at baseline, 3 and 6 months) in addition to standard clinical and echocardiographic assessment for cardiovascular status in patients with CKD. (b) To evaluate if change in BNP levels from baseline is associated with cardiovascular events (CVE) over a subsequent six-month period.

Materials and Methods : After approval of Institutional Ethics Committee, a prospective hospital based study was carried out in the Department of Medicine at Sikkim Manipal Institute of Medical Sciences, Sikkim Manipal University, Gangtok for a period of two years (01.11.2013 to 30.10.2015). Adults with CKD stage 3 or higher were included. Those with history of or presence of CV disease were excluded. Baseline demography, clinical assessment and point of care measurements were recorded. All patients were followed up at third and sixth month with clinical and echocardiographic assessment for cardiovascular outcomes and BNP measurement.

Results : Out of 150 patients, a purposive grouping of sample was done to study differences between BNP of patients with Cardiovascular events (CVE) and BNP of patients without CVE. After grouping, descriptive statistics was computed for mean, standard deviation (S.D) and confidence interval (C.I.). Correlation between BNP and CVE was analyzed by linear regression. For one occurrence of CVE, BNP value of 1164 was critical which was statistically significant at 95% C.I. (836.3, 1491.7). Number of patients who had a CVE at 3rd and 6th months were 18 (12%) and 9 (6%) respectively. Most important derivation of this study was that first CVE requires more rise i.e. 1164.05 but later only 642.1 is enough to cause CVE.

Conclusion : Thus it is seen that CVE & BNP levels is highly co-relatable with $p < 0.05$ and serial measurements are more informative.

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Key words : BNP, CKD, CVD, ESRD.

Chronic Kidney Disease (CKD) patients are at a high risk of cardiovascular complications due to increased incidence of cardiomyopathy, cardiac hypertrophy, heart failure and coronary artery

Editor's Comment :

- An important cause of mortality in Chronic Kidney disease is cardiovascular complications. In emergency settings, dyspnea due to heart failure can be distinguished from other causes by B type Natriuretic Peptide. The predictive value of this biomarker in CKD is not established. Adverse outcomes in CKD are associated with high levels of BNP but it is difficult to interpret one-time BNP measurement. Serial BNP levels may be more informative.

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diseases¹. Estimates reveal that 50% of mortality in patients with CKD are attributed to cardiovascular causes². Thus profiling and risk stratification for cardiovascular risk in these patients is essential so

as to identify those at a high risk and to upgrade therapeutic interventions. Echocardiography is recommended by current guidelines as a fundamental tool for this³. Lack of expertise and availability of echocardiography at point of care is a major barrier for its widespread use. Hence the need for a rapidly assayed biomarker which is ideal for cardiovascular profiling in ambulatory care settings. In emergency settings, dyspnea due to heart failure can be distinguished from other causes by B type Natriuretic Peptide⁴. As it is technically easy to perform, economical and reliable, thus it is widely used for clinical evaluation of congestive heart failure. The predictive value of this biomarker in CKD is not established. High levels of BNP are seen in patients with CKD and relation with adverse events have been documented. But it is difficult to interpret one-time BNP measurement in such patients. Serial measurements of BNP levels at various points maybe more informative. An increase from the baseline may be indicative of worsening of the CKD or of new onset cardiovascular events. This would guide the clinician to modify the treatment promptly and accordingly.

AIMS AND OBJECTIVES

A prospective hospital based study was carried out in the Department of Medicine Sikkim Manipal Institute of Medical Sciences, Sikkim over a period of two years (01.11.2013 to 30.10.2015) with the objectives

a) To perform point of care serial B-type natriuretic peptide testing (at baseline, 3 and 6 months) along with standard clinical and echocardiographic evaluation for cardiovascular status in CKD patients

b) To evaluate if change in BNP levels from baseline is associated with cardiovascular events (CVE) over a subsequent six-month period.

After obtaining approval from Institutional Ethics Committee, patients satisfying the following inclusion and exclusion criteria were informed about the study, written informed consent was taken and were recruited in the study.

MATERIALS AND METHODS

Inclusion Criteria :

1. Age more than 18 years
2. Known to have Chronic Kidney Disease stage III or higher based on reduced eGFR (below 60ml/min/1.73m² body surface area as determined by MDRD formula) which is either present for at least 3 months or more, or reduced eGFR in presence of bilateral small kidneys (longitudinal diameter less than 9cm) on ultrasonography, or patients with known ESRD on renal replacement therapy (hemodialysis or peritoneal dialysis)

Exclusion criteria :

1. Patients with a known past history of manifest acute myocardial infarction (as evidenced by clinical symptoms, suggestive ECG changes, and raised cardiac enzymes) or definite unstable angina (as evidenced by clinical symptoms and ECG changes at the time of episode).
2. Patients with atrial fibrillation, second or third degree heart blocks or valvular lesions present at baseline.
3. Critically ill patients who require ICU admission at first presentation for severe hypervolemia, hyperkalemia, uremic encephalopathy or uremic pericarditis.
4. Patients who normally reside outside Sikkim
5. Unconsenting patients

Procedure :

A baseline assessment was based on administration of a questionnaire, simple point-of-care measurements and cardiac assessment. Questionnaire was administered to collect demographic variables and history of renal and cardiac disease. Simple measurements examination, and Point-of-care testing for Glycosylated hemoglobin and BNP at baseline was done. Cardiac assessment at baseline included evaluation for clinical features of heart failure (using Framingham's criteria), electrocardiography (to look for any evidence of chamber hypertrophy, and asymptomatic ischemia, and bundle branch blocks). Assessment of Left ventricular size, left ventricular end diastolic & systolic function and presence of any valvular abnormality was performed and data recorded in a pretested structured proforma. Serial BNP assessment was done by Point-of-care Alere Heart check system at baseline, at 3 months and at 6 months.

Follow up : All patients were followed up at three-

Table 1 — Comparing the baseline variables of two groups (n=150)

	Group I n=40	Group II n=110	p value
Age	52.8±18.2	47.1±12.4	>0.05
Sex M:F	25:15	56:54	Not significant
Ht. (cm)	160 ± 8.1	161 ± 6.8	Not significant
Wt. (Kgs)	58.5 ± 12.2	60.6 ± 12.8	Not significant
Cholesterol	173.1 ± 47.2	160.8 ± 46.6	Not significant
TG	122.0 ± 27.8	130.5 ± 44.4	Not significant
HDL	36.7 ± 6.9	37.7 ± 8.7	Not significant
LDL	123.3 ± 31.5	118.5 ± 29.4	Not significant
CRP	23.7 ± 23.9	27.1 ± 25.8	Not significant
HbA1c	5.6 ± 0.7	5.6 ± 0.68	Not significant
LVID	5.2 ± 0.89	5.2 ± 0.91	Not significant
LVEF	52.9 ± 8.2	55.1 ± 10.8	Not significant

month intervals at third and sixth months after enrolment. The follow up included clinical assessment for cardiovascular outcomes, BNP measurement and echocardiographic assessment at each visit.

Outcome : Cardiovascular event was defined as cardiovascular death, new-onset acute coronary syndrome, pulmonary edema, or an arrhythmia requiring hospitalization and was a composite outcome. This outcome was verified using clinical presentation, electrocardiography or echocardiographic assessment as recorded by treating physicians.

Sample size : Anticipating a 20% event rate over the one year follow up from the baseline, a sample size of 138 would be sufficient to detect a hazard ratio of 0.60 with 85% power at two-sided alpha level of 0.05 and based on this 150 participants were recruited in this study.

RESULTS

Out of total data collection of 150 patients, a purposive grouping of sample was done to study differences between BNP of 40 patients with Cardiovascular events (group I) and BNP of 110 patients without Cardiovascular events (group II). After grouping, descriptive statistics was computed for mean, standard deviation (S.D) and confidence interval (C.I.).

Test of homogeneity of variances was done. Then analysis of variances was done to find whether or not differences of two groups of BNP were significant for CVE.

Mean BNP level of group I (i.e. CKD with CVE) at presentation was 1182.1 ± 121.4 (BNP1) and of group II (i.e. CKD without CVE) was 440.4 ± 367.4 (BNP4). The mean BNP levels of group I at 3 months and 6 months follow up was 1003.0 ± 831.6 (BNP2) and 1386.1 ± 115.5

(BNP3)

respectively. The

mean BNP level

of group II at 3

months & 6

months follow up

was 462.8 ± 413

(BNP5) and

606.1 ± 589.7

(BNP6)

respectively. The

inference is at any point of contact, either at baseline, at 3 months or at 6 months, the mean BNP level in group I was more than double of the mean of group II i.e. those without CVE (Table 2).

On comparing the mean changes from baseline to 3 months & 6 months between the two groups, it was seen that in group I there was a reduction of 179 from baseline to 3 months and an increase of 204 from baseline to 6 months. In group II, the mean BNP change from baseline to 3 months and to 6 months was an increase of 22 and 165 respectively. Comparison between the group in statistically and clinically highly significant ($P = 0.000$). Linear regression was chosen as statistical measure to analyse the correlation between dependent variable (BNP) which is continuous and independent variables (i.e. Cardiovascular events at 3rd & 6th month) which is categorical in nature and the results are as shown in Table 3.

For one occurrence of CV event BNP value of 1164 was critical which was statistically significant at 95% C.I. (836.3, 1491.7). Number of patients who had a cardiovascular event at 3rd and 6th months were 18 (12%) and 9 (6%) respectively. Most important derivation of this study was that patients with rise in BNP may have CVE with rise of 642.1 at a later date. That means first CVE requires more rise i.e. approximately 1164.05 but later rise of only 642.1 is enough to cause CVE. Thus it is seen that CVE & BNP is highly co-relatable with $p < 0.05$.

DISCUSSION

BNP has established its role in diagnosis of heart failure. But in patients with CKD, where elevated levels of BNP & NT pro BNP are frequently encountered, the role of BNP is not yet fully understood. Interpreting a single BNP level at presentation maybe unreliable due to the pre-existing elevated levels. However, serial measurements may provide more reliable information as a predictor of cardiovascular events⁵. 50% of

Table 2 — Comparing the serial levels of BNP between the groups (n=150)

Groups	BNP 1		BNP 2		BNP 3	
Group I (n=40)	Mean	C.I.	Mean	C.I.	Mean	C.I.
	1182.1±121.4	793.6 to 1570.5	1003.0±831.6	737.0 to 1268.9	1386.1±115.5	1016.1 to 1755.7
Group II (n=110)	BNP 4		BNP 5		BNP 6	
	Mean	C.I.	Mean	C.I.	Mean	C.I.
	440.4±367.4	322.8 to 557.5	462.8±413.0	330.6 to 594.3	606.1±589.7	417.5 to 794.7
Group I: CKD with Cardiovascular events, Group II: CKD without Cardiovascular events						
BNP 1: baseline BNP of Group I, BNP 2: BNP at 3 months of Group I, BNP 3: BNP at 6 months of Group I,						
BNP 4: baseline BNP of Group II, BNP 5: BNP at 3 months of Group II, BNP 6: BNP at 6 months of Group II						
C.I.: Confidence Interval						

Table 3 — Correlation between BNP and CVE

	R	R ²	p	F (ANOVA)	Coefficient (y=a+bx)	C.I.
CVE 3rd	0.500	0.250	0.000	49.283	y = 507.5 + 1164.05 x	836.3 – 1491.7
CVE 6th	0.543	0.295	0.000	61.907	y = 523.433 + 642.173x	480.8 – 803.4
CVE 3 rd : Cardiovascular event at 3 rd month, CVE 6 th : Cardiovascular event at 6 th month						

asymptomatic CKD patients and almost all of ESRD patients who are on renal replacement therapy have elevated BNP levels⁶ BNP cut point is influenced by GFR and as the GFR declines, the BNP cut point becomes higher. An upper limit of 200pg/ml for an estimated GFR of 60ml/min/1.73 m² has a high level of diagnostic utility with an area under the ROC curve of 0.80 across all CKD groups. BNP levels are strongly associated with left ventricular (LV) hypertrophy and LV systolic dysfunction as well as with renal dysfunction. Patients with CKD have high incidence of LV hypertrophy and LV systolic dysfunction but even in its absence, BNP levels were observed to be independently associated with GFR and 24 hrs urinary output. Studies have shown BNP to be a better predictor of renal function compared to LV systolic function. While comparing BNP levels with echocardiography in patients with CKD in CREED study sensitivity of 88% and a positive predictive value of 87% in diagnosing LV hypertrophy was observed however, the specificity was only 50% and the negative predictive value was only 53 %⁷.

D Logeart *et al*⁸ had concluded that among serial BNP measurements, pre-discharge BNP remains a strong predictor of death or re admission as compared to common clinical variables, BNP change during hospital stay and echocardiographic findings.

It has been observed that despite difficulty in interpreting BNP levels for diagnosis of LV dysfunction, high BNP is related with poor prognosis. Various studies have shown that highest tertile of BNP or NT-Pro-BNP predicts mortality and cardiovascular death and provides an early indicator of cardiovascular compromise before echo-cardiography. This study primarily aimed to evaluate if change in BNP levels is associated with Cardio Vascular events (CVE) and it was found that the rise in BNP levels had a statistically significant correlation with occurrence of CVE. Also the serial testing during the follow up showed that at a later stage a comparatively lower level maybe enough for a CVE.

CONCLUSION

Serial BNP levels maybe more informative of cardiovascular events in CKD. However, there are no definite guidelines which are available for interpretation of serial levels and how much increase over the baseline should be considered as clinically meaningful. Further studies can be carried out to detect the importance of pre-discharge BNP levels in predicting re admission or mortality in CKD patients.

Limitations : The co-relation between the echocardiographic findings and BNP levels was not done. Echocardiography was used to assess the cardiovascular status only.

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Original Article

Cotrimoxazole in the domiciliary management of patients with severe COVID-19 : A case series

Khawer Naveed Siddiqui¹, Mrinal Kanti Das², Alapan Bandyopadhyay³

Background : COVID-19 pandemic has resulted in nearly 55,000 deaths in India and over 800,000 deaths worldwide. Despite several clinical trials there is no effective proven treatment currently available for this condition and the mainstay of management is only supportive.

Methods : Data from successive patients presenting to a telemedicine clinic between May and August 2020 with severe COVID 19 and receiving domiciliary treatment with oral cotrimoxazole in addition to standard therapy was collected and retrospectively analyzed.

Results : 14 patients received cotrimoxazole in addition to standard therapy. Following start of the treatment regimen, all of the patients showed marked improvement in their clinical parameters including fever and oxygen requirements, following which all of them made complete recoveries. Only one patient required hospital admission for a transient period.

Conclusion : This observation warrants an urgent clinical trial. If the above results are replicated in future trials it may change the way in which we manage patients with this potentially life-threatening condition.

[J Indian Med Assoc 2020; 118(10): 34-8]

Key words : Severe COVID-19, Cotrimoxazole, Domiciliary treatment, Telemedicine.

Over the course of December of 2019, a cluster of patients with clinical presentations similar to viral pneumonia of unknown origin was reported in Wuhan, China¹. Analysis from lower respiratory tract samples of the patients, all of whom were connected to the Hunan Seafood Wholesale Market² indicated that the disease was caused by a novel coronavirus³. By the second week of March 2020, the disease quickly spread throughout China and crossed international borders to infect more than 100,000 people and kill over 4000 in over 100 countries worldwide⁴. Subsequently, the WHO declared the disease, named COVID-19, a pandemic⁵. The causative organism of the disease, was initially named nCoV-2019⁶, however, its name was subsequently changed to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) because of its genetic relation with the Coronavirus strain responsible for the 2003 SARS outbreak⁷. As of August, 2020, more than 20 million people have been reported to be infected by the SARS-

Editor's Comment :

- COVID-19 may have potential life threatening complications including acute respiratory failure from ARDS in a minority of cases.
- Early recognition and treatment of severe COVID-19 is vital to saving lives.
- The use of oral cotrimoxazole may be considered as a potential treatment option in patients with severe COVID-19.
- This may be due to its antimicrobial and anti-inflammatory properties. Urgent clinical trials are recommended.

CoV-2 in more than 210 countries and international territories, with a death toll of over 800,000. The disease has infected more than 2.9 million in India with more than 55,000 confirmed deaths⁸.

A respiratory infection of zoonotic origin, COVID-19 is transmitted from human to human through respiratory droplets⁹. The disease generally presents with respiratory symptoms, with fever, fatigue, myalgia, dry cough and dyspnea being the commonest^{10,11}. It has been seen that people with co-morbidities like, diabetes, cardiovascular, and cerebrovascular diseases, cancers and preexisting lung diseases like Chronic Obstructive Pulmonary disease have a higher risk of developing severe forms of the disease¹¹. In people with severe disease, this symptoms might progress to septic shock, coagulation disorders, Acute Respiratory Distress Syndrome (ARDS) multi-organ failure and even death¹². However, being an emerging

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disease, till date there has been no clear consensus regarding the management of the disease, with different countries and health bodies using their own sets of criteria and management guidelines.

MATERIALS AND METHODS

Data from successive patents presenting to a telemedicine clinic between May and August 2020 with severe COVID 19 and receiving domiciliary treatment with oral cotrimoxazole in addition to standard therapy was collected and retrospectively analyzed. The patients were diagnosed as severe COVID according to the WHO diagnostic criteria of fever and suspected respiratory infection, with any one of the following: respiratory rate >30 breaths/min; severe respiratory distress; or $SpO_2 \leq 93\%$ on room air from their diagnosis¹³. All of the consultations and follow-ups were made through tele-consultancy. All the patients were treated at home as they declined hospital admission. Informed consent was obtained from each patient regarding initiation of cotrimoxazole and collection, analysis and publication of the anonymous data.

STATISTICAL ANALYSIS

Continuous data will be presented using mean and standard deviation. Comparisons between two groups for continuous data will be made using the t-test. Categorical data will be presented as number of patients or percentage of patients. A p-value of <0.05 is considered to be significant.

RESULTS

The demographic and clinical characteristics of the patients are presented in Table 1. The mean age of the patients was 57 ± 8.1 years. Males constituted 9 of the 14 patients consulted (64%) and the rest were female. Of the 14 patients treated, 4 (29%) had Type 2 Diabetes, 3 (21%) had Ischemic Heart Disease, 1 (7%) had Bronchial asthma and 6 (48%) had controlled hypertension and 2 patients has no co-morbidities. High-grade fever (100%) was the most common symptom with which the patients presented themselves (Table 2). The next most common symptoms were

shortness of breath (93%) and persistent cough (93%). Only 2 patients among the 14 developed sore throats. The mean duration of symptoms for the patients was 4 ± 2 days.

Laboratory parameters of the patients were similar (Table 3). The mean oxygen saturations at room air was $87 \pm 5\%$. Mean WBC count was 6620.7 ± 1918.7 . Only 3 patients (21%) tested negative on RT-PCR of nasopharyngeal swabs for COVID-19 with strong clinical, biochemical and radiological suspicion of

Table 1 — Demographic and clinical characteristics of patients (n=14)

Characteristic	Patients (n = 14)	Percentage
Age in years (mean \pm SD)	57 \pm 8 years	
Sex		
Male	9	64%
Female	5	36%
Risk factors*		
Type 2 Diabetes Mellitus	4	29%
Ischemic Heart Disease	3	21%
Bronchial Asthma	1	7%
Controlled hypertension	6	43%
None	2	14%
Treatment Duration (mean \pm SD)	9.7 \pm 2.9 Days	

*More than one risk factors were present in multiple patients

Table 2 — Symptom profile of patients (n = 14)

Symptoms*	Patients (n = 14)	Percentage
Fever	14	100%
Shortness of Breath	13	93%
Cough	13	93%
Sore throat	2	14%

*More than one symptom was present in multiple patients

Table 3 — Clinical and biochemical parameters of patients at presentation (n = 14)

Patient	Duration of symptoms (days)	SpO ₂ at Room Air	Temperature at presentation (°F)	TLC	Neutrophil (%)	Lymphocyte (%)	CRP	RT-PCR for COVID
1	4	81%	101.5	11000	87	9	128	Negative
2	2	90%	101	5180	63	27	NA	Positive
3	3	92%	102	4430	70	15	NA	Negative
4	5	90%	102	6500	55	38	NA	Positive
5	4	93%	102	6140	65	28	NA	Positive
6	3	84%	103	5100	77	18	71.2	Positive
7	4	89%	102	7500	64	34	125	Negative
8	7	74%	103	5900	76	18	35	Positive
9	3	91%	101.5	6600	62	33	41.7	Positive
10	4	88%	102	5200	65	29	5.87	Positive
11	3	91%	101	6900	67	27	5.8	Positive
12	8	82%	103	10340	73	23	158	Positive
13	3	89%	102.5	5200	60	35	19.6	Positive
14	3	91%	104	6700	66	27	3.4	Positive
Mean	4	87	102	6620.7	67.9	25.8	59.4	-
SD	2	5	0.8	1918.7	8.2	8.3	57.9	-

COVID-19. Chest X-Rays were done for 9 patients (64.3%). Rest could not be done due to the ongoing restrictions of all travel/ home isolations. All of the Chest radiographs showed lung infiltrates, with bilateral infiltrates being the most common (Table 4). Only one patient had a high IL6 count of 37.5.

Of the patients, only one required hospitalization for 2 days. All of the rest were cared for at home, with regular follow-up through tele-medicine facility. All of the patients were given oral Cotrimoxazole (960 mg twice daily for 7 to 10 days) and Azithromycin (500 mg once daily). Moist Oxygen Inhalation was provided to 11 (79%) patients. Other drugs that were given to patients are shown in Table 5. The mean duration of treatment for the patients was 10 ± 3 days.

All of the patients made full recovery, with resolution of the presenting symptoms. Statistically significant increase was seen with regards to the mean SpO_2/FiO_2 ratio on presentation and at second measurement 48-72 hours later (mean \pm SD: 417 ± 26 versus 451 ± 12 , p -value <0.001 , Table 6). In addition majority of the patients required oxygen for upto 5 days ($n=8$) from the initiation of treatment. Only a minority of patients required oxygen for a longer period (two patients for 8

days and 1 patient for 6 days). Moreover there was significant improvement of body temperature 48-72 hours after initiation of treatment with cotrimoxazole (mean \pm SD : $102 \pm 0.8^\circ F$ versus $98.5 \pm 0.6^\circ F$, p -value <0.001 , Table 7). Furthermore the mean time taken for the fever to completely subside after initiation of treatment with cotrimoxazole was

69 ± 19 hours. Finally significant improvement was seen on repeat chest radiographs ($n=7$) at one to two weeks after intervention with cotrimoxazole.

DISCUSSION

In this report we have shown that patients with severe COVID-19 (COVID-19 with mild to moderate hypoxia) were reviewed and followed up by a physician via a telemedicine clinic and were provided with domiciliary treatment with cotrimoxazole in addition to standard therapy showing excellent outcomes.

Recent studies have indicated that the envelope spike protein receptor binding domain of the SARS-CoV-2 binds with the angiotensin converting enzyme 2 (ACE2) receptors of the host cells, generally the epithelium of the respiratory system and alveolar pneumocytes type 2 (AT2)^{14,15}. The virus then causes lysis of the infected cells, setting into motion the inflammatory immune response of the host by triggering release of proinflammatory cytokines like interleukin (IL) IL1, IL2, IL6, IL 7, interferon gamma, macrophage

Table 4 — Chest X-Ray PA View findings ($n = 14$)

Chest Radiograph Findings	Patients	Percentage
Bilateral Infiltrates	5	36%
Left Lower Lobe involvement	2	14%
Right lower lobe involvement	2	14%
Not Done	5	36%

Table 5 — Treatment and outcomes of patient with severe COVID-19 ($n = 14$)

Parameters	Patients	Percentage
Medications ^a		
Cotrimoxazole 960 mg PO*	14	100%
Azithromycin 500 mg PO	14	100%
Moist Oxygen Inhalation ^b	11	79%
LMWH 60 mg SC	7	50%
Ivermectin 12 mg PO	7	50%
Doxycycline 100 mg PO	3	21%
Methylprednisolone 30 mg PO	1	7%
Piperacillin-Tazobactam 4.5 g IV	1	7%
Favipavir 200 mg PO	1	7%
Outcome		
Hospitalization	1	7%
Home-based care	13	93%
Death	0	0%
Recovered	14	100%

*More than one medication was used in each patient

^bAs per required

PO: Per Oral; SC: Subcutaneous; IV: Intravenous; LMWH: Low Molecular Weight Heparin

* Cotrimoxazole was given orally at a dose of 960mg twice daily for 7-10 days

Table 6 — SpO_2/FiO_2 (S/F) ratio comparisons at presentation and after 48-72 hours

Patient	S/F ratio at presentation	S/F ratio after 48-72 hours
1	386	438
2	429	457
3	438	462
4	429	471
5	448	448
6	400	433
7	424	462
8	352	429
9	433	457
10	419	443
11	433	452
12	390	447
13	424	457
14	433	452
Mean	417	451
SD	26	12

Table 7 — Body temperature comparisons at presentation and after 48-72 hours

Patient	Body temperature at presentation	Body temperature after 48-72 hours
1	101.5	98.3
2	101	98.2
3	102	100
4	102	99.5
5	102	98
6	103	98.3
7	102	98.1
8	103	98.4
9	101.5	97.8
10	102	98
11	101	97.8
12	103	99.2
13	102.5	99.2
14	104	98.2
Mean	102	98.5
SD	0.8	0.6

inflammatory proteins, tumor necrosis factor alpha etc². In patients with severe forms of the disease, the excessive immune response by the host coupled with the continued lysis of the infected cells generate a cytokine storm syndrome (CSS). Damage Associated Molecular Patterns (DAMPs) released following mitochondrial injury in host cells lead to the stimulation of Formyl Peptide Receptors (FPRs) situated on the outer surface of the cell membrane of the neutrophils and monocytes, which in turn cause the recruitment of these cells to the lung. When stimulated, FPRs cause the release of Reactive Oxygen Species (ROS) in the tissue, leading to the release of even more cytokines^{16,17}. This leads to extensive tissue damage, causing rapid progression of mild respiratory symptoms like dry cough and fever into Acute Respiratory Distress Syndrome followed by multiple organ failure in susceptible patients². The key to managing severe COVID-19 is preventing this cytokine storm from taking place, in addition to making sure that there are no superimposed secondary bacterial infections in the already compromised lungs of the patient.

Cotrimoxazole is a commonly used antibiotic used to treat a wide range of diseases ranging from Urinary and Respiratory tract infections to opportunistic pneumocystis pneumonia and toxoplasmosis in people with HIV/AIDS. Composed of one-part Trimethoprim and five parts Sulfamethoxazole. Cotrimoxazole is a cheap drug with excellent efficacy and a high safety profile¹⁸. This has led it to being enlisted in the WHO list of essential medicines¹⁹ and being available as a generic medication²⁰. Research done *a priori* suggest that Cotrimoxazole can block the FPRs, leading to the prevention of inflammatory cell recruitment, release of cytokines and ROS in the damaged tissue^{21,22}. Cotrimoxazole have also been found to be effective at the reduction of pro-inflammatory cytokines like IL-1, 2, 6, 8 and Tumor Necrosis Factor α ²³. This might lead to prevention of the progression of the clinically severe COVID-19 into ARDS by thwarting the impending CSS. Furthermore, the drug is highly effective in the treatment of nosocomial and opportunistic infections. This might also have an effect in averting the progression of COVID to ARDS by preventing any secondary bacterial infection. The addition of this drug to standard therapy showed substantial improvement in the course of the disease. Low Molecular Weight Heparin was used in some patients with large number of co-morbidities and/or more severe disease to prevent venous thromboembolism commonly seen in patients suffering from COVID-19²⁴. The rapid and complete recoveries

that all of the 14 patients treated with Cotrimoxazole made thus lends credence to this idea that cotrimoxazole may be an effective drug to combat the disease and is in keeping with a recent report by Quadery and colleagues²⁵.

Another important aspect of the reported cases is that 13 out of the 14 patients were managed in a domiciliary setting through telemedicine, without needing admission to a specialized in-patient setup. Only one patient was hospitalized with a duration of stay of 2 days. In countries of South and South-East Asia, high population density, poor healthcare infrastructure, high out of pocket healthcare expenses, and rampant poverty makes it hard for a large part of the populace to avail and access healthcare²⁶. In this scenario, a domiciliary treatment regimen along with tele-medicine consultation that can help manage clinically severe COVID-19 in an out-patient setup and lessen the need to admit the patient in intensive care has the potential to alleviate a lot of burden not only from the patients but also from the healthcare facilities, whose resources are stretched thin in order to combat the pandemic. As all of the drugs forming the treatment regimen for the management of these 14 patients are common, widely used and inexpensive, they can be easily accessible to the patient population. Most of them are easily self-administrable (except for LMWH which may need a help or video supervision by a doctor during administering the drug), and which makes them ideal for home-based care. In countries where there is a dearth of specialized setups for the management of COVID-19, such a regimen that can reach patients in hard to reach areas by virtue of being prescribed and followed up through telemedicine can be of immense help, especially in the context of public health and healthcare delivery systems.

CONCLUSIONS

In this case series for the first time we are able to demonstrate excellent outcomes by adding oral Cotrimoxazole to standard therapy in patients with severe COVID-19 in a domiciliary setting where the patients were reviewed and followed up via a telemedicine facility. However, further research using comparison groups need to be done to substantiate and validate the findings reported in this report.

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Conflict of Interest : None

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This is a pilot study with promising results. The study is to be undertaken with adequate sample size in multiple centres along with control group.

Original Article

Retrospective Analysis of Fertility Rate and Family Planning Programme in One Thousand Families of Industrial Workers

Dillip Kumar Dutta¹, Indranil Dutta²

Objectives : The socio-economic factors, which were correlated with increasing fertility rate in industrial area, were studied to understand how these factors exert their influence on the increase in population in industrial sectors especially in developing countries like India.

Introduction : Family planning is important to development of nation. Family planning is often neglected or misunderstood in rural areas or in poor socioeconomic group of people leading to early unplanned pregnancies or more number of pregnancy leading to malnutrition and economic pressure on the earning member.

Material and Methods : One thousand families of Industrial workers were interviewed between January 2012 to January 2014 in and around Kalyani, West Bengal, India to find out various socio-economic factors responsible for high fertility rate & failure of family planning programme in industrial area.

Results : Eighty five percent of women are married before 20 years of age and 82 percent have 4 or more children. 91% did not have any basic education. Economic status of 90% was found to be very poor. 80% were reluctant to undergo any family planning operation. Only 11% tubectomy & 9% vasectomy operation cases were reported. The reason for non acceptance of sterilization operation were found to be desire for more children (50%), opposition from husband (10%), fear of operation (7.5%), religious prejudices (12%) alien to traditional culture (8.5%), interference with natural method of stopping childbirth (5%) and no reason (4.5%).

Conclusion : Success of family planning programme in an industrial area depends particularly on socio economic status of the family. Therefore vigorous promotion of family planning problem is essential in an industrial area.

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Key words : Family Planning, Fertility, Industrial worker, Sterilization, Contraception.

Access to healthcare sexual and reproductive is the key for sustainable development. Research suggests that maternal and child health outcomes can be averted by use of adequate contraception methods. This in turn can prevent 22% of maternal death and stillbirths¹.

But the major problem in our country lies in the fact that contraception is restricted to only married couples compared to unmarried because it is largely seen as a taboo in our country. Even if it is used in whatever amounts usually modern methods of family planning were not used².

Various International organizations have committed to Family Planning 2020. Sustainable Development Goals components also stress on family planning globally³.

Editor's Comment :

- Early marriage leads to early pregnancies, Early marriage has to be deferred to atleast 20 years of age.
- In poor socioeconomic conditions or religious bindings, if early marriage is unavoidable, proper contraception advice can defer pregnancies for some time.
- If family is complete contraception in form of male or female sterilization operations need to be popularized.
- Success of family planning programme in an industrial area depends particularly on socio economic status of the family. Therefore vigorous promotion of family planning problem is essential in an industrial area.

AIM

The socio-economic factors, which were possibly correlated with increasing fertility rate in industrial area, were studied to understand how these factors exert their influence on the increase in population in industrial sectors especially in developing countries like India.

MATERIALS AND METHODS

This survey was undertaken at Industrial area in and around Kalyani, India from January 2012 to January 2014. During this period 1000 families of Industrial

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workers were interviewed and analyzed to find out various socio-economic factors responsible for high fertility rate & failure of family planning programme. A complete history regarding types of workers, age of women at marriage, parity, literacy rate, economic status, nutritional status, pregnancy wastage, family planning operation and lastly reason for failure of sterilization operation was evaluated in details. These findings were tabulated and correlated with one another.

OBSERVATION

Out of 1000 families 80% had husband as worker where as 20% had female as worker (Table 1).

Out of the women 85% were married before 20 years of age (Table 2).

Most of the workers had four or more children (82%). A lower fertility rate was found in employed women as compared to unemployed women (Table 3).

Neonatal death within 7 days (12%) and neonatal death from 7 days to 28 days (8%) were found to be higher than stillbirth (5%) and infant death 12 days to 1 year (6%).

Most of the neonatal and infant death was found to be due to prematurity & infection because of unhygienic condition and poor sanitization which are easily preventable.

On further evaluation it was revealed that (Table 4) 91% did not have any basic education as compared to 9% primary school level. None of them had any knowledge as regards to fertility control, importance of ante, intra & post natal care & family planning programme.

From Table 5 it was found that economic status of 90% were found to be poor. They include 80% male worker and 10% female worker. Only 9% female worker were enjoying average economic status because of more earning member of the family. On further analysis 80% of women were consuming poor diet.

Most of the women had lost either one or two or more foetus or child because of various factor (Table 6). Perinatal mortality were found to be 170/1000 total births.

From the Table 7, it appeared that 80% of family was reluctant to undergo any family planning operation. Only 11% had tubectomy and 9% had vasectomy operation.

On further analysis from 800 non-acceptances of sterilization operation cases, it was found (Table 8) that desire for more children (50%) which leads to more employed hands in family, opposition from husband (10%), fear of operation (7.5%), against religion (12%), alien to traditional culture (8.5%), interference with natural method of stopping childbirth (5%) and no

reason (4.5%).

DISCUSSION

This study has shown that the acceptance of sterilization operation is low in industrial workers inspite of the high fertility rate. The reasons for high fertility rate in Industrial workers have been seen in the present study. There is a great desire to marry early because of customs, taboos and early sexual desire. 85% of women were

Table 1 — Distribution of worker

	Number	Percentage
Male worker	800	80
Female worker	200	20

Table 2 — Age at Marriage of Female partner

	Number	Percentage
10 - 15 Years	350	35
15 - 20 Years	500	50
21 - 25 Years	100	10
26 - 30 Years	30	3
31 - 35 Years	20	2
35 and above	-	-

Table 3 — Parity Distribution

Parity	Number	Percentage
1 - 2	30	3
2 - 3	50	5
3 - 4	100	10
4 - 5	250	25
5 - 6	270	27
6 and above	300	30

Table 4 — Literacy Rate

	Number	Percentage
Illiterate	910	91
Primary School Level	90	9
High School level	—	—
College Level	—	—

Table 5 — Economic Status

	Number	Percentage
Poor	900	90
Average	90	9
Good	10	1

Table 6 — Infant Mortality Rate

	Number (310)	Per 100 total Births
Still Birth	50	50/1000(5%)
Neonatal Death (within 7 days)	120	120/1000(12%)
Neonatal Death (7 days to 28 days)	80	80/1000(8%)
Infant Death (28 days to 1 year)	60	60/1000(6%)

married before 20 years of age, had 4 or more children. These young married women

showed lack of contraceptive knowledge as

compared to older married women

and were reluctant to discuss family

planning with interviewers.

Hence raising the age of marriage of

women above 20 years could have a

significant effect in curtailing the

effective reproductive span of women and

thereby, reduction in fertility could be

achieved because of better

understanding of family planning measures by

older women.

Another factor which has a profound influence

in reducing fertility, is the

literacy rate of couple, particularly that of the wife. In 1981 census only 24.88% of female and 46.74% of male were literate in India. In the present study 91% female were literate. Only 9% had attended the Primary school level. This signified that only when, the women's educational level reaches matriculation & above, then only it begins to have any noticeable influence on fertility. As it is seen that the better educated a woman is the more likely she is to use contraceptive^{2,7-9,11}.

There is a significant correlation between female employment and fertility. In India the percentage of female employment had slightly decreased from 32% to 28% in the period from 1901 to 1961. In the present series 20% of women were employed in Industrial area. And their fertility pattern was found to be lower (below 4 children) than the unemployed female worker (above 4 children), therefore fertility rate can be lowered if there is more employment opportunity for women in industrial area. Employed women are more likely to use contraceptive than women who have never worked^{7,11}.

Economic status is another factor which has an influence on fertility in an Industrial worker. High fertility rates were observed in families of Industrial workers with poor economic status (90%), as compared to low fertility rates in cases of families having average (9%), and high (1%) economic status respectively. All these socio Economic factors were very much correlated with increasing perinatal mortality rate (170/1000 per live births) and neonatal death (80/1000 per live births).

Family planning programme in industrial area were found to be very poor. 80% of family was reluctant to undergo any family planning operation.

Main reasons that have been found by the present study for non-acceptability of sterilization operation in industrial area were a great desire for more children 50% which leads to more employed hand in the family which indirectly increases the fertility rate.

Sterilization in whatever form is an operation. The general surgery phobia is a big problem in industrial area. 7.5% cases in the present series were afraid of Sterilization operation because of health risks after operation which can be properly predicted before operation⁴ with proper & adequate counseling. However the risk following sterilization was found to be minimal as compared to pregnancy. Pregnancy has higher risk

Table 7 — Acceptance & Non Acceptance of Family Planning Operation (n=1000)

	Number	Percentage
Non Acceptance	800	80
Tubectomy	110	11
Vasectomy	90	9

Table 8 — Reason for Non-Acceptance of sterilization Operation (800)

	Operation Number	Percentage
Desire more children	400	50
Opposition from husband	80	10
Fear of Operation	60	7.5
Too permanent	22	2.5
Against religion	96	12
Alien to Traditional culture	68	8.5
Interference with natural method of supplying childbirth	40	5
No reason	34	4.5

factors whether from induced abortion³ or from childbirth^{5,10}.

Opposition from husband (10%), against religion (12%), and alien to traditional culture (8.5%) in the present series is a real problem that have to be overcome with proper education & counseling. In counseling for Sterilization, the husband should be taken into confidence from the initial stage.

CONCLUSIONS

One thousand families of Industrial workers were interviewed between January 2012 to January 2014 in and around Kalyani, West Bengal, India to find out various socio-economic factors responsible for high fertility rate & failure of family planning programme in industrial area.

Eighty five percent of women are married before 20 years of age and 82 percent have 4 or more children. 91% did not have any basic education. Economic status of 90% was found to be very poor. Perinatal mortality rate was found to be 170/1000 total births in their reproductive period.

80% were reluctant to undergo any family planning operation. Only 11% tubectomy & 9% vasectomy operation cases were reported. The reason for non acceptance of sterilization operation were found to be desire for more children(50%), opposition from husband (10%), fear of operation(7.5%), religious prejudices (12%) alien to traditional culture(8.5%), interference with natural method of stopping childbirth (5%) and no reason (4.5%). It appeared from the study that success of family planning programme in an industrial area depends particularly on socio economic status of the family. Therefore vigorous promotion of family planning problem is essential in an industrial area.

More stress is laid on barrier IUCD oral contraceptive methods particularly to those women or couple who were reluctant to undergo sterilization operation. It is hoped that in near future we can also perform a good number of Sterilization operations.

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— **Hony Editor**

Original Article

Appendicular Lump : Revisiting with New Challenge

Mriganka Ghosh¹, Soumita Ghosh Sengupta², Samidh Shuddha Datta³

Background : Acute appendicitis is still probably the commonest cause of acute abdomen ,needing surgical intervention. But in case of prolongation of inflammation, appendicular lump may form in 2-6% cases. The traditional treatment of appendicular lump is conservative followed by delayed appendectomy. Another option is early intervention before the lump becomes well circumscribed when disturbing the anatomy is risky.

We performed an institution based observational study over all those patients clinically diagnosed with appendicular lump presented in indoor or outpatient Department of General Surgery in Medical College, Kolkata during a period of one and half year. We formulated a protocol strictly based on detailed history and meticulous clinical examination and sonology of abdomen and chose appropriate option of either early intervention or Ochsner-Sherren regime and followed up them for next 6 months.

Total 31 patients were taken into the study after exercising necessary exclusion and out of them, 21 patients could be successfully treated with immediate operation. No primary colonic resection was required and neither, there was any case of post-operative faecal fistula and incisional hernia. Of those patients, treated conservatively, 6 patients eventually underwent interval appendectomy.

Conclusions : With the use of good clinical acumen, sound knowledge of surgical anatomy and judicious help of imaging, early exploration in appendicular lump is hazardless, confirms the diagnosis, minimises the duration of hospital stay avoiding any chance of readmission and further expenses.

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Key words : Appendicular lump, Ochsner-Sherren regime, early intervention.

Acute appendicitis is probably the most frequent acute surgical pathology and emergency appendectomy is the best available treatment of it. But if not duly attended, the ongoing inflammation may sometimes be contained by the patient's own defence mechanisms and an inflammatory mass or an appendicular lump may result, as in 2-6% cases¹. Immediate surgery is often hazardous thanks to the distorted anatomy, problems in closing the appendiceal stump because of gross oedema and risk of injuries to intestines. Any operative endeavour could end up with colonic resections, ie, ileocectomy or right hemicolectomy or faecal fistula post operatively^{2,3}.

Conservative management, namely Ochsner-Sherren (OS) regime with interval appendectomy has conventionally been the most popular choice. But this protocol has recently been challenged as the risk of recurrence is negligible^{4,5}.

Moreover, the evil of conservative management is

Editor's Comment :

- Although traditional treatment of appendicular lump is conservative followed by delayed appendectomy, earliest intervention is the recent trend.
- If selected with proper clinical judgement and imaging support, early exploration is safe, and cost effective.

its failure, which may be observed in 10-20% of the cases when it demands more risky or demanding emergency surgery which carries more morbidity and mortality⁶. Another disadvantage is the obscurity related to other possibilities like malignancy of caecum, neoplasm or appendix, ileo-ileal intussusception and last but not the least, ileo-cecal tuberculosis, which may be spuriously misdiagnosed as appendicular lump, whose true diagnosis may be delayed⁷⁻⁹.

It is high time to move on from the traditional conservative management to immediate intervention, which allows clinician to diagnose the disease and then to cure which in turn effectively shortens hospital stay, obviating any further need of admission^{1,7,10}.

The present study was conducted with the objective to observe the course of appendicular lump with reference to its variant treatment modalities i.e. early intervention and conservative management in terms of overall outcome.

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MATERIAL AND METHOD

It was an institution based prospective observational study performed in the indoor and outpatient Department of General Surgery in Medical College, Kolkata. Each patient was required to give written informed consent prior to enrolment in the study and a prior clearance was taken as per the institute's ethical committee guidelines. A detailed history and a thorough physical examination during indoor admission and regular follow up and correspondence after the discharge of each patient formed the basis of the study. After making an appropriate clinical diagnosis, one or more of the special investigations – Ultra sound in this case was carried out for the confirmation of the diagnosis.

The idea of deciding early intervention in a patient with clinically palpable lump in right lower quadrant (RLQ) of abdomen is critical. Understanding the pathogenesis of appendicitis is utmost important.

Luminal obstruction of the appendix is probably the final common pathway towards involvement of appendiceal gangrene and perforation. Although initially, the lumen remains patent despite mucosal inflammation and lymphoid hyperplasia, with uninterrupted mucus secretion and inflammatory exudation, the blockage becomes imminent. Increased intraluminal pressure further affected lymphatic drainage, causing further edema and mucosal necrosis favouring bacterial translocation to the submucosa. Sometimes spontaneously or in response to any medical intervention with antibiotics, resolution may be achieved at this point. But if the condition is allowed to remain unchallenged and un-intervened, soon venous obstruction, then arterial obstruction and finally gangrenous changes in the appendix wall with generalized bacterial contamination of the peritoneal cavity may follow^{11,12}.

Even at this stage, possibilities are varied depending upon individual case, age, the immune status of the patient and the virulence of the organism. More commonly, greater omentum and small bowel loops rush to wrap and segregate the inflamed appendix, limiting the spread of peritoneal contamination and resulting in a phlegmonous mass or para-caecal abscess^{8,13}.

But the greatest threat is generalized peritonitis which results from an unchallenged frank perforation of a gangrenous appendix or dissemination from an otherwise localized appendicular abscess facilitated by aggravating factors like extremes of age, immunocompromise, diabetes mellitus and a free-lying pelvic appendix and previous abdominal surgery that limits

the mobility of the greater omentum.

Rarely, a mucus filled distended organ termed as mucocele of appendix can be a sequel even after the inflammation of appendix subsides completely.

Despite numerous advancement in imaging modalities, the diagnosis of appendicitis is still clinic based and there are typical signs and symptoms, pain abdomen, nausea, vomiting, tender right iliac fossa and others which give an suspicion of appendicitis. Now, conventionally, in any patient with right iliac fossa lump with prior symptoms suggestive of acute appendicitis, the next plan of treatment mostly sways towards conservative approach which is traditional and its success is well established.

But, we often use the term appendicular lump loosely and stamp its diagnosis in the mere presence of lump in RLQ, irrespective of its duration and variety of clinical presentation. Even any lump of appendicular origin has different implications. It could be mere conglomeration of gut (often spuriously interpreted as lump by sonography) or it could be an appendicular phlegmon (inflamed yet viable viscera just coming together to contain the inflammation) or an early lump (when components are adhered but not inseparable) and finally, it may be an well circumscribed classical appendicular lump and last but not the least, an appendicular abscess¹⁴.

Now if we go further deep, and consider all emerging symptoms and accompanying signs and underlying pathogenesis, we find there is an distinct correlation between different pathogenetic stages and their sequelae and the emerging symptoms and signs with their changing variation and severity. We believed and also past researchers vindicated that if we select those early cases, where lumps are palpable but not hard, tender, margins are irregular (reflecting that the inflammatory process is yet to be contained) a decision of intervention can be taken judiciously with good successful outcome. On the contrary, any attempt to disturb an already contained inflammation as reflected in an well circumscribed, nontender lump presenting after that golden period is likely to be hazardous.

Exclusion criteria for the study :

- diabetics
- immunocompromised
- lump with history of onset of pain > 10 days
- lump with strong suspicion of malignancy.

All interventions were done by experienced surgeons and all surgical specimens (including appendix, suspicious mesenteric lymph nodes and greater omentum) were examined by senior pathologist.

OBSERVATIONS

Out of 31 patients, 10 are managed conservatively while 21 were operated. This is not statistically significant difference in the mean age of the patients in either treatment modalities.

Pain was obviously the predominant symptoms; all patients had RLQ pain when attended or in the history, signifying RLQ pain to be most consistently presenting symptom.

The average duration of pain in conservatively managed patients was 7.8 days at the time of presentation whereas in operated patient it was 4.2 days: which is statistically significant (Fig 1/ Table 1).

There was no statistically significant difference in gender distribution in both management. Overall female: male is 3: 2. 60% of conservatively managed patients had history of anorexia whereas 85% of operated patients had history of same. Overall 77.4% patients had history of anorexia. More operated patients (81%) had complaints of nausea and vomiting than conservatively treated patients.

70% of conservatively treated patient had history of fever whereas only 38.1 % of operated patients had history of same. But this is statistically not significant.

30% of conservative patients had increased pulse rate whereas 90% of operated patients had the same. Overall 58% of patients had increased neutrophil count (40% of conservative and 66.7% of operative).

Now, in regards to the clinical appreciation of lump in RIF, overall 64.5% had firm lump, but there were other factors which dictated the decision of intervention and hence the outcome.

95% of those underwent surgery had lumps with irregular border whereas only 10% of lump with regular border was operated (Fig 2).

Overall USG done within 2-3 days of admission could diagnose a lump in 64% of patients. Of them, in conservative arm, USG detected lump in 100% cases.

Intraoperatively, in most cases, there were either grossly inflamed appendix or appendicular phlegmon (66.7%)(as shown in Fig 3) whereas 23.8% cases had suppurative appendix and 9.9% had gangrenous appendix (Fig 4). Histopathologically, all appendicular specimen revealed inflammatory aetiology, mesenteric lymph nodes and bits of greater omentum as collected showed reactive changes with no sign of any suspicious aetiology which demands further investigation.

Only 20% of conservatively managed patients were discharged within 7 days while rest 80% required more than 7 days (up to 14 days). On the same page 85.7%

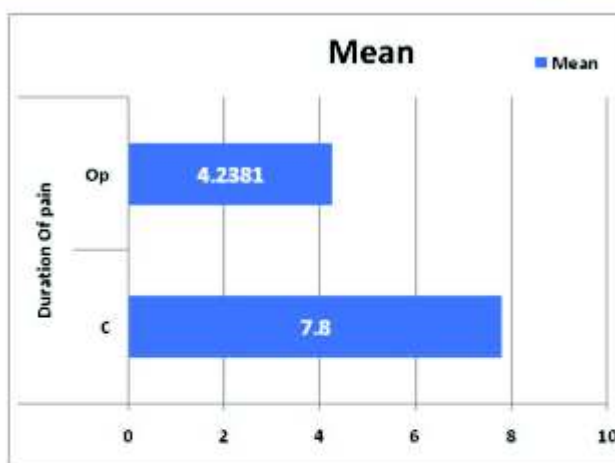


Fig1 — Mean Duration of pain : management

	Number	Mean	SD	Minimum	Maximum	Median	p-Value
Duration of pain C	10	7.8000	1.3166	6.0000	10.0000	7.5000	<0.0001
Op	21	4.2381	1.3381	2.0000	7.0000	4.0000	

of operated patients were discharged within 7 days.

Mean duration of hospital stay in conservative group were 8.7 days while in operative group it was 5.8 days which had statistical significance. This implies that the course of resolution of disease process took longer time in conservatively managed patients.

Operated patients had mild complications like wound complications, chest complications, whereas conservatively managed patients had complications of residual abscess, chest complications etc.

No patient in our study developed neither faecal fistula nor incisional hernia.

23.8% of operated cases had wound complications which is managed with regular dressing and antibiotics. 30% of conservative patients had residual abscess whereas there was no residual abscess in operated

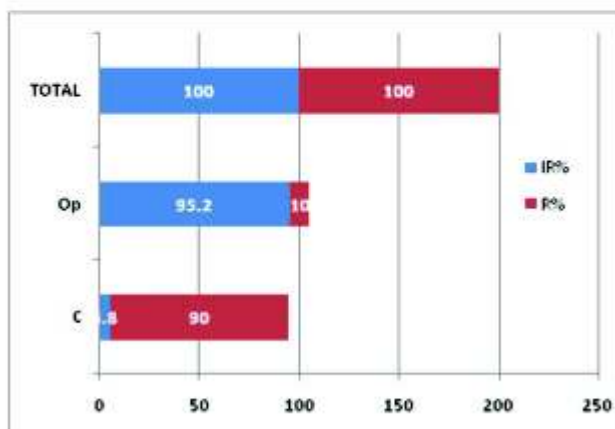


Fig 2 — IR (Irregular margin) % & R(regular margin) % Association of borders



Fig 3 — Showing appendicular phlegmon

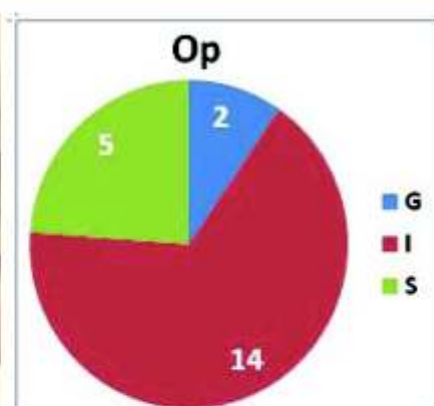


Fig 4 — Association of operative finding : management

patients. 40% of patients in conservative management had chest complications whereas only 14.3% of patients had chest complications in the surgical arm.

7 out of 10 conservatively managed patients could be followed up as 3 were lost after first revisit. Interestingly, 5 patients came with recurrent symptoms of appendicitis. Eventually, 6 patients underwent interval appendectomy and one patient didn't opt for appendectomy since that person was clinically symptom free.

DISCUSSION

Palpable lump in right lower quadrant of abdomen has varied implications. Prior history suggestive of appendicitis invariably substantiate the diagnosis of lump of appendicular aetiology where conservative management followed by appendectomy after 6 weeks or so is the golden rule of management. Immediate surgery was said to be more risky and non-operative option was favoured because of high success rate.

But the significance of OS regime has been lately paled into insignificance due to varied reasons. One is its failure that complicates the scenario and next is the ambiguity associated with differential diagnosis. The possibilities of different pathology in the form of malignancy, ilio-caecal TB and lympho proliferative disorders cannot be ignored. An apparently successful nonsurgical treatment of the lump may even delay the underlying diagnosis of cancer or Crohn's disease (CD) where role of imaging like CECT is often equivocal^{15,16}.

More decisively, many researchers opined that there is hardly any need for interval appendectomy as the vast majority (95%) of patients managed conservatively is unlikely to develop a recurrence^{6,17}. Secondly, the idea behind confirming the diagnosis of

appendicular origin during interval appendectomy or identifying alternative diagnosis like that of malignancy becomes irrelevant as the consequence of delay in diagnosis of any intra-abdominal malignant pathology could be sinister. The proponents of early surgery emphasizes on the added benefit of immediate diagnosis of serious diseases masquerading as an appendicular mass while leaving nothing uncertain for the future¹⁸.

Now it is observed, that even in the background of inflammatory pathology, the decision and its success with little

or no complication lies in the consideration of different stages of it and varying degree of fibroblast deposition and degree of protective containment. The guidance of imaging (USG/CT scan) which often spurious or misleading, should be taken with a pinch of salt. So clinical judgement is again superior than the rest.

If patient is examined with proper technique after fulfilling all general pertinent pre requisites (like pre-counselling, relaxing the patient satisfactorily, palpation starting from a quadrant radially opposite to the area of inflammation) which are often ignored, those clinical variants can be well appreciated. In a normal, immuno-competent patient, lump usually begin to form after 48 to 72 hours. Initially, the tenderness is most at or around McBurney's point but it is also felt in left iliac fossa (Rovsing's sign may be +ve), a very ill defined, irregular lump like feeling may be there which no way gives an idea of its shape. This is either appendicular phlegmon or early lump which is mostly seen during 3-5 days of onset of pain. The adhesion at this period is very much separable when the process of fibrosis hardly sets in. During this golden period (Table 2) if patient is operated by surgeon with good surgical experience and expertise, techniques adhering to surgical principle of good tissue respect, necessary finger dissection, avoidance of sharp, traumatic instruments—all these can ensure successful outcome. But on further progression of time, the phlegmon/early lump soon become well circumscribed, well defined, taking round or piriform shape, the fibroblast deposition becomes maximum, adhesions turns more organized when intervention is likely to be beset with high risks.

Appendicular lump is most commonly found in the age group of 21-30 years (C Pandey, R Kesharwani *et al*)¹⁹. In our study the mean age in conservatively treated patients were 34.5 years whereas in operated

Table 2 — The golden time zone for intervention

Days from onset	Symptoms		Clinical findings						
	Pain in RIF	Systemic (appetite/nausea/vomiting)	Tender RIF	Muscle guard in RIF	Rovsing sign	Lump tenderness	Shape/size	consistency	Margin/regularity
2-3	+++	+++	++	+/++	+ve	+++	No lump	—	—
3-4	+	+/++	+	+	-ve /+ve	+	- /oblong	Soft/ill defined	Vague/irregular
4-5	+	-	-/+	-	-ve	-/+	globular	Firm to hard	More defined and regular
5-8	-	-	-/+	-	-ve	-/+	globular	Hard	Well circumscribed

The best period to intervene
 Period, when intervention can be done with proper precaution

patients were 26.3 years. Overall mean age was 29 years which is similar to the other study. The mean duration of pain of conservatively treated patients were 7.8 days where as it was 4.2 days in operated patients till operated. In the literature average duration pain was found to be approximately 4 days which was concurrent to this study¹⁹. Early presentation influenced in a way towards decision for intervention.

Mean duration of hospitalization was 8.7 days in conservatively treated patients and in operated patients it was 5.8 days which was statistically significant and it shows that patients with surgical modality of treatment had a shorter course of resolution of symptoms and recovery. Other established studies showed similar outcome (V K Agarwal *et al*)²⁰. And slightly higher than another study

In our study we found there was female preponderance though not statistically significant with female : male ratio of 3:2. Reviewing the existing literature one study showed F:M ratio of 1.9:1 (C Pandey *et al*)¹⁹ whereas another showed almost equal distribution in both sexes (R S Bhandari *et al*)¹⁸. Probably it varies from region to region, dietary habits, lifestyles.

In our study all patients, at some stage of their disease progression, presented with pain in the right lower quadrant. This is also in line with other studies¹⁹.

70% of our conservatively treated patients had history of fever whereas only 38.1% in the surgical arm had febrile episodes. Overall 48% patients had fever as complaint. Available studies show this to be in line with their findings (C Pandey *et al*)¹⁹.

85.7% of operated patients had anorexia where as 60% of conservatively treated patients had the same. Overall 77.4% of patients had anorexia. Anorexia, apart from other systemic complaint like nausea, vomiting is one the specific sign guiding towards the diagnosis

of appendicular aetiology and reviewing the literature yielded similar findings (C Pandey *et al*)¹⁹.

Overall, 71% of patients had pulse rate more than 90 per minute at the time of presentation. 90.5% of operated patients had increased pulse rate while only 30% of the conservatively managed patients had

the same. It was statistically significant. The logic is obvious as the lump localises and inflammation subsides, tachycardia associated with it also decreases.

51.6% of all patients had TLC > 12000. this finding is also corroborated by Pratik H Vyas *et al*. 40% of conservatively treated patients had increased leukocyte count at admission, whereas 57.1% operated patients had the same. Quite similarly, 66.7% operated patients had neutrophilia with shift to left whereas conservative group had 40% patients with same. Over all 58.1% had neutrophilia with shift to left. Shift to left has been among one of the most defining criteria in diagnosis of appendicitis but correlation with appendicular lump doesn't translate with same sensitivity. It may be due to the fact that when appendicular lump forms, infection is more on the controlled side.

USG is the most commonly prescribed initial imaging for suspected appendicular pathology and various studies reflected its sensitivity to be approximately 90% with appendicitis or appendicular lump. In our experience, it detected a lump 64.5% of times, where USG detected lump in all conservatively treated pts but for operative group the yield fell short, only 47.6%.

Consistency of the lump goes a long way in deciding which cases to operate but was not the only deciding factor. We found 20 patients with firm lump all of which could be operated, whereas only 1 out of 11 cases with hard lump where we successfully ventured, thanks to other favourable factors.

Borders or margins were also influential deciding criteria. 95.2% cases with irregular margins could be operated. But only 1 out of 10 cases with regular borders could be operated. Regular margin signifies localisation of infection with well-formed lump.

In all patients with lumps of varying consistency,

borders and other dictating factors, appendix, when intervened, invariably showed variable stages like appendicular phlegmon, or appendicular abscess or gangrenous change depending upon the course of the particular case. In present study we found inflamed appendix 66.7% of operated cases, suppurative cases 23.8% cases, and gangrenous changes 9.5% cases. This was similar to what B Patel *et al* found in their study²¹.

CONCLUSION

In the light of present study, we realized that both treatment options of appendicular lump as its own weightage. The clinician and operative surgeon must exercise good and sincere clinical acumen and take help of investigation judiciously before choosing appropriate methods in each individual case. More prospective randomized controlled trials are in demand for comparing the outcomes of different treatment options of appendicular lump, so to identify which method is superior, cost-effective and more importantly hassle free.

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Original Article

Factors influencing the outcome of thrombolysis in acute ST-segment elevated myocardial infarction based on ECG criteria

Meenaxi Sharda¹, Nitesh Kumar Baudh², Devendra Ajmera²,
Naresh Kumar Meghwal³, Pravin Kumar⁴

Objective: The aim of our study was to find out the overall success rate of thrombolysis in acute STEMI based on electrocardiography (ECG) criteria, and to assess the effect and correlation of various parameters such as age, sex, pre-infarction angina, smoking status, history of hypertension, history of diabetes mellitus, time interval between onset of pain and initiation of thrombolytic agent, Killip's class and territory of MI on outcome of thrombolysis.

Material and Methods: A total of 100 randomly selected STEMI patients satisfying the inclusion criteria were studied at New Hospital Medical College, Kota. All patients underwent thrombolysis with streptokinase. ST-segment elevation on ECG was assessed before and after 90 minutes of completion of thrombolytic therapy.

Results: A total of 57 patients (57%) show successful thrombolysis using streptokinase. The success rate is significantly higher in patients presenting within 3 hours of index chest pain ($P < 0.05$) and who have inferior wall MI than any other wall MI ($P < 0.05$). The patients presenting with higher Killip class had less success rate ($P < 0.05$). Other risk parameters (age, sex, pre-infarction angina, diabetes, smoking and hypertension) did not affect outcome significantly ($P > 0.05$).

Conclusion: The overall success rate of thrombolysis with streptokinase was 57%. The earlier presentation, inferior wall infarction and Killip class-1, are associated with statistically significant higher rate of successful thrombolysis.

[J Indian Med Assoc 2020; 118(10): 49-52]

Key words : Myocardial Infarction, Thrombolysis, ECG criteria.

The cardiovascular disease (CVD) is the leading cause of death worldwide, including India¹. Ischemic heart disease (IHD) and stroke being the predominant causes are responsible for >80% of CVD deaths in India, with IHD most predominant cause². Ischemic heart disease (IHD) or coronary artery disease typically occurs when there is an imbalance between myocardial oxygen supply and demand. The most common cause of myocardial ischemia is atherosclerotic disease of an epicardial coronary artery (or arteries)³.

The current definitive treatment modalities for acute STEMI includes thrombolysis and percutaneous coronary intervention (PCI). The preferred reperfusion option for patients with STEMI is timely primary PCI. Many people suggest that fibrinolysis have no place

Editor's Comment :

- Success rate of thrombolysis with streptokinase is significantly associated with certain determinants like earlier presentation Killip class and inferior wall infarction.
- Knowledge about these factors will help in proper management.

in the era of primary PCI whereas others believe fibrinolysis is needed because primary PCI cannot be delivered to all patients with STEMI within the evidence-based time frames needed for full effectiveness⁴.

The principal goal of fibrinolysis is prompt restoration of full coronary arterial patency. Coronary angiography is the gold standard to determine coronary artery patency after reperfusion therapy but it is an expensive, invasive and not always readily available modality. Therefore, bedside noninvasive markers are more attractive options. Among these, ECG has good predictive value and sensitivity which is an easily available and cheaper option. Sutton *et al*⁵ showed that patients with less than 50% resolution of ST-Segment elevation in the worst lead have 87% chance (positive predictive value) of <TIMI-3 flow in infarct

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related vessel with sensitivity of 81% and specificity of 88%.

Along with this it is well recognized that thrombolytic therapy can fail in a significant proportion. We need to identify the risk factors that are responsible for failure of thrombolysis. With this background, we decided to conduct a study in a subgroup of ACS patients who receive thrombolysis for STEMI as an option of reperfusion and not PCI due to some or the other reason.

MATERIAL AND METHOD

An observational prospective cohort study of randomly selected 100 patients receiving thrombolytic therapy for acute STEMI were studied at New Hospital Medical College, Kota, from 01 January 2019 to 31 December 2019.

Inclusion criteria: Presence of typical chest pain suggestive of acute myocardial infarction and/or ischemic angina equivalents without typical chest pain along with ECG evidence of STEMI undergoing thrombolytic therapy.

ECG criteria for diagnosis of STEMI: New ST-elevation at the J-point in two contiguous leads with the cut point ≥ 1 mm in all leads except leads v_2 and v_3 where the cut-points are: ≥ 2 mm in men ≥ 40 years and ≥ 2.5 mm in men < 40 years, or ≥ 1.5 mm in women regardless of age⁶.

Exclusion criteria: Recurrent STEMI and Presence of left bundle branch block.

Criteria for successful thrombolysis: Electrocardiographically:- $\geq 50\%$ ST-segment resolution in a lead which show maximum ST elevation initially.

Data Collection and analysis: The data was collected from all eligible patients after taking written consent. A detailed clinical history, complete physical examination, routine investigation and ECG on admission and after 90 minutes of completion of thrombolytic therapy were noted.

A detailed standard statistical analysis by "Pearson's Chi-squared test" was carried out at the end of study to conclude the results.

OBSERVATIONS AND RESULTS

A total of 100 patients are studied out of which 75 are males (75%) and 25 females (25%). The mean age of patients is 57 years (range from 32 to 82 years). Overall success rate of thrombolysis is 57%. The outcome of thrombolysis in sex and age group wise is shown in Table 1. The success rate is higher in younger age (Age ≤ 40 years) group than elderly but statistically it is not significant with $\chi^2=0.6528$ and p value >0.05 . The successful thrombolysis is seen in 57% of males

and 56% of females but statistically it is not significant with $\chi^2=0.0136$ and p value >0.05 . Comparison of window (time) period, location of MI and hemodynamic killip class with outcome of thrombolysis is shown in Table 2. Those patients who received thrombolytic therapy within 0-3 hours have highest success rate (75%) than those who received it later with statistically significant values ($\chi^2=9.5122$ and p value <0.05). Inferior wall infarction shows higher (72.5%) success rate compared to other location MI, values are statistically significant with $\chi^2=9.5437$ and p <0.05 . Patients with killip class-1 have higher (64%) success rate compared to killip class-2, 3 and 4 with a statistically significant values ($\chi^2=6.3658$ and p <0.05). The presence of risk factors and outcome of thrombolysis are shown in Table 3. 52 patients are smokers (52%), 17 are hypertensive (17%), 7 are diabetic (7%) and 13 patients experienced pre-infarction angina (13%). These factors (pre-infarction angina, diabetes, smoking and hypertension) did not affect thrombolysis outcome significantly (P >0.05).

Table 1 — Outcome of thrombolysis in different age groups and sex

Age/Sex	Number of Patient	Success	Failure	Chi square (χ^2) test and P value
Age ≤ 40 years	17	11 (65%)	6 (35%)	$\chi^2=0.6528$, P= 0.88 Not significant
Age 41-60 years	60	33 (55%)	27 (45%)	
Age 61-70 years	17	10 (59%)	7 (41%)	
Age ≥ 70 years	6	3 (50%)	3 (50%)	$\chi^2=0.0136$, P= 0.91 Not significant
Male	75	43 (57%)	32 (43%)	
Female	25	14 (56%)	11 (44%)	

Table 2 — Comparison of time window period, location of MI and killip class with outcome of thrombolysis

Window period :	Number of Patient	Success	Failure	Chi square (χ^2) test and P value
0-3 hour	20	15 (75%)	5 (25%)	$\chi^2=9.5122$, P= 0.0232 Significant
4-6 hour	28	18 (64%)	10 (36%)	
7-9 hour	25	15 (60%)	10 (40%)	
10-12 hour	27	9 (33%)	18 (67%)	
AWMI	48	25 (52%)	23 (48%)	$\chi^2=9.5437$, P= 0.048 Significant
IWMI	40	29 (72.5%)	11 (27.5%)	
ALWMI	5	1 (20%)	4 (80%)	
IPWMI	4	1 (25%)	3 (75%)	
LWMI	3	1 (33%)	2 (67%)	
Killip class-1	84	54 (64%)	30 (36%)	$\chi^2=6.3658$, P= 0.0414 Significant
Killip class-2	10	3 (30%)	7 (70%)	
Killip class-3	4	1 (25%)	3 (75%)	
Killip class-4	2	0 (0%)	2 (100%)	

Table 3 — Effect of various risk factors on outcome of thrombolysis

Risk Factor	Number of Patient	Success	Failure	Chi square (χ^2) test and P value
Pre-infarction angina (PIA)	13	7 (54%)	6 (46%)	$\chi^2=0.0606$, P=0.80
No PIA	87	50 (57.5%)	37 (42.5%)	Not significant
Smokers	52	32 (61.5%)	20 (38.5%)	$\chi^2=0.9104$, P=0.34
Non-smoker	48	25 (52%)	23 (48%)	Not significant
Hypertensive	17	10 (59%)	7 (41%)	$\chi^2=0.0278$, P=0.87
Non-hypertensive	83	47 (57%)	36 (43%)	Not significant
Diabetic	7	3 (43%)	4 (57%)	$\chi^2=0.6143$, P=0.43
Non-diabetic	93	54 (58%)	39 (42%)	Not significant

DISCUSSION

In this study, the overall success rate of thrombolysis with streptokinase is 57%, based on ECG criteria. Our results are almost similar as obtained by Girish Ronad *et al.*⁷ and Abhishek Chaudhary *et al.*⁸ where overall success rate of thrombolysis with streptokinase was 61.9% and 64% respectively. In our study success rate is high in comparison to a study done by Lee YY *et al.*⁹ where it was 43.2%.

In this study, patients with age ≤ 40 years achieved higher (65%) success rate compared to higher age groups but statistically it is not significant. In our study, statistically significant difference is not found based on the gender.

In present study, patients with inferior wall infarction are found to have higher (72.5%) success rate compared to other MI. Our results are in concordance with study done by Girish Ronad *et al.*⁷ and Lee YY *et al.*⁹. The reason for this differential response is evident as we look into the physiology of coronary circulation in the left coronary arteries. Blood flow in the right coronary artery is relatively independent of the phase of cardiac cycle being present in both systole and diastole. Whereas flow in the left coronary artery is almost absent during systole and may even be reversed in conditions of heightened micro-vascular tone and left ventricular hypertrophy¹⁰. Gibson, Murphy and Braunwald *et al.* (TIMI subgroup) found that TIMI grade III flow rates were lower for left coronary and circumflex artery (LAD and LCx) compared to right coronary artery after thrombolytic therapy¹¹.

In this study, success rate is higher (75%) in patients who were thrombolysed early (within 3 hours from the onset of symptoms) than presenting later.

Our results are in concordance with Girish Ronad *et al.*⁷ who concluded that those presenting within 0-4 hours of symptoms onset had higher success rate compared to those presenting later ($P < 0.01$). Our results are also in concordance with study done by Lee YY *et al.*⁹ in which a longer door-to-needle time was significantly associated with failure of thrombolysis using streptokinase (PP%0.02). The study of S.S. Iyengar, T. Nair *et al.*¹² has shown that delayed administration of tenecteplase (>6 hours of onset of symptoms) gives lower success rates (85.38%; $P < 0.0001$), as against those patients who received tenecteplase within 3 hours of onset of symptoms (96.54%; P P% 0.006).

In our study, killip class has significantly affected the outcome of thrombolysis indicating that higher the killip class, higher will be the failure rate. The results are in concordance with Girish Ronad *et al.*⁷ who concluded that patients with higher killip class had high failure rate ($p < 0.05$). Our results are also in concordance with study done by S.S. Iyengar, T. Nair *et al.*¹² which showed that patients with killip class 1 & 2 had a higher thrombolysis success rate with tenecteplase than killip class 3 & 4.

In this study, there is no significant difference in outcome of thrombolysis among groups with or without pre-infarction angina ($P > 0.05$). Felicita Andreotti, Vincenzo Pasceri, Attilio Maseri *et al.*¹³ in their study observed that patients with AMI who have intermittent infarct related pain or unstable angina in the seven days preceding the infarction have faster coronary artery perfusion and smaller infarcts after thrombolytic therapy (t-PA) than patients without pre-infarction angina. In our study thrombolytic agent used is streptokinase, t-PA is a better thrombolytic agent as has been shown in various studies. Moreover we observed only 90 minutes ECG and have not correlated it angiographically to demonstrate TIMI flow which is definitely a better assessor.

In present study, there is no significant difference in outcome of thrombolysis in relation to history of hypertension ($P > 0.05$). Lee YY *et al.*⁹ reported that the success rate of thrombolysis is lesser in hypertensive patients (33.8%) than normotensive (48.8%) but statistically it is not significant. In our study success rate of thrombolysis is almost equal in hypertensive versus normotensive patients (59% v/s 57% respectively). The possible reason for this difference could be because of more number of hypertensive cases in their cohort (37%) while in our study it is only 17%.

In our study, smokers shows higher success rate

than non-smokers (61.5% v/s 52%) but is statistically insignificant. The possible reasons attributed by them were that they were of relatively younger age, without diabetes and hypertension and more often consuming alcohol.

In present study, the success rate of thrombolysis is lesser in diabetic patients than non-diabetic patients (57% v/s 42%) but statistically it is not significant. Our results are concordance with Lee YY *et al.*⁹ where 64.9% of the diabetic patients did not achieve successful thrombolysis using streptokinase with three times risk of failure in compare to non-diabetic.

Limitation of Study :

There are few limitations of our study:

- The criteria for successful thrombolysis is based solely on ECG, and achievement of TIMI grade flow is not confirmed with coronary angiography, which is the gold standard.

- We have used streptokinase instead of recombinant tissue-type plasminogen activator (t-PA) because it is cheap and easily available in our setting.

- Pre and post thrombolysis echocardiography and further follow up was not done in any patients.

CONCLUSION

The effect and correlation of various factors which influence the outcome of thrombolysis in acute STEMI in the present study are:

- The overall success rate of thrombolysis is 57%.

- Time window period significantly ($P < 0.05$) influence the outcome of thrombolysis as those with short window period have a better success rate.

- Killip class significantly ($P < 0.05$) affects outcome of thrombolysis as failure rate is more with higher killip class.

- Inferior wall myocardial infarction has statistically significant better success rate than anterior wall myocardial infarctions and lateral wall infarction or in combination.

- Age and gender are not found to influence the success rate of thrombolysis.

- Pre-infarction angina has statistically insignificant effect on the success rate of thrombolysis.

- Smokers have a better success rate than non smokers but it is statistically insignificant.

- There is no difference in the success rate between hypertensives and normotensive patients.

- Non-diabetic patients have better success rate than diabetic patients but it is statistically insignificant.

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Conflict of Interest : None

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Image in Medicine

Bhoomi Angirish¹, Bhavin Jankharia²

Quiz 1

Axial CT scan images of a smoker with smoking index of 12.5 pack year shows combined pulmonary fibrosis and emphysema (CPFE) and a solid round nodule in inferior lingula.

Answers :

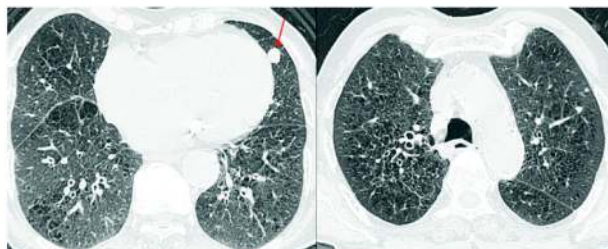
1) **Category 4A** - Suspicious. The Lung-RADS category 4A includes **solid nodule** 8mm and <15mm at baseline OR growing <8mm OR new <6 to 8mm and **part solid nodule** 6mm with solid component \geq 6mm to <8mm OR with a new or growing <4mm solid component.

Questions :

(1) The solid nodule (arrow) seen in inferior lingula measures 10 mm. What is the Lung-RADS category?

2) What are the management recommendations of this nodule?

3) What are the guidelines for LDCT screening?



2) The management recommendations for 4A category nodule are 3 month LDCT or alternatively PET/CT may be used, when there is a \geq 8mm solid component.

3) The 2013 US preventive service task force (USPSTF) recommendations for lung cancer screening includes individuals between 55-80 years with \geq 30 pack year. The proposed 2020 USPSTF recommendations are age group of 50-80 years with \geq 20 pack year. These includes current smokers or individuals who have quit smoking within past 15 years.

Quiz 2

A 32 year old lady presented with painless swelling around lower thigh since 3 months.

Answers :

(1) A well defined osteolytic lesion (arrows) with non-sclerotic margins and with narrow zone of transition is seen in the metaphysis of lower end of femur, extending into the epiphysis and reaching adjacent to the articular surface. There is thinning and focal breach (arrowheads) of the overlying cortex. These imaging findings are typically seen in giant cell tumour (GCT), which was confirmed on biopsy.

(2) The most common locations of GCT are around knee involving distal femur and proximal tibia. Other known locations are distal radius, sacrum and vertebral body.

(3) The imaging differentials of GCT are

i) Chondroblastoma: which is an epiphyseal lesion and occurs in immature skeleton whereas GCT is epi-metaphyseal lesion occurring in closed growth plate.

ii) Chondromyxoid fibroma: shows well defined sclerotic margins, whereas GCT shows non-sclerotic margins.

Questions:

(1) What is the diagnosis?

(2) What are the common locations of this lesion?

(3) What are the differential diagnosis?



iii) Aneurysmal bone cyst: usually occurs in younger age group, however it may co-exist with GCT.

Picture This by Jankharia, Mumbai, Maharashtra

¹MD, DNB (Radiology)

²MD, DMRD (Radiology)

Student's Corner

Become a Sherlock Homes in ECG

M Chenniappan¹

Series 5 :

ECG

"Watch the watch"

This ECG of a 53 years old Diabetic male complaints of chest pain.

1. Describe the ECG changes?
2. Why is this clue?
3. What are practical implications?



Answers :

ECG FINDINGS

ECG shows sinus tachycardia, Tall R wave in V1, Left atrial abnormality and normal axis. There is also prominent septal q in V5,V6 as well as L1 and aVL. There are many causes for Tall R wave in V1 like RVH, RBBB, Dextrocardia, Type A WPW pattern, Hypertrophic Cardiomyopathy, Duchenne Muscular Dystrophy, etc. In our patient the cause of tall R wave is likely to be due to counter clockwise rotation. This is unlikely to be Asymmetrical Septal Hypertrophy because there are no deep narrow septal q waves in V5,V6. Counter clockwise rotation is diagnosed if equiphase zone in chest leads shifted to right. In our ECG, equiphase zone is in V1 and V2.

Description about clockwise and counter clockwise rotation.

- Clockwise and counterclockwise rotation refer to a change in the electrical activity in a horizontal plane through the heart.

- Imagining the observer standing at the feet of the patient who is in bed.

- If the electrical activity of the heart has turned more to the right side of the patient this is called *counter clockwise rotation*.

- If the electrical activity of the heart has turned more to the left side of the patient this is called *clockwise rotation*.

- Clockwise and counterclockwise rotation can be assessed only in the chest-leads (V1 - V6).

- Normally the R wave amplitude increases from V1 to V5. Around V3 or V4 the R waves become larger than the S waves and this is called the 'transitional zone'.

- If the transition occurs at or before V2, this is called counterclockwise rotation.

- If the transition occurs after V4, this is called clockwise rotation (Fig 59a).

- **Causes of clockwise rotation were:**

- intraventricular conduction abnormalities secondary to myocardial degeneration

- right ventricular heart disease

- shift of the septum to the left

- dilated cardiomyopathy

- shift of the whole heart

- pulmonary emphysema

- vertical heart (usually thin and tall persons)

- **Causes of counterclockwise rotation were:**

- electrical shift to the right

- right ventricular hypertrophy

- WPW Syndrome

- Posterior myocardial infarction

- Left post. fascicular block

- shift of the septum to the right

- hypertrophic cardiomyopathy

The deep terminal negative component of P in V1 is suggestive of left atrial abnormality and so left ventricular dysfunction has to be excluded.

Clue:

The clue is about the Counter "clock"wise rotation as the cause of Tall R wave in V1. Observing or watching the watch (clock) will give the diagnosis.

Practical implication :

Counterclockwise rotation, the most prevalent QRS transition zone pattern, demonstrated the lowest risk of CVD and mortality, whereas clockwise rotation was associated with the highest risk of heart failure and non CVD mortality. These results have implications on how to interpret QRS transition zone rotation when ECG was recorded.

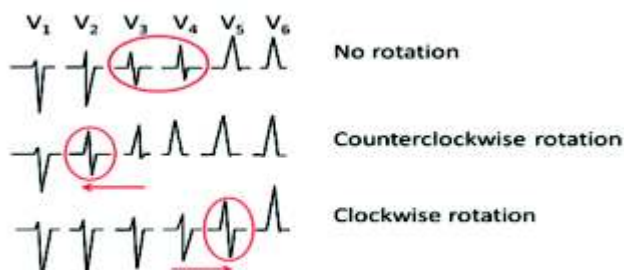


Fig 59a : Showing ecg patterns of various rotations in chest leads

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Case Report

A Case of Atherosclerotic Moyamoya Syndrome

Aditya Ganguly¹, Subhasis Maitra², Nebedita Dutta¹, Koushik Mal¹, Mahudul Mondal¹

Moyamoya disease is an idiopathic, noninflammatory, nonatherosclerotic, progressive, occlusive disease of the cerebral vasculature with a particular predilection for the circle of Willis and the arteries that arise from it.

The term moyamoya disease is reserved for the idiopathic, sometimes familial variety of the disease. However numerous other conditions mimic the angiographic appearance of moyamoya disease. In that case, we use the designation moyamoya syndrome or phenomenon or pattern. These diseases include atherosclerosis, sickle cell vasculopathy, neurofibromatosis type 1, Down syndrome, Turner syndrome and Allagille syndrome.

Here we present a case of an adult male presenting with seizures caused by an infarct due to atherosclerosis induced Moyamoya syndrome.

[J Indian Med Assoc 2020; 118(10): 55-7]

Key words : Moyamoya, Atherosclerosis, Stroke, Seizures.

CASE REPORT

A 38 year old, hypertensive, diabetic male presented with a history of acute onset seizure like movements of the lower left part of his face for the past 24 hours. There was no associated loss of consciousness, weakness of limbs, difficulty in swallowing, slurred speech, sensory abnormalities or any other abnormal movements. There was no history of any such occurrence in the past or among his close family members. He was a smoker, smoking around 3-5 cigarettes/day and was also poorly compliant with his antihypertensive and antidiabetic medications.

General examination was unremarkable except for a blood pressure of 160/96 mm Hg and random capillary blood glucose of 312 mg/dL.

Neurological examination revealed a rapid jerky movement of the lower left part of his face with tensing movements of the jaw suggestive of seizures. The rest of the examination was unremarkable.

Considering his risk factors and the acuity of onset, we considered a vascular lesion and an urgent noncontrast CT brain was done. This revealed a hypodense lesion in his right frontal region suggestive of an infarct.

His complete blood count, liver function tests and serum electrolytes were unremarkable. HIV 1 and 2, hepatitis B and hepatitis C serologies were non reactive. FBS and PPBS were 210 mg/dL and 396 mg/dL respectively. His fasting lipid profile was remarkable for an LDL cholesterol of 168 mg/dL.

The patient was started on levetiracetam and once the seizures were controlled, an MRI brain (plain+contrast) with MR angiography of brain and neck vessels was obtained (Fig 1).

Editor's Comment :

- Atherosclerosis is common in the Indian population and the cause of substantial cardiovascular morbidity and mortality. This usually manifests in the form of large vessel ischemic strokes, intracerebral bleeds, acute coronary syndromes and peripheral arterial disease.
- Moyamoya syndrome is a relatively uncommon presentation of this atherosclerotic process, but the widespread prevalence of this atherosclerosis merits consideration of this entity in the differential diagnosis.
- Due consideration will allow quicker diagnoses and faster treatments, thereby facilitating better outcomes for patients.

The MRI brain showed diffusion restriction of the right frontal region with perilesional edema. Contrast imaging showed mild gyriform enhancement. The lesion was hypointense on ADC (apparent diffusion coefficient) mapping with the ADC in ischemia limit suggestive of a subacute infarct.

MR angiography showed decreased flow in the middle cerebral arteries (MCA) bilaterally, more on right side. The circle of Willis lacked artery-to-artery anastomosis. Few small vessel signals and neovascularization were seen near the circle of Willis.

Considering the possibility of moyamoya syndrome, we obtained a digital subtraction angiography (DSA) of the arch of aorta, its branches and the cerebral vasculature (Fig 2).

The DSA revealed 48% diffuse narrowing of the right internal carotid artery with severe (78%) narrowing of its supraclinoid part. The left internal carotid artery showed severe (76%) narrowing of its supraclinoid part. The A1 segment of the right anterior cerebral artery (ACA) and M1 segment of the right middle cerebral artery (MCA) were markedly narrowed with a few thin and slender branches of M2 and M3 segments of the right MCA visualized. The A2

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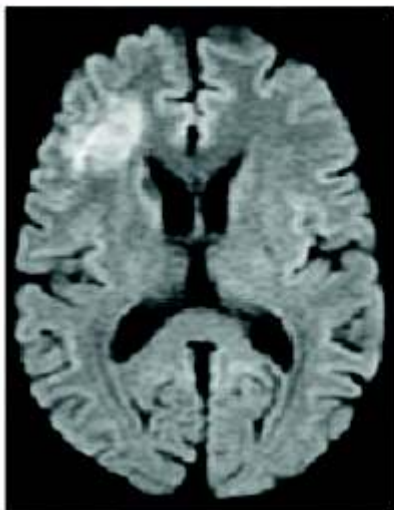


Fig 1 — MRI brain showing hyperintense lesion in the right frontal area

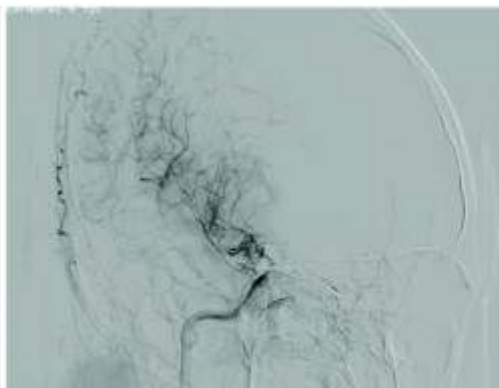


Fig 2 — DSA images showing typical puff of smoke appearance of the cerebral vasculature

and A3 segments of the right ACA were filled by the left ACA through the anterior communicating artery. The filling of the left posterior cerebral artery (PCA) was through the left posterior communicating artery from the left internal carotid artery. Extensive collaterals from the PCA through the posterior communicating arteries on both sides and, in addition, branches of the external carotid artery were seen supplying the brain in the MCA territories. This gave the 'puff of smoke' appearance suggestive of a moyamoya syndrome.

The patient was diagnosed as a case of facial seizures secondary to stroke due to moyamoya syndrome caused by atherosclerosis.

He was managed with long acting insulin analogues and human regular insulin transitioned into oral hypoglycemic agents, statins, calcium channel blockers and levodopa. He was then referred to neurosurgery for management of his moyamoya syndrome.

Discussion

Moyamoya disease, first characterized by Suzuki and Takaku in 1969, is characterized by a chronic, progressive occlusion of the supraclinoid part of the internal carotid arteries with reduction of blood flow in the anterior circulation. This leads to the development of collateral vasculature near the apex of the carotid, on the cortical surface, leptomeninges and branches of the external carotid artery supplying the dura and base of skull. In rare cases, the disease process may affect the posterior circulation as well^{1,5}.

The characteristic angiographic appearance of the abnormally dilated collaterals, after which the entity is named, has been likened to that of 'something hazy, like a puff of cigarette smoke' which in Japanese is moyamoya. Different workers have tried to rename the disease but the International Classification of Diseases (ICD) 10th revision endorses the term moyamoya disease¹.

It must be kept in mind that moyamoya is simply an angiographic appearance, referring to the 'puff of smoke' appearance of the collateral vessels. Moyamoya disease refers to the idiopathic, sometimes familial, noninflammatory, nonatherosclerotic variety. Moyamoya

syndrome refers to a vasculopathy with the characteristic angiographic appearance developing in the background of a number of well characterized conditions which include atherosclerosis, diabetes mellitus, sickle cell syndrome, Graves disease, antiphospholipid antibody syndrome, Down syndrome, Alagille syndrome etc².

The idiopathic variety has a strong geographical and familial predilection and commonly affects people of Japanese and

Korean ancestry. The incidence in East Asia is almost 10 times that of Western countries³. It usually affects females more than males and in Japan, moyamoya disease is the most common pediatric cerebrovascular disease with a prevalence of approximately 3/100,000 children. The epidemiological data on moyamoya syndrome, pertaining to India is not well known but case series from a number of centres across the country are gradually becoming available^{3,9}.

Moyamoya disease is familial in almost 10% cases in Asia and in 6% in North America. A polymorphism R4810K in the gene RNF 213 at chromosome 17q25.3 is a genetic susceptibility factor for East Asian populations. HLA A*24, B*46, B*54,6q25 etc have also been identified as risk factors^{1,6}.

The etiopathogenesis of moyamoya disease involves stenosis beginning at the distal intracranial internal carotid artery (ICA) at the bifurcation. This then progresses to involve the proximal ACA and MCA. The posterior circulation is involved in the later stages. The stenotic process is accompanied by collaterals developing at the base of the brain and the lateral ventricles which perfuse and nourish the threatened brain. Finally, the anterior and middle cerebral circulations are supplied and reinforced by dural and extracranial arterial networks.

Histopathology of the stenotic vessels reveals endothelial hyperplasia, intimal thickening, duplication of the internal elastic lamina and attenuation of the tunica media. The moyamoya collaterals on histopathology show fibrinoid necrosis, fragmentation of elastic lamina and microaneurysm formation. The latter may explain why some patients present with intracranial hemorrhages. On the other hand, some of the collaterals on histopathology show collapsed and thrombosed lumens, perhaps accounting for the ischemic symptoms. Moyamoya syndrome secondary to atherosclerosis shows the characteristic atheromatous changes in addition to many of the findings present in the idiopathic variety.

Clinical presentation varies between ischemia and bleeding manifestations. Pediatric patients classically present with ischemic features specially TIA and infarcts. This may be precipitated by seemingly minor events such

as crying and induction of anesthesia for minor surgical procedures. The presumed mechanism is that normal cortical vessels, already maximally dilated due to chronic ischemia, may constrict in response to lowered arterial CO₂ levels due to hyperventilation, thus causing infarction. Dehydration and bleeding due to any cause, renders the patient unusually susceptible to ischemic symptoms. Older patients usually present with intracranial bleeds. The usual location is intraparenchymal (mostly basal ganglionic), intraventricular and often subarachnoid. In fact, moyamoya should be in the differential for CADASIL and all nonhypertensive spontaneous intracerebral hematoma especially primary intraventricular hemorrhage^{1,5,9}.

Headache is also a common symptom in moyamoya syndrome, caused by dural nociception by the dilated collaterals. It is migraine like and often resistant to both medical therapy and revascularization procedures.

Diagnosis is suggested by CT and MRI imaging of the brain and cerebral vasculature but diagnosis is confirmed by conventional catheter angiography. It is believed that advances in noninvasive neurovascular imaging will eventually allow it to reach the same level of diagnostic certainty as that of the latter. The disease severity is also determined at the time of diagnosis using the Suzuki system developed in 1969^{1,5,7}.

EEG is a helpful adjunct since it shows the characteristic 'build up' and 're-build up' phenomenon induced by hyperventilation. This finding, characteristic of moyamoya disease is thought to arise from reduced arterial CO₂ tension, which causes vasoconstriction of previously maximally dilated normal cerebral vessels and leads to cerebral ischemia. PET CT and SPECT studies are also used.

Treatment of moyamoya disease or syndrome is complex and involves both medical and surgical components. It is ideally suited to centres that deal with these cases in large volumes and have developed considerable clinical expertise in the same.

Medical therapy involves antiplatelet agents for prevention of ischemia developing from microthrombi in arterial stenoses. Calcium channel blockers may also be used for the moyamoya headache. But it should be remembered that these often induce hypotension that is potentially deleterious and might cause infarcts. Potential new agents include angiogenic growth factors and gene therapy.

Neurosurgery is the mainstay of therapy and involves creating anastomoses between the blood starved arteries of the circle of Willis and the external carotid circulation. Surgical options include the direct bypass procedures like STA-MCA bypass and indirect ones like EDAS (encephaloduroarteriosynangiosis), EMS (encephalomyosynangiosis) and multiple burr hole procedures.

At present, hybrid procedures involving both methods are being used at multiple centres. This is more beneficial for children with moyamoya disease where the donor vessels are quite thin and patency is an issue.

Surgery should be recommended for all symptomatic patients with angiographically proven moyamoya disease. It is unclear at this time whether the same can be

recommended for atherosclerotic moyamoya syndrome. Controversy exists as to the optimal management of these patients and the means by which it should be done – medical or surgical. Endovascular procedures have been tried but have had high rates of recurrence and complications. However, in case of symptomatic ischemia and hemorrhage, neurosurgical referral for revascularization procedures may be recommended. Optimized management of the underlying atherosclerotic risk factors must not be overlooked in these patients.

It should thus be remembered that atherosclerotic vasculopathy can present as a moyamoya syndrome, especially in the Indian population. In such cases, a secondary cause should be sought after in order to exclude a potentially treatable disorder. Since the Indian population is a high risk population with respect to lifestyle diseases like atherosclerosis, diabetes, hypertension, coronary artery disease and stroke, proper evaluation of an atherosclerotic etiology is crucial. This becomes more important if the patient has underlying risk factors for atherosclerosis as in our case – diabetes, dyslipidemia, hypertension and smoking.

In such cases, prompt confirmation of diagnosis using angiographic methods and prompt referral to neurosurgery will help reduced the morbidity and mortality associated with this disease.

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Case Discussion in Medicine

The Autonomic Nervous System (ANS) : An appraisal and revisit

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The autonomic nervous system has a cardinal role in maintaining the internal homeostasis of the body. Yet, till today it somehow remains as a neglected or less understood aspect of neurology. Disturbances of autonomic nervous system may have protean manifestations and with recent advancements pathogenesis of many diseases have been linked to autonomic dysfunction. In this review, the authors intend to discuss about the basic anatomy and physiology of the autonomic nervous system and also a brief highlight of clinical examination as well as concerned laboratory investigations to detect autonomic dysfunction.

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Key words : Autonomic nervous system, examination, laboratory investigations.

The autonomic nervous system has remained a Cinderella specialty. The motor and sensory system examinations are carefully drilled into every medical student ever since they enter the clinical curriculum and is discussed and recapitulated throughout their clinical career. Unfortunately, the poor cousin, the autonomic nervous system and its relevant examination remains a nuance even to post graduate neurology trainees and even to established practitioners of neurology globally. The potential explanation for this may arise from the seemingly complex network, architecture and organisation of the autonomic nervous system compared to the rather straight forward layout of the peripheral motor and sensory pathways; these start to get complex only when they enter the cerebrum. For this same reason, the cerebral association pathways have been traditionally inadequately approached although with work in the dementias, epilepsies and movement disorders and the modern imaging, these are also slowly getting rectified¹.

Case Scenario :

A 53-year-old gentleman without any comorbidity, on mixed diet was admitted in the Neurology ward of a

Editor's Comment :

- Autonomic nervous system is an integral part of nervous system which is necessary to maintain the internal milieu.
- The paucity of specific history, examination and limited resources have hindered the exploration of the autonomic nervous system compared to other aspects of neurology.
- With advanced research and growing resources, multiple disease pathogenesis have been linked to autonomic dysfunction.
- The autonomic nervous system may be incorporated into the curriculum of medical students with equal importance as compared to motor and sensory system of human neurology, to necessitate better understanding of the subject and improved patient care.

tertiary care hospital with chief complaints of slowing of activities for 3 years followed by urinary urgency and incontinence as well as recurrent falls for last 1 year.

History of present illness :

The patient experienced a gradually progressive slowing of daily activities over the last 3 years. His wife first noticed that his walking speed had a significant decline and he used to take a lot more time than usual to stand up from sitting position and even turning on bed. He was also experiencing undue stiffness of his limbs and that hampered his daily activities. One year back, he started to experience urinary urgency followed by incontinence. He used to suffer from dizziness when standing up from supine position and had a few episodes of pre-syncope. He has been suffering from erectile dysfunction for the last 5 years. He developed mild tremor of both hands on activities but not at rest. Gradually, he became

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stooped with history of recurrent falls, without any loss of consciousness, seizures. His wife has recently noted that his speech has become slurred and he also had two episodes of choking sensation while swallowing food. No history of forgetfulness or psychotic outbreaks were obtained.

No history of addiction or any significant family history was obtained. He has received a combination of levodopa/carbidopa over the last 3 years, with minimal improvement.

Clinical Examination

- Conscious, alert and oriented
- Normal higher function/cognition
- BP= 140/80 mmHg (supine), 110/70 mmHg (standing); Pulse rate= 86/min (regular)
- Masked facies
- Hypophonia
- No signs of meningeal irritation
- Cranial nerves
 - ◆ No restriction of extraocular movements, occasional square-wave jerks, hypometric saccades with broken pursuit; bilateral gaze evoked nystagmus.
 - ◆ Brisk jaw jerk, gag reflex intact
 - ◆ Mixed dysarthria
 - ◆ Other cranial nerves were normal
- Motor system: Symmetric rigidity in all 4 limbs with normal bulk and power. Axial rigidity markedly present. Bradykinesia in all 4 limbs with a postural/action tremor on distal bilateral upper limbs.
 - Deep tendon reflexes 2+
 - Bilateral flexor plantar
 - Sensory system: normal
 - Mild impairment of coordination on both sides
 - Broad based gait with short shuffling steps, freezing of gait, stooped posture, reduced bilateral arm swing.
- Retropulsion and lateropulsion test was positive.

How to approach the case from history?

- Slowing of activities and walking speed suggestive of bradykinesia (differential of bradykinesia such as depression, hypothyroid unlikely)
- Stiffness of limbs suggestive of rigidity, probably due to extrapyramidal system involvement.
- Tremor on activity suggestive of action tremor
- **Urinary urgency and incontinence, pre-syncope, dizziness, erectile dysfunction suggestive of significant autonomic nervous system.**
 - Recurrent falls suggestive of postural instability
 - Slurring of speech is suggestive of dysarthria and choking may be due to dysphagia.

How to approach the case from examination?

- Postural drop in blood pressure suggestive of orthostatic hypotension.
- No supranuclear gaze palsy, other ocular findings suggestive of both extrapyramidal and cerebellar involvement.
- Possibility of pseudobulbar palsy due to brisk jaw jerk, likely UMN type dysphagia and mixed dysarthria.
- Symmetric bradykinesia with appendicular and axial rigidity suggestive of atypical parkinsonian features.
- Incoordination may suggest cerebellar involvement.

Analysis of the case:

- Bradykinesia, rigidity and postural instability are suggestive of parkinsonian features.
- Chronic progression is suggestive of probable degenerative etiology.
- Absence of rest tremor, lack of asymmetry, **early and significant autonomic dysfunction** and lack of levodopa response suggests atypical parkinsonism.
- **Involvement of the autonomic system in a background of atypical parkinsonism may point towards the diagnosis of Multisystem atrophy (MSA), probably MSA-P (Multisystem atrophy with predominant parkinsonism)**

DISCUSSION

The autonomic nervous system does not lend itself to individual pathway delineation akin to an electrical circuit but rather assesses the complex interplay of the sympathetic and parasympathetic systems (Figs 1,2) which are essentially controlled by adrenaline, noradrenaline and acetylcholine (and the various receptor types-Table 1) and the pre and post ganglionic ganglia neurochemicals and receptor subtypes and nerve endings and in the central connexions and influences from higher cortical centres. From the history taking perspective patients also find it difficult to describe rather diffuse symptomatic presentations (Table 2) of dysfunction of the autonomic nervous system that makes localisation on history challenging².

The autonomic nervous system which essentially helps to maintain the internal milieu or homeostasis (Claude Bernard)^{3,4} has important ramifications in the regulation of the cardiovascular system, gastrointestinal system, sudomotor system and the urogenital functions all of which are taken for granted as part of our everyday existence. Again, with dysfunctions in these various systems coming on gradually it becomes difficult to delineate from history

the impact of progressive dysfunctions in this system and are liable to be confused or confounded with motor system dysfunctions of which there is a significant overlap anyway⁵. Again, the autonomic nervous system dysfunctions are predominantly diagnosed and confirmed through lab tests which we have not utilised traditionally through lack of availability and resources. The degrees of assessment of the ANS tends to get more and more complex as one develops a deeper understanding of the domains of dysfunction⁶.

We believe the knowledge of the physicians happens to be the main limiting factor and the lack of regular discussions of the autonomic nervous system as part of the general undergraduate and postgraduate medical discourse now deserves rectification. Certainly, in the post graduate neurology curriculum a practical and detailed approach to the autonomic nervous system assessment needs to be established with due emphasis akin to strokes, Parkinson's and epilepsies⁷⁻⁹.

The perceived neglect of the autonomic nervous system has also stemmed from the interdisciplinary ramifications of diseases that ANS causes. The cardiologists, gastroenterologists, internal medicine colleagues, ophthalmologists, endocrinologists, pulmonologists, dermatologists and psychiatrists and all physicians who have prescribing responsibilities are stakeholders in the ANS as either the primary symptoms or drug side effects that these specialties deal with are often manifestations of the ANS dysfunction. This multispecialty stake holding status has resulted in one particular specialty or clinician failing to take complete ownership of assessment of the autonomic nervous system as it is perceived as a very complex and elaborate subspecialty. Hence in the West, practitioners of autonomic nervous system medicine tend to be restricted to a handful with elaborate ANS labs that satisfy the needs of anyone of the above-mentioned stakeholders in the field¹⁰.

With diabetes casting it's wide net and its impact on the autonomic nervous system and a wide spectrum of medications that we are using in every specialty which have an impact on the sympathetic and parasympathetic pathways including the medications used by our psychiatric colleagues for modulation of cortical and limbic and frontal and parietal circuits there is a need for all of us to become more fluid in our understanding, diagnosis and our advice to patients and judicious use of corrective measures including general lifestyle advice which often entrains and modulates the autonomic nervous

system dysfunctions to restore normality in our patients lives¹².

Use of pharmacotherapy carefully to identify offending medications that result in the autonomic nervous system disorders also becomes mandatory. Neuroimmunology has resulted in the identification of a large number of antibodies which operate at neuronal level or ganglion level resulting in transmission disturbances at the preganglionic and postganglionic nerve endings and more are likely to be identified with technological progress of bioassay techniques. This will lead to immunomodulatory therapy based on evidence.

Time has come when autonomic clubs need to be established by a spectrum of specialties including medical and surgical and not necessarily restricted to neurosciences which will lead to the benefit of our patients. This reflects the large number of specialties that the patients with diffuse ANS symptoms may land up with.

Anatomy and physiology :

A) History :

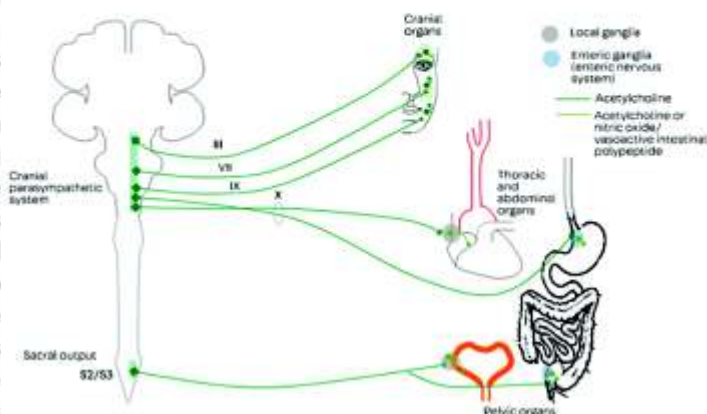


Fig 1 — Organisation of the Sympathetic nervous system

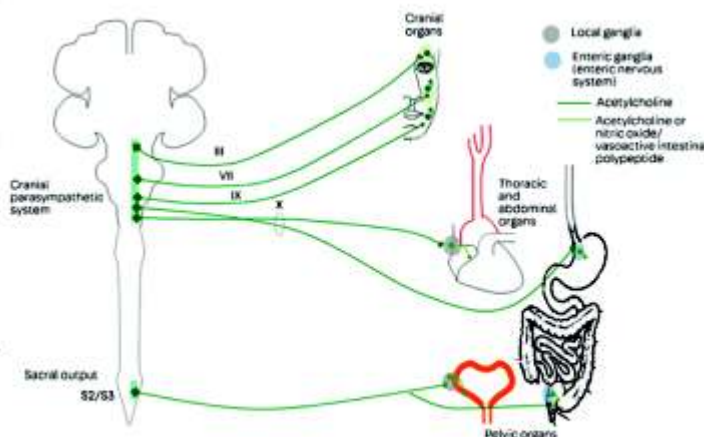


Fig 2 — Organisation of the parasympathetic nervous system

There is never a single clearly articulated localising symptom for ANS disorders that makes history taking a true exercise in deductive reasoning skills. As usual the onset, temporal course and profile and any aggravating or alleviating factors for any of the symptoms the patient describes, relationship to environmental temperature and postural changes, role of dietary supplements, over-the-counter medications and traditional remedies (homeopathic and ayurvedic) and the impact of the symptoms on the patient's quality of life needs to be deftly obtained. The intention here is to identify the syndromic dysautonomia resulting from involvement of the sympathetic, parasympathetic and enteric divisions. The sympathetic nervous system comprises noradrenergic,

adrenergic and cholinergic systems in which the primary chemical messengers are norepinephrine, epinephrine and acetylcholine, respectively. Sympathetic noradrenergic and cholinergic neurons, which are non-myelinated and slowly conducting, derive from thoracolumbar segments of sympathetic ganglia. Sympathetic adrenergic neurons are myelinated and rapidly conduct and pass through the sympathetic ganglia without synapsing to innervate the adrenal medulla. Parasympathetic neurons arise from the brainstem or sacral spinal cord and being myelinated rapidly conduct and are cholinergic with their ganglia near to or embedded in their target organs.

The enteric neurons derived from neural crest cells are embedded in the lining of the gastro-intestinal tract. The myenteric plexus controlling gastrointestinal motility receives parasympathetic innervation from the vagus and sympathetic innervation from post ganglionic sympathetic neurons. The submucous plexus which provides secretomotor innervation receives parasympathetic innervation only¹³.

I. The sympathetic noradrenergic disorders present with symptoms of orthostatic hypotension (OH) with patients reporting dizziness, light-headedness, weakness, fatigue, dimness of vision and difficulty in thinking or maybe entirely asymptomatic. These symptoms are often worse during early morning hours (through relative dehydration), heat exposure, exercise and meals due to the redistribution of circulating blood volume and effects of vasodilators, diuretics and alpha blockers can unmask OH. Male ejaculatory failure, eyelid ptosis and lack of piloerection in response to cold are other symptoms. Sympathetic noradrenergic hyperactivity can cause palpitations, hypertension, tachycardia, pupil dilatation, cutaneous vasoconstriction. Intake of stimulant medications either over the counter or prescribed need to be scrutinised. Reduced adrenaline secretion from the adrenal medulla results in non-specific symptoms of fatigue while excess adrenaline production manifests as palpitations, pallor, dilated pupils and sweating¹⁴.

II. Sympathetic cholinergic disorders: failure of the system results in loss of sweating, impairing thermoregulatory function as acetylcholine is the primary neuro chemical messenger at eccrine neuro effector junctions. Patients do not tolerate hot weather particularly when exercising and feel lightheaded and tired and prickly paraesthesia in hot environments. In absence of sweating

Table 1— Effects of the sympathetic and parasympathetic nervous system on various target organs (with autonomic receptor subtypes in brackets)

Target	Sympathetic (Receptor)	Parasympathetic (Receptor)
Pupil	Dilation (α)	Constriction (M_3)
Ciliary muscle	NA	Accommodation (M_3)
Salivary and lacrimal glands	Inhibition (α_2)	Stimulation (M_3 , vasoactive intestinal polypeptide receptors)
Heart	Stimulation (β_1)	Inhibition (M_2)
Bronchi	Dilation (β_2)	Constriction (M_3)
Skeletal muscle vessels	Constriction (α) Dilation (β_2)	NA
Skin vessels	Constriction (α) Dilation? (nitric oxide?)	NA
Cranial and visceral vessels	Constriction (α)	Dilation (nitric oxide, vasoactive intestinal polypeptide)
Sweat glands	Stimulation (M_3)	NA
Gastrointestinal motility	Inhibition (β_2)	Contraction (M_3) Relaxation (nitric oxide, vasoactive intestinal polypeptide receptors)
Gastrointestinal secretion	Inhibition (α_1)	Gastric acid secretion (M_3); intestinal secretion (M_3 , vasoactive intestinal polypeptide receptors)
Bladder detrusor	Inhibition (β_1, β_2)	Stimulation (M_3)
Bladder neck	Stimulation (α)	Inhibition (nitric oxide)
Rectal smooth muscle	Inhibition (β_2)	Stimulation (M_3)
Erectile tissue	Constriction (α)	Dilation (nitric oxide)
Vas deferens	Contraction (α)	NA

NA = not applicable.

Table 2 — Autonomic Symptoms and Signs

Function	Sympathetic		Parasympathetic		
	Noradrenergic	Adrenergic	Cholinergic	Cranial	Sacral
Decreased	Orthostatic hypotension, lack of tachycardia, Horner syndrome	Fatigue, hypoglycemia	Decreased sweating	Dry mouth, mydriasis, constipation	Urinary retention, male erectile failure
Increased	Palpitations, increased systolic blood pressure, tachycardia, mydriasis, sweating, cold hands, salivation, piloerection	Palpitations, increased systolic blood pressure, tachycardia, mydriasis, pallor, cold hands, slowed gastrointestinal transit, anxiety, tachypnea, bronchial dilation, hyperglycemia	Increased sweating	Salivation, bradycardia, bronchial constriction, miosis, lacrimation	Nausea, urinary frequency, increased gastrointestinal transit

cutaneous flushing occurs and heat exhaustion and heat stroke may result. Compensatory hyperhidrosis may occur in body regions that retain sweat function. Medications including anticholinergic drugs, carbonic anhydrase inhibitors cause reduced sweating. Hyperhidrosis is a common side effect of opioids, SSRIs and SNRIs from sympathetic cholinergic hyperactivity¹⁵.

III. Parasympathetic nervous system disorders: the cranial component dysfunction results in easily recognised dry mouth, dilated pupils, increase in heart rate, decreased heart rate variability and constipation. Failure of the sacral competent results in urinary bladder retention and male erectile failure. Parasympathetic overactivity manifests as increased salivation, slow heart rate, nausea and urinary frequency and urgency.

IV. Enteric nervous system disorders: nausea, bloating, early satiety, reflux, gastroparesis, constipation and colonic pseudo obstruction may result¹⁶.

B) Autonomic physical examination

The examination is informed by an intelligently gathered autonomic history as above.

1) Orthostatic vital signs: measurement of blood pressure and heart rate while standing compared to baseline values obtained when seated and supine. The key diagnostic distinction is to identify neurogenic orthostatic hypotension and differentiate from dehydration, heart failure, deconditioning or vasodilator drugs.

2) Pupillomotor signs : pupillary size asymmetry dependent on sympathetic and parasympathetic denervation are more noticeable in the dim and bright light respectively and easily detectable in the clinic although formal pupillometry studies offer objective and follow-up pupil size measurements.

3) Sudomotor signs : dry skin is detected by palpation compared to normal skin. Focal hyperhidrosis is seen in the dark by shining a bright torch when the sweat droplets render the skin shiny.

4) Secretomotor signs : dry eyes and dry mouth in Sjogren's syndrome are well recognised

5) Vasomotor signs : facial flushing occurring during emotional arousal, menopause and hormonal disbalance, anticholinergic and antioestrogen medication use, carcinoid syndrome, polycythaemia vera or mastocytosis can be seen in photographs while bystanders will report facial pallor preceding neutrally mediated syncope. In Harlequin syndrome the sympathetically denervated pale and dry half of the face is the abnormal side and not the flushed side

that shows compensatory overactivity. Distal arteriolar vasoconstriction manifests as cold feet and hands in patients with autonomic neuropathies and vasomotor instability leads to venous pooling resulting in red or purple erythema in the extremities¹⁷.

C) Laboratory tests¹⁸

In addition to the peripheral neuropathy blood screening tests, supine and standing catecholamines, nicotinic acetylcholine receptor antibodies, alpha galactosidase (Fabry disease), subcutaneous fat pad biopsy or genetic testing (transthyretin amyloid neuropathy), antibodies for Sjogren's syndrome, plasma free metanephrines for pheochromocytoma, 24-hour urine five hydroxy indole acetic acid for carcinoid, plasma histamine for mast cell disorder, Schirmer's test and Rose Bengal test for assessment of tear production, gastrointestinal motility studies, tests for leverage in a bladder through either post-voidal residual volume or more detailed urodynamic studies are general ANS assessment studies.

The more detailed studies of sections of the sudomotor, cardio vagal and sympathetic cardiovascular tests follow.

1) In sudomotor (sympathetic cholinergic) testing the quantitative sudomotor axon reflex test (QSART) and thermoregulatory sweat test (TST) help to inform function of this arm of the ANS. It is important to rule out medication influences mediated by M3 acetylcholine receptors (atropine, oxybutynin, glycopyrrolate, amitriptyline, diphenhydramine, tolterodine. In QSART sudomotor nerves at four standard sites are tested in a quantitative manner through iontophoresis of acetone calling at the skin surface which activates an axon reflex mediated by post ganglionic sympathetic sudomotor axon and the impulse generated travels antidromically reaching a branch point in the peripheral nerve and from there travels orthodromically to evoke a sudomotor response in the adjacent eccrine glands. The evoked response is measured by the moisture detected in a capsule placed on the skin. In the TST the body is heated under controlled temperature and humidity and in this test a lesion anywhere along the thermoregulatory pathway from the brain to the spinal cord, to preganglionic nerves, to sympathetic ganglia and to post ganglionic nerves is studied with dyes that delineate colour changes mediated through sweating patterns.

2) Cardio vagal testing analyses the parasympathetic (vagus nerve) influence on heart rate by the response to deep breathing or by the Valsalva ratio. Heart rate response to deep breathing is

measured by the RR interval on ECG tracing converted to beat to beat heart rate traced along with respiration. For the Valsalva manoeuvre the recumbent patient exhales against resistance and maintains a column of mercury at 30 to 40 mmHg for 15 seconds. Power spectrum analysis of ECG signals is also possible although the "sympathovagal balance" is an unclear derivation of low-frequency power spectrum analysis.

3) Vasomotor adrenergic testing (Fig 3): dynamic changes in blood pressure during the Valsalva manoeuvre are valuable indices of baroreflex-sympathoneural function. The Valsalva manoeuvre is divided into four phases where the late phase 2 (reflex sympathetic response is first seen causing increase in peripheral vasoconstrictor tone, cardiac rate in normal subjects) and phase 4 (an overshoot in blood pressure occurs when cardiac filling returns to normal as the peripheral vasculature remains constricted in normal subjects) provide critical information. Likewise, in the tilt table test, useful in the assessment of orthostatic hypotension, orthostatic intolerance and unexplained

syncope, continuous beat to beat monitoring of blood pressure and heart rate is undertaken during head up tilting to 70° where in patients with baroreflex sympathoneural failure the initial BP drop does not recover and declines further and the heart rate response is decreased. In neurogenic orthostatic hypotension a response is obtained within five minutes while a longer duration of tilt is needed for delayed OH and syncope. The tilt table testing differs from active standing as there is reduced activation of leg muscles and assessment of the autonomic response to orthostatic stress is revealed.

4) Cardiac MIBG or F Dopa PET scan has become an especially important tool in the assessment of the autonomic nerve supply to the cardiac muscles. This is used to distinguish various forms of parkinsonism and primary autonomic failure and in diabetic autonomic neuropathy and that from amyloid cardiomyopathy

5) Skin biopsy for epidermal nerve fibre density measurements, used in the assessment of small fibre neuropathies, is indicative of nerve fibre loss in the epidermis and is a biomarker of autonomic neuropathy.

6) Corneal confocal microscopy has validated data in diabetic small fibre neuropathy where the arborisation of the unmyelinated fibres can be quantitatively estimated to show the loss of nerve fibres secondary to autonomic neuropathy.

7) Gastrointestinal motility studies to demonstrate functioning of the enteric plexus using various motility markers is clinically used by neurogastroenterology specialists.

8) Urodynamic studies – a whole discussion in itself and in clinical use by neurourologists

9) Microneurography – a niche test used by Neurophysiologists and pain specialists to study the subtypes of pain small fibres

10) Sympathetic skin response: not a pure pathway test in itself and used for overall estimation of the axon reflex and easily recorded in stimulation of the palm.

CONCLUSION

ANS disorders can present with brain, spinal cord peripheral nerve or dorsal root ganglia involvement and can present with orthostatic intolerance and paroxysmal vasomotor and sudomotor disorders. There is a profound effect of medications (over-the-counter and prescribed) that can influence ANS test results and patient's clinical presentation and drug interactions with polypharmacy and novel selective receptor specific new drugs that are emergent which are essential in the ANS diagnostic work up and management.

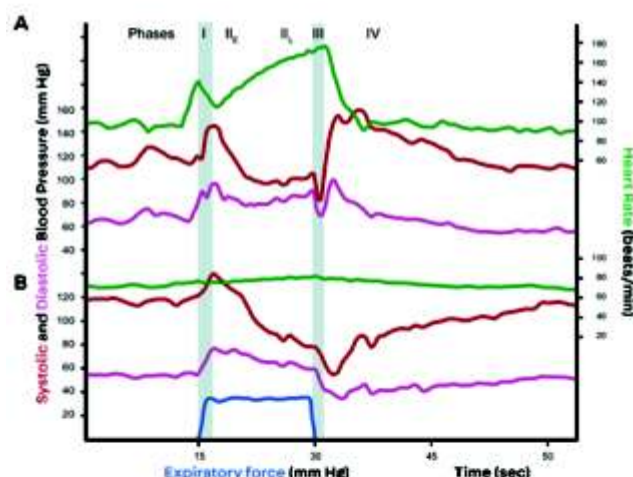


Fig 3 — Beat-to-beat blood pressure and heart rate responses to the Valsalva maneuver.

A, In healthy individuals the decrease in blood pressure during early phase II (II_E) recovers during late phase II (II_L) as the heart rate gradually increases, as an indicator of noradrenergic sympathetic outflow. During phase IV, blood pressure returns rapidly to baseline and then overshoots as cardiac output increases in the presence of peripheral vasoconstriction.

Parasympathetic vagal activation causes a decrease in heart rate. B, In a patient with multiple system atrophy (a Parkinsonian variant) with autonomic nervous system failure, the decrease in blood pressure during phase II_E persists without recovery during II_L . During phase IV, a long delay of 20 seconds for blood pressure to return to baseline is seen and no overshoot is seen. Little sympathetic cardio-acceleration or parasympathetic bradycardia is seen as there is preganglionic failure of autonomic functions

In the last few years portable or wearable smart watches and other devices are being increasingly worn by people displaying heart rate and blood pressure data is the go about their daily lives¹⁹. Since these are not validated many individuals who obsessively track this data as part of health monitoring may develop anxiety in patients predisposed to somatic hypervigilance. A number of companies have now entered the market with software claiming to evaluate the ANS without physician interpretation generating diagnosis and treatment recommendations as well. Till such time ICMR or FDA and suchlike health regulatory bodies approve of these gadgets careful counselling of the population needs to be undertaken to reduce anxiety for non-existent illness or treatment side effects from nonphysician advice. Simple lifestyle advice²⁰ goes a long way in the management of orthostatic intolerance and other autonomic nervous system disorders and a careful scrutiny of autonomic side effects of common medications we use helps avoid ANS symptoms.

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Pictorial CME

Weber's Syndrome — An Interesting Case of Crossed Hemiplegia

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55 years old male noticed weakness of left arm and leg and diplopia on waking in the morning. He had been a diabetic and hypertensive for the past 10 years. On examination, he had complete right 3rd cranial nerve palsy (drooping of eyelid, lateral deviation of eye) with involvement of pupil (Fig 1) and left hemiparesis (Fig 2). MRI Brain T2W (Fig 3) and FLAIR (Fig 4) sequences showed infarcts in right side of midbrain (cerebral peduncle). Hence the diagnosis of Weber's Syndrome was made. He was treated with antiplatelets, statins and physiotherapy. Patient improved over a period of 3 to 4 weeks.

Weber's syndrome was first described by Sir Herman David Weber, a German physician in 1863¹. It is a form of stroke characterised by oculomotor nerve palsy and contralateral hemiparesis or hemiplegia. It is caused by infarction of midbrain as a result of occlusion of paramedian branches of posterior cerebral artery or of basilar bifurcation perforating arteries^{2,3}. This lesion is usually unilateral and affects several structures in midbrain including the corticospinal tracts and oculomotor nerve fibres producing ipsilateral oculomotor nerve palsy and contralateral hemiparesis.

This interesting case highlights the importance of



Fig 1 — Showing right oculomotor palsy



Fig 2 — Showing Left hemiparesis

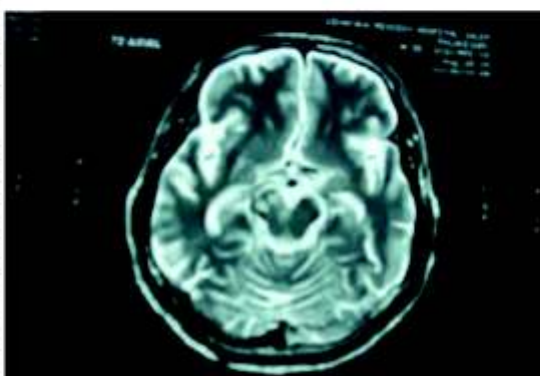


Fig 3 — MRI Brain (T2W) Showing infarcts in rightside of midbrain (Cerebral peduncle)

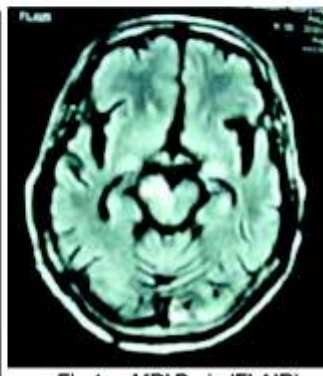


Fig 4 — MRI Brain (FLAIR) Showing infarcts in rightside of midbrain (Cerebral peduncle)

neurological localisation and clinico-radiological correlation.

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NEW IDEAS REGARDING DIABETES MELLITUS

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When I was asked to preside over the medical session of this Conference and to speak on some medical subject, I felt I could do nothing better than to tell you something about a disease which is very common in my province and I am sure is common over the rest of India, and to compare notes regarding our views as to its causation and treatment.

In Bengal, diabetes used to be more prevalent in the generation preceding mine and more common among the intelligentsia than among the working classes, so much so that it was a common saying that the occurrence of this disease indicated the social status of the sufferer. However that be, the fact remained that one of the first results of the adoption of western type of civilization, culture and mode of living was the widespread occurrence of this disease amongst those who left their rural habitat and migrated to the town areas with their artificial surroundings and manner of life. Personally speaking, it is one of the diseases which interested me most, as many members of my family, both on my mother's and father's side, suffered from it and ultimately died as a consequence.

Take any ordinary book on diabetes mellitus and you will find it defined as follows:

Diabetes mellitus is a disease of metabolism due to inadequate supply of the pancreatic hormone. While

this sentence gives you the relevant facts as we see them in diabetes, yet this definition does not give us the complete picture of the disease nor the comprehensive disturbance of metabolism that we find. We have to consider not merely the changes met with in the utilisation of carbohydrates, but also the way in which the diabetic deals with the products of digestion of fats and proteids; we have to consider not merely the variation in the quantity and quality of the pancreatic hormone but also the extent to which there are variations in the nature and character of hormones of other ductless glands; we cannot ignore the part played by the liver which stores sugar and the tissues which utilise them. In a diabetic we often find marked uric acid dyscrasia, alternating with glycosuria; we find the presence in the system products of irregular and incomplete fat and proteid metabolism. Any discussion regarding diabetes as being a disease of metabolism naturally raises the issues of proteid and fat metabolism as well and any attempt to ascribe the whole blame to disease of the pancreas must ignore the corresponding and concomitant changes met with in the suprarenals, pituitary and thyroid.

Let us consider for a moment the definition given above. Supposing we accept the proposition that diabetes is due to inadequate supply of the pancreatic

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hormone—a question will immediately arise—what causes this inadequate supply? Is diabetes due merely to static causes, like changes in the pancreatic tissues, or are those changes due to some other vital processes going on with the system? Why should inadequate pancreatic secretion produce a metabolic disease?

There was a time in the middle of the last century when we had a static conception of diseases. From time to time, diabetes mellitus came to be regarded as a disease of the kidneys, or of the stomach, of the nervous system, of the liver and finally of the pancreas. At present, it appears that the pancreatic theory holds the field; and yet cases are recorded where post-mortem has shown the pancreas to be absolutely healthy, although sugar appears in the urine. The famous experiment of Claude Bernard—the puncture of the IV ventricle—resulted in glycosuria, but not due to inadequate supply of the pancreatic hormone. Hypersecretion of the anterior pituitary body alone may cause symptoms resembling diabetes. The frequent association of acromegaly with diabetes is significant. Recent experiments have shown that this action of the anterior pituitary is partly due to the influence of suprarenal cortex on carbohydrate metabolism, an influence quite distinct from that of suprarenal medulla. Is there any justification for us to distinguish between pancreatic and non-pancreatic diabetes?

Before proceeding to consider the question, it would be interesting to trace the fate of carbohydrate in the system which has been carefully worked out, and it would be interesting to trace the salient features of carbohydrate metabolism in the system. All carbohydrates are converted by the gastrointestinal juices into disaccharides like maltose, lactose and sucrose. These again, by the action of the invertases, are converted into monosaccharides like glucose, fructose and galactose, of which glucose and to a certain extent fructose are utilised by the system as available sources of energy. A portion of these sugars are converted into glycogen and stored up in the liver and muscles, a portion is excreted by the kidneys and the rest circulates in the system to be utilised as a source of energy. It may be that a portion is stored up as fat. To meet special needs or to provide more energy, glycogenolysis occurs and the blood sugar level rises. In a normal individual, however, nature attempts to keep a constant

level of fasting blood sugar. The internal secretion of the pancreas which controls glycogenolysis on the one hand and possibly the utilisation of the sugar by the tissues on the other is the chief agency for keeping a constant fasting blood sugar level. The secretion of the pancreas is controlled by the nervous system. Besides pancreas, other ductless glands have influence on the carbohydrate metabolism; the most modern view is that the suprarenals promote glycogenolysis and helps the tissues to oxidise sugar, that thyroid and anterior pituitary bodies exercise their influence on carbohydrate metabolism through the suprarenals. Recently, Houssay demonstrated that after hypophysectomy, animals become very sensitive to the action of insulin and that in depancreatized dogs, this operation alleviates the symptoms of diabetes. Houssay believed that anterior pituitary glands stimulate the formation of sugar from proteids as also from fats. The alleviation of symptoms of diabetes is due to the fact that the removal of the anterior pituitary stops sugar formation from proteins and fats.

The recently developed methods of determining the physico-chemical changes of the blood underlying metabolic processes within the body have supplied us with more accurate knowledge of the mechanism by which the sugar content of the blood is normally maintained at a particular level; and we should look to a failure or disturbance of this mechanism for the hyperglycæmia and glycosuria seen in diabetes.

What is this mechanism which maintains a constant blood sugar level in the system?

Normally food increases the sugar content of the blood and raises its fasting level. It is known also while proteids and carbohydrates produce equal rises, with fats and oils there is actual reduction of blood sugar level; if hydrochloric acid be added to the meal, the maximum of blood sugar level is reached quicker and is higher than it would be if no hydrochloric acid were given, and conversely with the addition of alkali to the food, the maximum is less and reached later. Experiments with rabbits injected with Locke's solution to which acid or alkali are added show that with acid the glycogen of the liver is more easily hydrolysed than when Locke's solution is given alone and is much more so than if alkali is added to it. After food, here is at first a flow of gastric juice and an alkaline tide is met with in the blood; there is a corresponding fall of blood sugar.

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But soon after, within half an hour or so, the influence of secretion of alkaline juices by the pancreas and intestines soon asserts itself and as alkalipenia develops, the amount of sugar in the blood rises and continues to do so, so long as alkaline juice continues to be secreted. When this ceases, the normal fasting relation between fixed acids and bases is gradually restored, the percentage of sugar in blood falls until the fasting level is reached. We fed animals with hydrochloric acid and found, as Elias did in 1912, and Cammidge in 1920, that this resulted in glycosuria and hyperglycaemia. In 1921, Underhill showed that intravenous injection of soda bicarb in animals produced hypoglycaemia. The influence that hydrochloric acid secretion in the stomach has on blood sugar level is further proved by the following experiments:

In 1915, Blohm showed that while giving sugar by the mouth increases the blood sugar level, the introduction of sugar per rectum causes no such increase, obviously because, while in the former process, hydrochloric acid is secreted, in the latter, sugar is directly absorbed and passes into the liver; he argued that there was no alteration in the gastric and pancreatic secretions nor any consequent disturbance of acid base equilibrium in the blood, no hyperglycaemia was noticed when glucose was given per rectum. There is thus a clear relation between the sugar value of the systemic blood and the fixed acid base balance at any particular moment. This is further proved by taking the dissociation constant of haemoglobin of the blood at different intervals after food intake; with increased alkalipenia, the dissociation constant falls and the blood sugar rises. It has also been proved that the level to which the blood sugar rises after the digestion of food varies in different individuals and one of the causes of such variation is whether the person experimented upon suffers from hyper- or hypochlorhydria. Besides such conditions of the stomach, similar disturbances of acid base equilibrium and resulting hypoglycaemia are noticed under other circumstances.

In 1911, Pavy and Godden showed that in chloroform anaesthesia, glycosuria is produced and the patient is injected with soda bicarb the glycosuria is diminished and urine becomes sugar free after a time.

In 1920, Chautrairie found an increase of blood sugar after ether and CHCl_3 narcosis and that this

hyperglycaemia disappears if alkali is injected intravenously in sufficient amounts to lower the hydrogen ion concentration of the blood.

In 1920, Fatum found that after haemorrhage there is disturbance of acid base equilibrium along with hyperglycaemia. Reismann proved that after operation partly due to anaesthesia and partly due to haemorrhage, acidosis developed and he found acetone and diacetic acid present in a large number of cases.

In asphyxia, Underhill and McLeod proved that hyperglycaemia and glycosuria appear and is proportional to the extent to which respiration is interfered with; he further proved that the presence of excess of CO_2 or acidemia is the direct exciting cause of asphyxial hyperglycaemia.

In 1923, myself and Dr. Mukherjee found that in any typical case of bronchial asthma, the R.P.H. (residual hydrogen ion concentration) varied between 8'1 to 8'4 and that the blood sugar is below normal fasting level. We argued that the lowering of the fasting blood sugar level in these cases was due to the fact that all the available circulating sugar in the blood was utilised towards meeting this condition of acidosis in the asthmatic; such utilisation was possible because in an asthmatic both adrenalin and insulin in sufficient quantities are available for the purpose.

Looking at the clinical and experimental evidences there seems no doubt, therefore, that hyperglycaemia occurs under varying conditions of health and disease whenever there is a lowering of alkalinity of the blood or a tendency towards acidosis. Let us discuss for a moment the other methods which are available to the system, besides hyperglycaemia, to meet any condition of acidosis.

The following processes are at work whenever a condition of acidosis tends to develop in the system:

(1) Bases like soda bicarb and the phosphate combined with the acid radicle; in the former case, excess of CO_2 is formed in the blood and is eliminated by the lungs; in the latter case, acid phosphates are eliminated by the kidneys. (2) These fixed bases also combine with the acids and when they reach the kidneys, ammonia is substituted for them and ammonia salts of the acids are eliminated by the kidneys; the fixed bases are thereby retained in the

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system. (3) Oxyhaemoglobin is comparatively more acidic than haemoglobin though both are very weak acids. During acidosis oxyhaemoglobin is converted into haemoglobin and this means an increase in the amount of bases, which helps in maintaining acid base equilibrium. (4) In acidosis, there is a shift of hydrochloric acid from plasma to corpuscles and base is thus liberated which form bicarbonate so essential to preserve the necessary pH value.

If there be on account of faulty metabolism, and in spite of the operation of the processes described above, there is excessive production or deficient elimination of the acids acidosis develops.

In various pathological conditions this acid base balance has a tendency to be upset. For example:

- (a) In nephritis, cholera, uraemia—due to failure of phosphate secretion acidosis results.
- (b) In decompensated heart disease and in emphysema—defective elimination of CO_2 will cause acidosis.
- (c) In certain diseases like diabetes, vomiting in children, fasting etc.,—increased production of diacetic acid and acetone causes acidosis.

In these conditions of health and disease, nature attempts to relieve acidosis by the ordinary methods mentioned above; when these methods fail, then hyperglycaemia is produced and becomes established for a long or short period. This excess of sugar in the blood is in the first instance the result of break down of glycogen in the liver reservoir; very soon proteins and fats begin to be broken down in large quantities in order to continue the hyperglycaemia. The object of this hyperglycaemia is evidently to reduce or control acidosis. How is this brought about? One can suggest three possible theories which either singly or in combination can explain how this control is brought about.

- (1) In any condition of acidosis, the sodium buffer substances are utilised in the first instance to neutralise the acid; as a result the $\text{H}_2\text{CO}_3/\text{NaHCO}_3$ ratio is disturbed, the numerator CO_2 being in excess, increased respiratory movements follow; very soon, however, the balance is disturbed the other way, partly because CO_2 is thus largely eliminated and partly because of the inter-

action of sodium salt of the fixed acid with H_2CO_3 reproducing the buffer substance. It may be that after the buffer substances have failed to maintain the ratio, excess sugar is produced to compensate acidosis. The sugar is burnt up and the liberated excess CO_2 acts in the manner mentioned above and restores $\text{H}_2\text{CO}_3/\text{NaHCO}_3$ balance.

- (2) It may be that acidosis lowers insulin production the result of which is, as I shall show presently, hyperglycaemia. There is some experimental evidence in favour of this view. It was found by Young in 1937 that repeated injections of anterior pituitary substance increased the fat and protein destruction which led to ketosis and acidosis; simultaneously with it, destruction of islets of Langerhans were found;
- (3) It may be that if sugar is available for combustion, fat metabolism becomes more complete. The amount of intermediate substances like β -oxybutyric acid which are produced in incomplete combustion of fat becomes less and acidosis is relieved.

There are several organs which are regarded as having direct concern with glycogenolysis and oxidation of sugar in tissues. The pancreas acts through its internal secretion, insulin; the most recent view is that insulin controls glycogenolysis and perhaps influences tissue oxidation. There is a strong difference of opinion as to whether the pancreas helps glycogenesis, but the majority of opinion is that the pancreas has no such influence. On the other hand, the suprarenals and all organs which influence the sympathetic system directly or indirectly (like the anterior pituitary and thyroid) excite glycogenolysis and also promote tissue oxidation. In Claude Bernard's classic experiment, puncture of the 4th ventricle, the hyperglycaemia was due to stimulation of the sympathetic.

As is well known, the pancreas has two types of secretion, external and internal. It is also well established that these two secretions cannot be fully produced simultaneously; if the external secretion is increased there is a corresponding diminution in the internal secretion. The internal secretion of the pancreas influences carbohydrate metabolism through a ferment which is antagonistic in action to the glycogenolytic ferment of the liver and other gly-

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glycogen containing tissues. Therefore, with an increased external secretion which necessarily implies lessened internal secretion—the restraining influence—antiferment action—of the pancreas is taken off, and autolysis goes on unhindered resulting in hyperglycaemia. There is an intimate relation between the amount of hydrochloric acid secreted by the stomach and the amount of external secretion of the pancreas. Increased hydrochloric acid secretion in the stomach will produce increased external secretion and proportionately lessened internal secretion and this will lead to hyperglycaemia.

It is also believed by many observers that hyperglycaemia and glycosuria associated with diseases of the suprarenal, thyroid, and pituitary—whatever the mechanism of such glycosuria be—produce pathological changes in the pancreas. The pancreas, as stated above, will all along try through the restraining influence on glycogenolysis, to prevent any condition of hyperglycaemia in whatever manner it is produced, by increased internal secretion. Such hypersecretion of these ductless glands continued for a long period of time, produces fatigue of the pancreas and eventually to permanent defects causing histological changes in the pancreas and the islets as are found in a case of confirmed hyperglycaemia. In such cases, the islets are found sclerosed and destroyed.

Any condition of the stomach, like hyperchlorhydria, any fault in the diet like alcohol habit or the habit of taking excess of sugar, overwork, anxiety and worry, catarrhal condition of the gastrointestinal tract, septic teeth and tonsils causing changes in the intestinal flora might, by excessive formation of secretion of hydrochloric acid and by increasing external secretion of the pancreas, diminish the internal secretion and will tend to produce hyperglycaemia. The same results will follow if the pancreas owing to congenital defect or defects or through overwork loses its internal secretion.

If we imagine a condition where the internal secretion of the pancreas is totally abolished, then the glycogenolytic ferments of the liver and other tissues will have full play, little or no glycogen will be stored in the liver and other tissues, all the carbohydrate will pass into the circulation as sugar; if, however, the control is only partially impaired, glycogenesis and glycogenolysis will go on side by side but both will be imperfectly carried out, soluble

intermediate bodies like dextrin and other polysaccharides will be circulating in the blood. Such a type of carbohydrate will not be available to the tissues for metabolic purposes until dextrin is hydrolysed into sugar.

Let me now consider the various theories that have been put forward from time to time to explain the metabolic disease diabetes mellitus. Claude Bernard originally suggested two possible causes of diabetes:

- (1) Excessive production of sugar from the storage in liver (over-production theory),
- (2) inability of the extrahepatic tissue to utilise sugar (under-utilisation theory).

More recently McLeod has suggested that the cause of diabetes is uncontrolled hepatic gluconeogenesis i.e., in all cases of diabetes there is excessive formation of sugar from non-carbohydrate sources (proteins and fats) along with non-utilisation of sugar by tissues. Although the level of blood sugar may be due to the adjustment of the processes of sugar formation and utilisation, it is just possible that in diabetes, with an aberrant sugar metabolism, the blood sugar level is shifted to a pitch much higher than normal.

The theories mentioned above were based on the assumption that ordinarily the constant blood sugar level is maintained by an adjustment between the amount of sugar that reaches the blood either from the liver by glycogenolysis or from fats and proteins by the process known as gluconeogenesis and the amount of sugar utilised by the tissues. If the controlling influence of insulin is lost then glycogenolysis goes on unchecked. If the pituitary body and suprarenals are stimulated glycogenolysis and tissue oxidation are increased. In diabetes, it is suggested that this adjustment between sugar production and sugar utilisation is lost and then either the increased blood sugar is produced or the tissue oxidation becomes less.

But the question still remains—what is it which diminishes the internal secretion of the pancreas or stimulates the sympathetic system?

In 1923, Dr. Mukherjee and myself reported that in practically every demonstrable case of diabetes, while the urine shows no abnormal constituents indicating acidosis, the R.P.H. value is below 8.45 (the normal value); the value some time going down

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ROY

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to 7.65 (in a case of diabetic coma). In all such cases, there is usually hyperglycemia, the value varying between 16 per cent to 5 per cent. Let me give you a picture of the metabolic processes in the diabetic as I conceive them. Owing to faulty over-eating, nervous excitement, worry, dyspepsia (with hyperchlorhydria), infection of gastro-intestinal or biliary tracts, we may have hyperchlorhydria and resulting acidosis and hyperglycemia. Under such circumstances, the acidosis as I have explained above, alters the balance between glycogenesis and glycogenolysis and abnormal products of glycogen destruction, dextrin and other polysaccharides, appear in the blood which, therefore, cannot be utilised by the tissues. If the cause which brought about acidosis persists, the acidosis continues; this leads ultimately to fatigue of the islets of Langerhans. As the pancreas owing to lessened insulin production loses its controlling influence over glycogenolysis, sugar of abnormal types continues to be produced in the blood; the tissues, though bathed in blood containing higher percentage of sugar, cannot utilise it; the adrenals are stimulated and promote further destruction of glycogen into sugar and thus a vicious circle is established. When the glycogen reservoirs are emptied, perhaps even before that, abnormal sugars are produced from the destruction of fats and proteins. The metabolism of fats under such conditions of non-combustion of sugar is incomplete; abnormal bodies like the oxybutyric acid appear in the urine.

I have said above that the tissues in diabetes do not utilise the sugars produced under such circumstances. It was at one time suggested that they have

lost their faculty of oxidising sugar altogether. In our communication to the press in 1935 and 1939 we gave it as our experience that a diabetic is able to utilise sugar given intravenously in the form of glucose in large quantities, say 200 c.c. of 25 per cent i.e., about 50 grammes of glucose a day without permanently increasing the blood sugar; in fact, our experience has been, as the charts will show, that the sugar level is lowered and even reaches the normal values and concomitant glycosuria disappears. I have here several charts to prove this point (vide charts). Therefore, the tissues have not lost their power of oxidation. And further, in the majority of cases, with suitable dietetic regimen, the pancreas regains its normal function. Of course, the initial causes of acidosis, the hyperchlorhydria, the worry, the nervous excitement, the overfeeding, should all be corrected or else the vicious circle will start again.

Let me now put the facts I have presented above in seriatim and place before you my answer to the question—"What is diabetes due to?" Various organs of the body exercise their influences on the carbohydrate metabolism. It is safe to assume that the rate of removal of sugar from the blood is dictated and directed in some way through nervous system perhaps—by the needs of the organism; fluctuation in sugar concentration in the blood being compensated for by the variation in the rate of output. The fluctuation in sugar level and the compensatory mechanism are governed by the following factors:

- (1) *Acidosis*—This is the essential element in the production of diabetes. In our experiments we proved that the acidity of blood

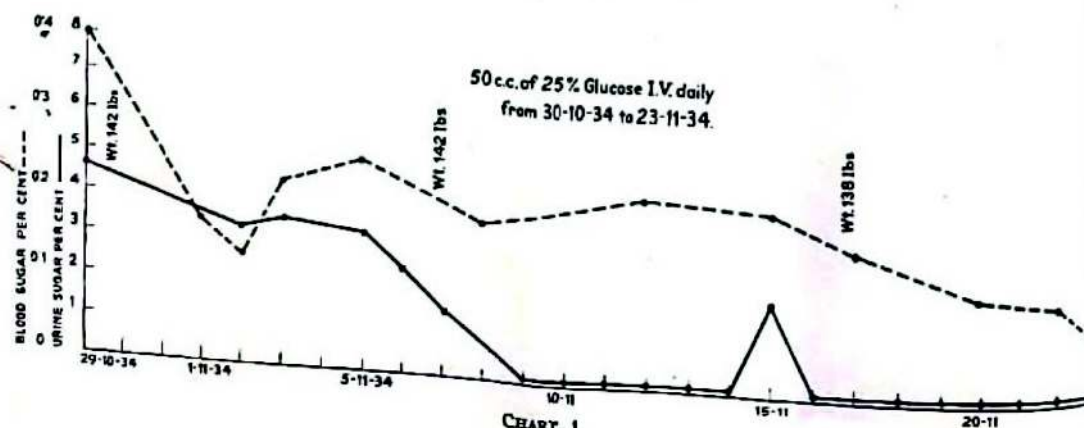
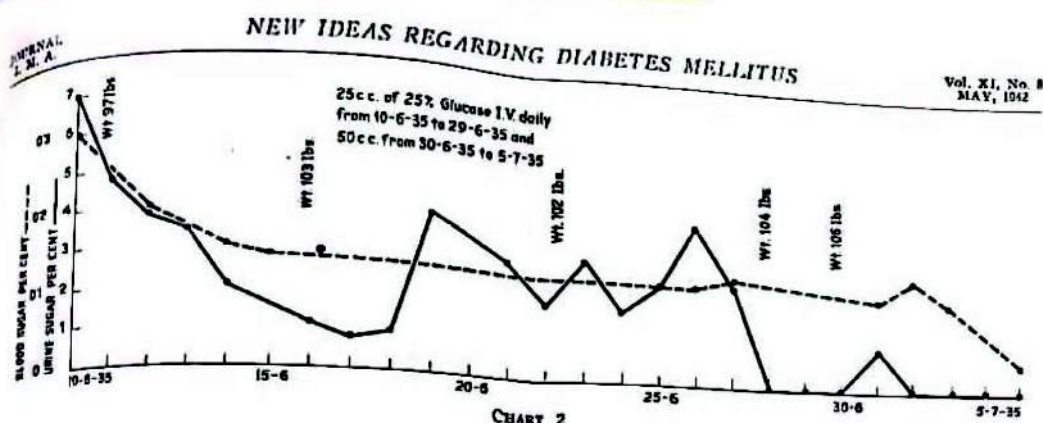


CHART 1

— 230 —

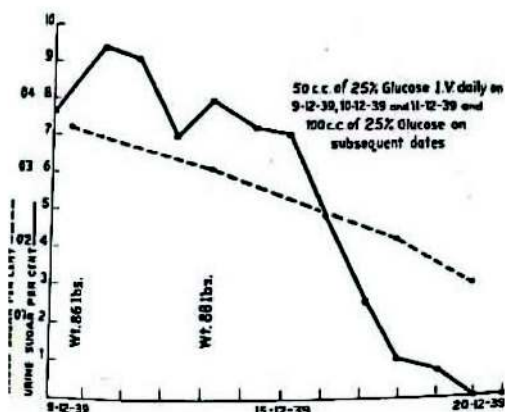
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in the diabetic becomes high, at a much earlier stage than the appearance of abnormal substances in the urine indicating ketosis. As this acidosis sets in, insulin secretion is diminished, glycogenolysis follows.

- (2) Hyperglycæmia—In diabetes, the excess of blood sugar is a physiological attempt on



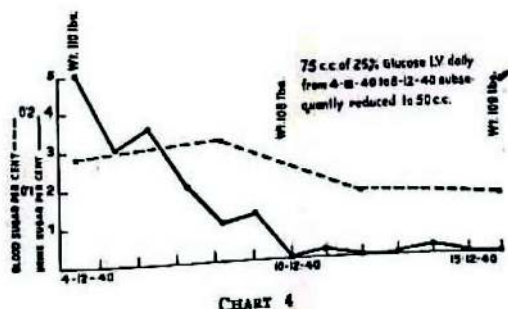
the part of nature to neutralise acidosis. It is an active phenomenon. The difficulty lies in the fact that the sugar is presented to the tissues in a form which they cannot utilise—their call for more is partially satisfied by glyco-neo-genesis, by abnormal breaking down of fats and proteids to produce sugar. Such abnormal fat and proteid

metabolism results in the accumulation in the system of β -oxybutyric acids etc. (products of their incomplete combustion) and there is increase of acidosis. This acidosis increases hyperglycæmia. A vicious circle is, therefore, established.

- (3) Tissue metabolism—It has been suggested that in diabetes tissue oxidation is deficient. But our experiments proved conclusively that the tissues of a diabetic could oxidise sugars if present in a suitable form. If large quantities of glucose are injected into the veins and utilised by tissues the call for sugar will be lessened, the abnormal production of sugars from proteids and fats—the gluco-neo-genesis—is also lessened in a marked degree. !

In treating diabetes, therefore, the rule I follow is this—

- (1) I put the patient on water only for four days and note the amounts of blood and urine



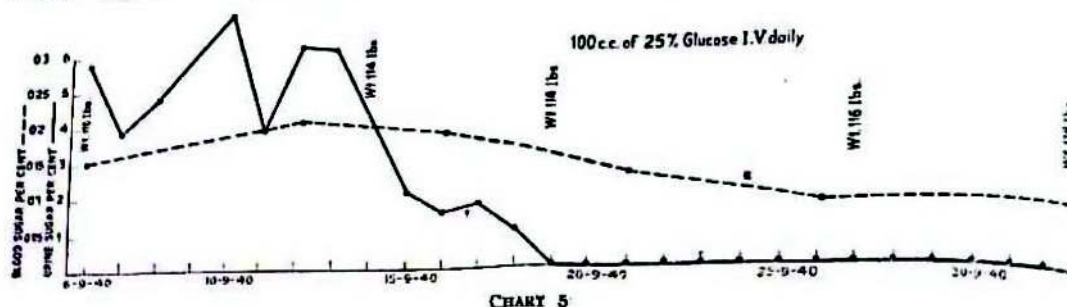
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ROY

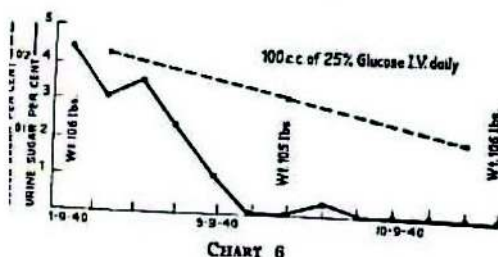
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sugar before and after this period. If necessary, I give him a little soda bicarb in order to minimise the chances of acetonaemia after fasting.

- (2) In many early cases, this period of fasting sets the machinery in good working order. The blood sugar level falls to normal, the urine sugar disappears. Then the patient is allowed for 6 days 400-500 calories of food, with 35 per cent of proteins, 25 per cent of fats and 40 per cent of carbohydrates. If everything goes on normally, the food is gradually increased in caloric value keeping as far as possible to the above proportion of proximate principles until he is given 1500 to 1800 calories and he is allowed to remain on this for 4 to 6 months.



- (3) If, however, with the preliminary four days treatment it does not reduce blood sugar to normal and if the urinary sugar persists, then I give him daily for a fortnight, while

at rest in bed, 100-200 c.c. of glucose 25 per cent to 50 per cent intravenously. Usually I allow him some food, more of a starchy type which fills the stomach but does not interfere with metabolism. If the diet be so restricted, the external secretion of the pancreas is lessened, and, as I have indicated above, the internal secretion is correspondingly increased in amount, which thereby controls glycogenolysis. In my experience, the injection of glucose for 2 to 6 weeks will restore the system to normal. If the original troubles causing acidosis, the hyperchlorhydria, the worry and excitement etc., be removed, one need not fear relapses. Glucose by the mouth does not serve the purpose, because so long as the pancreas is at all functioning, this means imperfect glycogenesis and glycogenolysis; the abnormal sugars then released to the tissues cannot be utilised.

- (4) I use insulin only if I am forced to. When there is an infection or the pancreas refuses to take up its normal role, then a help in the shape of insulin—a stick for an old man—is necessary.

This then is my view of the disease and the line of treatment that in my opinion is rational and satisfactory.*

* Presidential Address delivered at the Section of Medicine, Scientific Session, XVIII All-India Medical Conference, Hyderabad-Deccan, December, 1941.

Commentary

Legendary Prof BC Roy in December 1941 delivered his Presidential Address at the 58 th All India Medical Conference in Hyderabad -Deccan on Newer Ideas on Diabetes Mellitus which was published in JIMA May 1942 issue . Today as we near a centenary of discovery of Insulin (we are in the 99th year) many of Prof BC Roy's ideas are relevant today .He first noticed in his state Bengal Diabetes was a diseases linked to social status and today we know it's link with affluence and we often link it with affluenza and modernisation .In 1941 he predicted that westernisation of habits and culture will lead to wild spread occurrence of the disease which is prophetic because we went on to become the diabetes capital of the world . It was only in 2011 we lost the first rank to China and now we aim to be the Diabetes care capital of the world .Dr BC Roy clearly describes the rural urban divide as well as the familial penetrance of the disease .He clearly predicted how type 2 Diabetes runs in families as well as its polygenic nature which form the major bulk of the burden today.He postulated then the endocrine and metabolic cross talk and it's link even to Uric acid then. He described the classic experiments of Claude Bernard of the puncture of the fourth ventricle leading to glycosuria. He described diabetes seen with endocrine disorders like acromegaly and went on to distinguish pancreatic and non pancreatic variants of diabetes. He elegantly described the pathophysiology of the intermediate steps of metabolism linked to food and blood glucose regulation and gave a detail analysis of the carbohydrates breakdown which occurs in energy homeostasis. The treatise contains experimental work done from 1900s in those four decades in animals and humans how glucose was controlled. With ensuing hyperglycaemia and as glucose rises it switched the acid base imbalance which he does in his own descriptive style where he lays the foundation of acidosis which occurs in diabetes .He then describes the toe theory concept of Claude Bernard for diabetes namely the excess hepatic glucose output (the sugar over production theory from liver) and inability of the extra hepatic tissue to utilise glucose (under utilisation theory).

Prof BC Roy then describes his own work with Dr Mukherjee each of the diabetes glycosuric cases has some degree of acidosis and described various biological mechanisms involved. There is a description of a triad of acidosis , hyperglycaemia and tissue metabolism. In 1940s Prof BC Roy describes the treatment of diabetes starting from pure hydrotherapy with water with some times little sodabcarb to reduce the ketosis for four days. Simple fasting in early cases normalised glucose and the cases are allowed 6 days of 400 to 500 calories with 35 percent proteins, 25 percent fats and 40 percent carbohydrates with a gradual resumption of normal food group components and calories over next 6 months .Today we know from the various work done last decade by Roy Taylor's group from various studies till the randomised DIRECT trial on diabetes reversal ,actually Dr BC Roy and his group had described it in early 1940s of very low caloric diets. Even then Insulin was only reserved for infection or lack of pancreatic insulin secretion. His personalised views has rationality then and possibly deep relevance even today.

In the fast paced evidence based world there is hardly any role of descriptive narratives yet look at the vision eight decades back BC Roy has insights into protocols like reversal of diabetes to Insulin .He has deep knowledge of physiology and pathology of the disease process and the cross organ talks of pancreas, liver, muscle and fat. He underlines role of glucose in urine which we now therapeutically exploit with SGLT2 inhibitors. He illustrated the role of hepatic glucose production and we know most modern age diabetes medication including metformin turn of the liver glucose tap overnight to control fasting blood glucose. Prof Roy has clear idea of role of water and sodabcarb apart from insulin in managing acidosis and emergency of diabetes. Clinical medicine is built it's foundations from bench side experiments in animals to astute clinical observations systematically recorded.

Dr BC Roy's masterpiece treatise gives us glimpses how he predicted the diabetes epidemic due to westernised habits as well as its natural history including treatment protocols prevalent then with principles which are even applicable today.

India today has the second largest population as well as people living with diabetes .Currently we have approximately eighty million Indians with diabetes and possibly an equal of larger number with prediabetes. Its rapid adaptation of westernised habits, culture and lifestyle which prof BC Roy predicted in 1941 which has lead to this epidemic. We all aim to become the Diabetes care capital of the world .my prevention mantra draws inspiration from the legendary prof BC Roy "Eat Less, Eat on time, Eat right, Walk More, Sleep well & on time and Smile."

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Medical History

The History of Medical Journals In India

Rudrajit Paul

Science is a branch of knowledge which has always flourished due to the confluence of brilliant minds. For thinkers and researchers to communicate among themselves, journals form an indispensable link-road. The concept of scientific journals in India is entirely an offshoot of European influence. Medieval India had some literature related to various scientific disciplines, including medicine. But there were two problems. Firstly, in the Hindu society, the right to knowledge was entirely a privilege of the upper caste. So, there was not much dissemination of knowledge. Secondly, the books written in the medieval period were mostly a mixture of religion and mythology interspersed with some scientific facts. Thus, it was often difficult to find a secular treatise dealing with pure science.

The concept of publishing scientific journals for the intellectual minds of the society came only after establishment of European rule. In Europe, the concept of scientific journals had started by the eighteenth century. The boundary between the various disciplines were fluid at that time and any "Science" journal at that time would have a mixture of articles dealing with say, physics, medicine and geology one after another and even some article on Philosophy or architecture. One example is the **Edinburgh Journal of Science**, published between 1824 and 1832. In one issue of this journal (1825), one can find the following successive articles: -

1. Observations on the Vision of Impressions on the Retina, in reference to certain supposed Discoveries respecting Vision
2. An Account of a Plant allied to the Genus Piper
3. On the Theory of the Existence of a Sixth Sense in Fishes

So, the successive articles were on ophthalmology, Botany and Fishery Science!!

However, as the treasure-trove of knowledge in each discipline expanded, the need was felt to publish journals dedicated to particular branches of science and medical science was no exception. Some of the early medical journals included *Medical Essays and Observations* (UK, started, 1731) and *Medical Repository* (USA, 1797).

Right after the commencement of the trend for medical journals in Europe, a similar phenomenon took place in colonies like India. In those early days, there

were almost no person trained in Western Medical Science in this country and thus, the first Indian medical journals were published by Europeans, for European professionals, in European language. We will discuss a few of those here.

The Early Journals:

1. Medical Board Proceedings (1786-1858) :

This was not exactly a medical journal in the strict sense. This was mainly an official medical document. It was hand-written and mainly for official use. The document would be kept in government archives for reference. At that time, there were very few people conversed with English language in India and even if this document was published and circulated, very few people would actually be able to read it. While there were some scientific discussions in these documents, the majority were official topics like medical expense or onset of any new sickness among the British troops.

These proceedings have considerable historical value. For example, the 3rd April 1787 proceedings contain the first mention of a lunatic asylum in Calcutta. The outbreaks of various diseases in Indian cities are also documented in these pages.

2. Transactions of the Medical and Physical Society of Calcutta (TMPSC) : This was the first proper medical journal-like publication in India. It started in 1825. In 1823 (March 1st), under the directive of the new colonial government, the Medical and Physical Society was established in Calcutta. This society had two objectives. Firstly, to collect new papers related to discoveries in Medicine including indigenous medical system. These papers were read and then the proceedings of those seminars were published in the TMPSC. Secondly, this society also had the objective of forming a scientific medical library, the first of its kind in India. The publishers were Messrs Thacker and Co., St Andrew's Library, and printers were the Baptist Mission Press. Since the Christian missionaries were the first to establish printing press in India, naturally they were the publishers of the first medical science journals.

Why was this journal established? In their preface they wrote :

"The immediate object was to give a concentric impulse to the detached members of the service, and

afford them augmented facility of information, as well as a new excitement to emulative exertion." Also, they wrote, "Whatever advantage may be realized from enquiries thus favourably instituted, will be shared by us with our brethren of the West; but some benefits may be expected from an improved circulation of useful information amongst ourselves, which may be regarded as exclusively our own."

Thus, right from the beginning, this journal was aimed to provide for exchange and dissemination of knowledge. The British government had then formed the Medical Board of Bengal. Members of this board acted as patrons of this journal. Also, the government of Bengal provided free postage to this journal.

This journal covered topics pertinent to the local population and not just European diseases. For example, some of the topics covered in its issues included:

- An Essay on Kushta, or Leprosy as Known to the Hindus
- Snake bite
- On the Exhibition of Phosphorous in Cholera Morbus

Although formed by the European doctors, this society had Indian members too: **Radhakanta Deb, Madhusudan Gupta, Kalikrishna Bahadur and Ramkamal Sen**. These Indian members wrote a few articles on Indian Medical system in the journal.

However, this journal was short-lived. It was published once annually in 1825, 1826 and 1827. Then it was published every second year. In 1835, the name was changed to Quarterly Journal of the Calcutta Medical and Physical Society (QJCMPS). By that time, the first Medical school of Asia, Calcutta Medical College had been established and professors of that institution took up the work of editing. H. H. Goodeve and W. B. O'Shaughnessy, two illustrious teachers of this college were the editors. The journal had colour plates with clinical images. It ceased publication in 1845. Now, it is notoriously difficult to get reprint copies of this journal. The author of this article (Rudrajit Paul) could only find a few scraps of information online.

This journal had a surprisingly smart editing, which can be considered modern even for today. It was divided into three parts: -

- **Part-I** : This had the original articles and case reports
- **Part-II** : This had reprint of medical articles from Europe. Not only English but also French and German articles were reprinted with translations
- **Part-III** : This had contemporary news. For example, the news of a plague outbreak was mentioned in one issue.

Some interesting articles published in this journal included

- Post-mortem report of William IV, the monarch of England
- Case of Tetanus, Cured by a Preparation of Hemp (This was probably the first publication of medical use of Cannabis)
- Observations on the fever which prevailed at Howrah during the months of June and July, 1834 (one of the earliest descriptions of malaria in Bengal)

Some pictures from this journal are given below (Figs 1 to 3):

308 OBSERVATIONS ON THE FEVER

after an hour. It brought away masses of accumulated faeces, and after sitting in a tepid bath, at the temperature of 95°, for half an hour, he was ordered to take

R. Calomel ʒ. i.
Scrap: gr. x.
In three pills.

At 9 P. M. he was asleep, and perspiring; he declared himself free from pain. Pulse 110; had had no stool since last visit.

R. Calomel, gr. xv.
Ipecacuan, gr. iij.
Opil gr. i.
Extract. Colocynth. Comp. gr. xv.
In four pills, to be taken immediately, and
Oil Ricini ʒ. i. at four A. M. to-morrow.

Fig 1: A page from Transactions of the Medical and Physical Society of Calcutta (TMPSC) showing treatment protocol for fever

CASE

ARROW-WOUND OF THE HEAD.

By A. STORM, Esq.

Presented by the Medical Board.

CAPTAIN —, while on service, received on the morning of the 24th of October two arrow wounds, one in the head, and the other in the back. For some marches the detachment was without tents, and exposed during the night to heavy rain. On the morning of the 27th I met them returning. Captain — informed me, that he felt slightly stunned when wounded, and that the arrow could not be withdrawn without force; but he did not complain of much uneasiness. The wound was in the middle of the occipital bone, and was partially closed. We reached cantonments on the evening of the 29th. On the 31st; as he complained more of his head, and felt feverish, he was reported sick on the 1st of November; had a purgative on that day, and in the evening was bled to syncope, and next day 50 leeches were applied to the head.—2nd. He felt greatly better, and his bowels had been acted on, two or three times; the wound appeared a little puffy; it was opened with a lancet, and a poultice applied: tongue very foul and loaded. —3rd. Complained of head-ache; tongue still foul;

Fig 2: A case report from TMPSC: Arrow wound, treated with leeches

APPENDIX.

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No. 8.

A letter from Dr. SEILAHURU, describing two cases of Severe Wounds penetrating the Abdominal Cavity, occurring in Natives.—Addressed to W. TWISING, Esq.

The extreme facility, with which Natives of this country recover from wounds of all kinds, cannot have escaped the notice of the profession. Two severe ones both penetrating the cavity of the Abdomen, have occurred to me within a few days of each other; a slight account of which you may perhaps deem worthy of laying before the Society.

The first was that of a grasscutter, a stout healthy young man about 25, whom I was called to, on the evening of the 6th of June last, having just then been gored by a spotted deer. The horn appeared to have passed just over the spermatic cord of the left side, entering the inguinal canal and penetrating into the cavity of the abdomen upwards and inwards (doomed), nearly in the direction of the canal.

Fig 3: Letter to the editor in TMPSC, describing two cases of penetrating abdominal injury by horns of animals: Deer and Buffalo

3. Indian journal of medical science (IJMS):

This was another journal which was published in 1834. After two years, it was renamed India Journal of Medical and Physical Science (IJMPS) and publication continued till 1845. This journal was published by the personal efforts of two individuals, J. Grant and J.T. Pearson. The main aim of this journal was to save time of expenses of the medical men of this country, so that they would not need to import European periodicals. Also, this journal was devised not to foster scientific discussions, but to discuss "on the causes, symptoms, and treatment of maladies, to which they are but too liable, when exposed at detached stations and factories, remote from immediate medical aid." This journal was meant to cater to both medical men and veterinarians.

This journal was also divided into many sections: original articles, medical topography, hospital reports, native remedies, medical jurisprudence, entomology, medical botany, biographies: just to name a few. Thus, there was something for every reader and even there was a section on medical issues written in non-technical language for the lay person.

There is a bit of history behind publication of this new journal, IJMS. The earlier journal, TMPSC concentrated only on pure scientific matters. But in that society, there were people like J. Grant, who wanted to widen the scope of the journal and publish articles related to other aspects of the profession. However, this idea was strongly opposed by many influential members of the society, including the president Mr Wilson. When Mr Grant became the Apothecary General of Calcutta, he took a great risk and started the IJMS on his own, separate from the

Medical and Physical society of Calcutta.

At first, this new journal faced opposition from many learned citizens. They had to do all the editorial work on their own, including review of the submitted articles. Since this was an English journal, the circulation remained confined within the European society of Calcutta. There were many interesting articles like

- On the Fever (that prevailed in Calcutta During the Months of September, October, November and December 1833): written by a surgeon at Fort William

- Vaccination (this was written by an Indian, Radhakanta Deb)

- Blood-letting as a treatment for cholera
- The Cerebral Development of Rajah Rammohun Roy (a particularly important and significant article; This was reprinted from Phrenological Journal, London): at that time, Phrenology, or the study of skull anatomy to deduce personality and genius was a very popular pastime

- There were many hospital reports of interesting cases at the PG hospital of Calcutta

In 1836, the journal was renamed, as mentioned earlier and its motto was also changed:

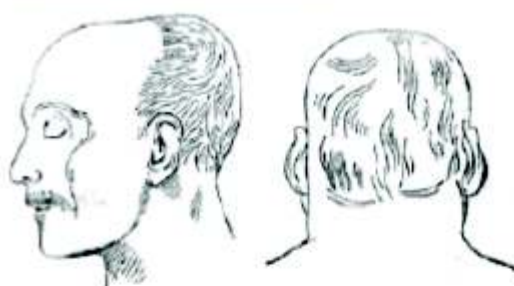
...."we shall endeavour to avoid all invidious distinctions or partialities we shall not fail to submit, in respectful terms to the notice of the ruling authorities, suggestions tending to benefit not only individual, but the medical profession at large"

Thus, in addition to fostering scientific discussion, *this journal also wanted to take part in policy making.* At inception, many intellectuals of Calcutta were sceptical of such a private journal and commented that it would soon fade into oblivion. However, that did not happen and the journal soon gained popularity. Some issues were sent to Europe and USA to get comments and approval. The setting up of the first medical college of India in 1835 also gave a further boost to this journal. By 1838, it had a monthly circulation of 400 copies, which was an extra-ordinary feat for a medical journal, written in English, in a colonial city at that time.

In 1843, Dr Eveleigh of Dharmatala area became the editor. He set the price at 16 rupees per annum. However, due to failing health, he had to leave India soon. After that, there was no one to continue the official works and publication of the journal stopped. One interesting article of IJMS is mentioned here (Fig 4).

4. The Transactions of the Medical and Physical Society of Bombay (TMPSB): This journal came into being in 1838, 13 years after the Calcutta journal. Similar to Calcutta, a Medical and Physical society had been established in Bombay and this society started its own journal. This journal wanted to

The following sketches will convey to the reader an accurate general idea of the appearance of the head.



The dimensions of the cast, and the cerebral development are as follows:

DIMENSIONS IN INCHES	
<p>Greatest circumference of Head, (measuring horizontally over Individuality, Destructiveness, and Philoprogenitiveness, none.) 24 1/2</p> <p>From Occipital Spine to Individuality, over the top of the Head, 15</p> <p>Ear to Ear vertically over the top of the head, (measuring from upper margin of the mastoid.) 14 1/2</p> <p>Philoprogenitiveness to Individuality, in a straight line, 6 1/2</p> <p>Conscientiousness to Concentration, 11</p>	<p>From Ear to Philoprogenitiveness, none 4 1/2</p> <p>Individuality, 5 1/2</p> <p>Benevolence, 6 1/2</p> <p>Veneration, 6 1/2</p> <p>Firmness, 6 1/2</p> <p>Destructiveness to Destructiveness, 6 1/2</p> <p>Seriousness to Seriousness, 6 1/2</p> <p>Cautiousness to Cautiousness, 6 1/2</p> <p>Ideality to Ideality, 4 1/2</p> <p>Constructiveness to Constructiveness, 5 1/2</p> <p>Mastoid process to Mastoid process, 5 1/2</p>

Fig 4: The Phrenological analysis of cast of the skull of RamMohan Roy, as published in Phrenological Journal and reproduced in IJMS, Calcutta

promote medical research which was relevant for Indian conditions. Although all the editors were British, this journal stressed on medical conditions resulting from changes in geography, climate or food habits in both Europeans and the Indians. One example of this approach was the article, "The manner of rearing children of Europeans in India", which discussed the paediatric diseases prevalent among European children in Indian conditions.

Dr Morehead, the editor, stressed on the need to develop a scientific medical education system in India. He also felt the need to develop modifications of medical practice suited to Indian conditions.

The journal was at first printed by The American Mission Press of Bombay. After 1851, printing was done at the Bombay Education Society Press. Some important articles of this journal are mentioned below:

■ Report upon the Cases of Tetanus in the JamsetjeeJeejeebhoy Hospital, from January, 1845 to December 1851

■ Reports on the plague epidemics in different parts of Bombay province

■ Medical History of the Central Schools of Bombay for the Five Years Ending the 1st July 1852; Including a Visitation of Measles Contains Some

Useful Illustrations of Infantile Disease

The journal was in circulation much longer compared to the earlier Calcutta journal and continued till the first or second decade of Twentieth century. Some glimpses from this journal are presented in figures 5 to 8 below.

NATIVE TROOPS AT AHMEDABAD, FROM 1841 TO 1852.

Monthly Ratio of Admissions and Deaths.

Months.	Fever.			Dysentery.			Diarrhoea.			Cholera.			Scarlatina.			ALL DIARRHOEAS.		
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
January	50.00	0.00	7.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00
February	40.00	0.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	80.00	0.00	0.00
March	30.00	0.00	20.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	60.00	0.00	0.00
April	20.00	0.00	30.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	40.00	0.00	0.00
May	10.00	0.00	40.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	20.00	0.00	0.00
June	0.00	0.00	50.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
July	0.00	0.00	60.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
August	0.00	0.00	70.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
September	0.00	0.00	80.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
October	0.00	0.00	90.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
November	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
December	0.00	0.00	110.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

A Admissions to 1,000 of Strength. B Deaths to 1,000 of Strength. C Deaths to 1,000 of Admissions.

Fig 5: A chart showing the monthly mortality and morbidity among troops in Ahmedabad in 1841



Fig 6: Painting of a snake in an article about poisonous snakes of Sindh region. This snake was killed in a military barrack in 1863

No. 11.

Case of attempted Suicide of a Sepoy by Fire-arms. By T. M. LOWND, M.D., Assistant Surgeon.

Presented July 1853.

Fig 7: A case report published in the journal

A Case of Twins, in which the Birth of the second Child was obstructed by the protrusion of a Hand by the side of the Head. By Mr. ATHARAM PANDORUNG, Graduate of the Grant Medical College.

Presented by the Grant College Medical Society.

Early in the morning of the 2nd of March 1853 I was called to see a Mahanta woman in her fifth labour, residing in Girgaum. She was about 26 years of age, of native spare constitution. I found her sitting on the floor, with her legs stretched out. She was supported in this position by an attendant sitting behind. Before her lay a full-grown newly-born child. It was wrapped up in a piece of cloth, and was not separated from the placenta, which was still within the uterus. A midwife in attendance stated that there was another child in the womb, but that the pains being feeble, it could not be delivered, and hinted that some medicines were required to excite effective pains. The size of the abdomen was such as to indicate the possibility of there being a second child. I proposed that first of all the infant already born should be separated; but the idea was quite opposed to the usual mode of procedure of the people of this country in such cases, and associated

Fig 8: Another case report published in the journal by an Indian Medical graduate

5. Madras Quarterly Medical Journal (MQMJ):

This was another short-lived journal (1839-43). This was the brainchild of a famous surgeon of the Madras region. The aims of the journal were:

"to bring before the profession authentic reports on the principal diseases to which the Europeans were subjected to in India and the investigation of the diseases prevailing amongst the native population"

This journal also discussed the herbal remedies used by indigenous practitioners for various diseases. Also, it published reprints of papers from other branches of science related to medicine.

It was a Quarterly journal and published by Messrs J.B. Pharaoh of Madras. The journal was mainly circulated among army medical officers. In the very first volume itself (1839), the importance of statistics in medical research had been stressed in the preface. An interesting point to note is the instruction of the journal regarding the sections into which an original article was expected to be divided. The sections, **as given in the preface of the 1839 issue**, are mentioned below:

- Topographical description of the military barrack
- Condition of buildings etc in the cantonment
- Diet
- Clothing, bedding and nature of duty
- Recreational exercise
- Numbers of European and native troops
- Endemic diseases
- Description of the cases/epidemic
- Age-wise mortality
- Vaccination status
- Mode of treatment used

As this instruction manual makes clear, this journal wanted to get a whole description of any disease,

including the topographical and social history. This was an exceptional approach at that time and shows the level of erudition of the editor. The following is an article from that journal describing treatment for fever (Fig 9).

Treatment. On the setting in of the cold stage, especially if any precursory symptoms marked its approach, an opiate with a few drops of sulphuric ether was administered, with a view either of checking it altogether, or of shortening the cold stage: occasionally it produced the former effect, more frequently the latter. In the hot stage where the head-ache was severe, it was sometimes necessary to apply leeches to the temples, but it was rarely requisite to have recourse to general bleeding. Purgatives were almost always used in the first instance, to clear the alimentary canal, and to pave the way for the bark. Where there was much heat of skin, a combination of diaphoretics and purgatives, as the liq: acetat: ammoniac and sulphat: magnesiae, or calomel and James' powder, were attended with benefit:—But in putting a stop to a return of the paroxysms, our chief dependence was placed in the quinine or bark, which rarely if ever deceived us. In the milder cases, where the stomach would admit of it, the bark was used in the form of decoction or powder:—But in more serious or complicated cases, or where nausea and gastric irritability were present, the quinine was used, in doses of

Fig 9: treatment of fever, as published in the MQMJ in 1839; as seen here, opiate was used, leeches were applied on the forehead, purgatives were used in high fever as was something called "James' Powder"

In another report, the rise in venereal diseases among British troops in India has been reported (Fig 10).

The number of admissions of venereal in the first three quarters of last year (1837) were

1st Quarter.....	610
2d Quarter.....	540
3d Quarter.....	576

In the corresponding periods of this year (1838) they have been

1st Quarter.....	577
2d Quarter.....	702
3d Quarter.....	599

Shewing an increase of 159 in these last 3 quarters.

Fig 10: Table showing the military personnel admitted with venereal disease in 1837 and 1838

At that time, there were frequent disease outbreaks among the European colonizers. One such report of a dysentery epidemic is given below (Fig 11).

There were other short-lived medical journals in Madras like the Madras Journal of Medical Science (MJMS) (1851-54) and Madras Quarterly Journal of Medical Science (MQJMS) (1860-1869). Many teachers of the illustrious Madras Medical College were associated with these journals.

6. Madras Quarterly Journal of Medical Science (MQJMS): This was a short-lived Journal but had some historically important articles. Some of the writers in

"The disease," continues Mr. H. in a subsequent part of his report, "which is now found so generally to afflict the European Soldiers, and with such fatal visitation, is Dysentery combined with a scorbutic taint of constitution. The disease does not appear to possess any other striking peculiarity in its character than the extreme fatality that attends it, and which may be reasonably accounted for from its combination with scurvy, aggravated by the previously debilitated and exhausted constitutions of its victims. When the patient does not sink rapidly under the disease, he falls into a Dropsical state, the swelling commencing in the feet and extending upwards, when the belly becomes tumid, respiration laborious, deglutition difficult, the countenance bloated, and his sufferings continue to increase, until terminated by death."

Fig 11: Description of an epidemic among European soldiers in MQMJ

this journal were personal physicians to the then Indian Maharajas (rulers of native princely states). One such person was Edward J. Waring, physician to the King of Travancore. He wrote some important articles like:

- Notes on Some of the Indigenous Medical Plants of India
- Notes on the Affection Called 'Burning of the Feet'

The MQJMS had some important articles. For example, in one article of Volume 2 of this journal, there is mention of an attempt to grow the Cinchona plant in India (Figure 11A).

THE CINCHONA IN INDIA.

In our October number (page 491, Vol. I) we alluded to the mission of Mr. Clements Markham in introducing into this country the quinine yielding plants of South America, and promised to keep our readers informed of the progress of the experiment then about to be made.

We regret to learn that the plants brought by Mr. Markham have all perished. They suffered so much from exposure to cold, in his journey across the Cordilleras, that very few of them survived the voyage to England, and from thence overland to the Western coast. Cuttings were made by Mr. Melvor from some of the most promising looking plants, and it was hoped that these might be propagated; but by the latest accounts, we understand that all have perished. A second supply of young plants of the grey and yellow bark, have lately been received, as well as seeds. The plants, it is understood, are in a very unsatisfactory condition, but there is every hope that the supply of seeds will enable Mr. Markham to establish the practicability of growing the cinchona in this country. Mr. Markham has recently stated in a letter to the "Madras Times" that a further supply of plants and seeds is expected from the Ecuador, and that arrangements have been made with duly qualified agents, to continue sending supplies of both, so long as may be necessary. Attempts will at the same time be made to naturalize the cinchona in the Hills of Jamaica, and Ceylon.

Fig 11A: Article about the initial attempts to grow Cinchona plant in South India

This journal also published reprints of articles from other European countries. For example, when Dr Virchow of Germany was collecting data on leprosy, this journal published an appeal (Figure 12) to the readers for information.

APPEAL ON BEHALF OF THE HISTORY OF LEPROSY. BY PROFESSOR RUD. VIRCHOW OF BERLIN.

"It is now several months since I appealed to physicians, historians and travellers to assist me in composing a history of leprosy (*Lepros Arabum, Elephantiasis Græcorum*), and I must gratefully acknowledge having received very abundant contributions from many quarters. I have already published a portion of these observations which have especial reference to leprosy in Germany, in the 18th volume of my Archives for Pathological Anatomy and Physiology, and for Clinical Medicine; other communications are in the press and will appear in the 19th volume of the Archives. Many other facts which relate to foreign countries, and to questions specially of medical, geographical, linguistic or civilizational interest, I must put aside for the present, on account of their too great bulk.

"Meanwhile, however, I cannot dispense with the continual assistance of other investigators, and since a personal correspondence cannot be carried on with unknown friends, I once more choose the way of publicity. If there is still any occasion to refer to the great importance of the subject, a glance at the excellent monograph, which Dr. Aug. Hirsch has published concerning leprosy in the second part, which has just appeared, of his Manual of Historico-geographical Pathology, will speedily bring conviction to the mind of everybody. A malady, which once pervaded the whole world, which even now attacks thousands in every quarter of the globe, and to the ravages of which the most ancient historical records bear witness, is certainly worthy of the most zealous study.

Fig 12: The appeal in MQJMS for information about Leprosy

7. Indian medical gazette (IMG): This Medical journal was founded in 1866 by Dr David Boyes Smith, Deputy Surgeon general of the Indian Medical Service, the first sanitary commissioner to the government of Bengal and later, Principal of Medical College, Calcutta. It was started in Calcutta as a monthly medical journal on January 1st, 1866. In its first issue, the journal announced that "our pages should be the medium of really practical knowledge". Many people, remembering the fate of earlier medical journals in India, were sceptical of the longevity of this new journal. But this journal continued till 1955 and is fully indexed in the PubMed archives online.

The first writers were mostly British. There is a very small statistical article (Figure 13) by one Bengali author in the first issue.

Also, they published articles on Indian system of Medicine, like the article on Indigenous drugs of India by Kanai Lal Dey. Some issues of the journal discussed recently published books on medical science (almost all European) (Figures 14 and 15)

This journal is a valuable resource for any medical researcher since it has been nicely preserved by the American national library. This journal also dealt with historical issues. For example, one issue of 1919

STATISTICS OF CASES OF TETANUS TREATED IN THE MEDICAL COLLEGE HOSPITAL DURING 1861-62-63 AND 64, SHOWING ITS RATES OF MORTALITY AND CURE, AS ALSO ITS PREVALENCE, IN DIFFERENT MONTHS AND YEARS.

By BANOO GOBIN CHUNDER CHATTERJEE.

Total No. of patients admitted during 1861-62-63 & 64	32,314
Of these there were Christians	14,524
" " " " Natives	17,790
of tetanus cases	132, or 1 in 244.8 cases.*
" " " " Christian 18,	1 " 806.88
" " " " Native 114,	1 " 156.05
" " " " traumatic 96,	1 " 336.6
" " " " idiopathic 36,	1 " 897.6
about 24 times less frequent than traumatic cases.	
" " cured 53, or 1 in 249, i. e., 40.15 per cent. of cure.	
" " " " traumatic 37,	38.54
" " " " idiopathic 16,	44.44
" " died 70, or 1 in 1.88,	53.03
" " " " traumatic 53,	55.2
" " " " idiopathic 17,	47.22
Total No. of tetanus cases in	
January, 1861-62-63 & 64,†	14
Do. February, do. do. do.	12
Do. March, do. do. do.	16
Do. April, do. do. do.	11
Do. May, do. do. do.	8
Do. June, do. do. do.	11
Do. July, do. do. do.	10
Do. August, do. do. do.	2
Do. September, do. do. do.	7
Do. October, do. do. do.	13
Do. November, do. do. do.	11
Do. December, do. do. do.	10
Do. 1861-62-63-64.	29
29 35 27 35.	

Fig 13: Statistics about Tetanus at Medical College Calcutta by an Indian author in IMG (1866)

Hints on the diagnosis of Eye Diseases. By R. B. CARTER, F.R.C.S. (Dublin; Falconer.)

This is a pamphlet which displays a very perfect knowledge of the subject upon which it treats. It does not, however, contain much original matter; and while it may prove useful to the general practitioner, we do not see that it confers any benefit upon the ophthalmic surgeon.

Cholera Prospects. By TILBURY FOX, M.D. (London; Hardwicke.)

Dr. Tilbury Fox has been travelling in Egypt, and has watched the progress of cholera at Alexandria. He assures us that the epidemic is regularly brought from India by pilgrims to Mecca; and that nothing short of a perfect system of quarantine can prevent the incursions of cholera into Europe. He suggests the prevention of the pilgrimage, or the examination of the pilgrims.

Fig 14: Discussion about newly published books in the IMG in 1866

Reviews

LIPPINCOTT'S QUICK REFERENCE BOOK FOR MEDICINE AND SURGERY.—By G. E. Rehberger, A.B., M.D. Thirteenth Edition. 1946. J. & B. Lippincott Company, Philadelphia and London. Pp. ix plus 1461. Illustrated. Price, 80s.

The first ten parts of this book deals with general medicine and surgery, gynecology, genito-urinary diseases, obstetrics, diseases of skin, eye, ear, nose and throat, and orthopaedics, and the last one with the

Fig 15: A discussion on the newly published Lippincott's book in 1947 issue of the IMG

discussed plague, as described in the diary of Emperor Jahangir, in 1618. There were also other sections of the journal like hospital practice, review article and case reports.

Later Journals :

At the turn of the twentieth century, many more medical journals came into being in India. The Indian journal of medical research was started in July, 1913. The man behind this journal was Sir Charles PardeyLukis, one of the most illustrious doctors of that time. He was a professor of medicine at the Calcutta medical College, Director General of Indian Medical Service and one of the inspirations behind setting up of the Calcutta School Of Tropical Medicine.

The present journal, JIMA, was started in 1930. Eminent physicians like Dr NilratanSarkar and Dr Bidhan Ch. Roy were associated with this journal in its initial days.

The Indian Journal of Dermatology, published since 1955, is the oldest dermatology journal in Asia and one of the oldest peer-reviewed dermatology journals in the world. The same year, the Journal of association of Physicians of India (JAPI) was started and this has also continued uninterruptedly after that.

Finally, the author would like to end with mention of another journal: The Calcutta Journal of Natural History (CJNH). This was not a medical journal but at a time when other medical journals had stopped printing and there was a void, this Calcutta journal published some interesting articles on medical science and kept the lamp of medical publishing in India alive. It was in vogue from 1840-47.

It had some interesting medical articles like the one mentioned below (Figure 16).

Remarks on Dracunculus. By Mr. J. McCLELLAND.

A communication from Mr. Brett, in the August number of the "India Journal of Medical and Physical Science," reminds me of a promise I had made to examine three specimens of Guinea-worm with which he very kindly favoured me. About fifteen years ago the subject created much interest in India, particularly in Bombay, where the disease is very common throughout a large proportion of that Presidency. The first volume of the transactions of the Medical and Physical Society of Calcutta contains no fewer than six papers

Fig 16: an article in CJNH on Dracunculiasis (1841), which mentions previous articles published in TMPSC and IJMPs

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History : Remembering the Stalwarts

Rudrajit Paul, Jyotirmoy Pal

Dr Maria Montessori was an Italian doctor who revolutionized the concept of child education. She was born in 1870 in Italy and entered the Medical school in Rome in 1893. At first she was strongly discouraged from joining the medical profession because of her gender. However, she was persistent and even after facing some hostility from colleagues and teachers, she managed to pass with flying colours in 1896. She was interested in Paediatrics and started her private practice in Rome.

Dr Montessori soon became interested in children with early dyslexia. She continued to develop her medical practice and at the same time, started speaking out for women's rights and children with learning difficulties. Very soon, this became her life's work. She wrote numerous articles on the topic of educating children and also became a trainer for teachers working with children having learning difficulties. In 1902, she enrolled for a course in Philosophy in Rome to better study the psychology of children. Also, she independently studied anthropology and educational philosophy. As her research progressed, she thought of applying the techniques of education used for specially abled children to the



Maria Montessori

This image is in public domain

mainstream child education.

Dr Montessori was a pioneer in the field of child education. She was the first to observe children in the classroom and note their behaviour. She found which practical activities the children preferred and how self-discipline emerged in the child psyche. She found that forcing a rigid curriculum on children did not help in learning; rather, mixing of activities and intellectual exercises helped them in gaining proficiency at an early age. In other words, a child has a natural ability to learn and the duty of teachers is just to create an environment to stimulate learning. Her school, Casa-dei-Bambini, soon became very famous

and opened numerous branches. She wrote extensively about her method of child education and this was quickly accepted by scholars all over the world.

The Indian poet, Rabindranath Tagore was influenced by her teaching methods and in his own school, tried to implement her method in an Indianized version. He met Dr Montessori many times in Europe. Dr Montessori came to Madras in 1939 for a training lecture.

Famous quote :

**"The greatest sign of success for a teacher.....
is to be able to say, 'The children are
now working as if I did not exist.'"**

Perspective

Need of the hour : Health Worker safety

Rudrajit Paul, Jyotirmoy Pal

17th September was **World Patient Safety Day**. During this current pandemic, the WHO celebrated this day with the theme "*Health worker safety: A priority of Patient safety*". This was a much needed focus on the dire working condition of doctors and nurses in most parts of the world, including India. While there are numerous legal safeguards and pressure groups for patients' rights in India, there are almost no organized groups for doctor or other health workers' safety. Thus, a doctor, if in any jeopardy, is likely to find himself/herself completely alone in the face of adversity.

On September 16, 2020, Shaw et al published an excellent article in *The Lancet* journal discussing some very pertinent topics on this issue. According to them, the current pandemic has exposed the precarious working conditions of healthcare workers all over the world. Health workers like doctors are already working in a high-risk environment, where they run the risk of physical and mental harm. This pandemic has exposed that raw underbelly in a glaring manner. The authors argue that unless health worker safety is ensured, patient safety can't be obtained. Many countries have failed to provide health workers with adequate protection during their Covid duties and this has exposed these hapless workers to undue danger. Thousands of doctors all over the world have died from the infection contracted during patient care. The authors also argue that these incidents are just the tip of the iceberg. Health workers, especially doctors, are daily exposed to physical and mental health challenges. There is the risk of burnout, lack of workplace safety and the palpable danger of violence. Thus, the authors have called for the recognition that patient safety is only possible when there is health worker safety. Unless health workers can be assured a safe and nurturing work environment, good health care will remain elusive.

The following table gives the approximate number of health workers dying from Covid-19 in different countries till the third week of September, 2020.

India is the country with the highest death toll among physicians. Such death devastates the family and the

Country	Doctors dying from COVID-19	Total Health workers mortality
USA	Around 100	695
Italy	Around 150	More than 200
India	At least 382 (IMA data)	Not known
UK	At least 30	540
Spain	5	63
China	21	23

colleagues and demoralizes the entire workforce. In countries like India with no social security network, such death also means economic devastation for the family, as some recent data have shown.

While death at the frontline is one of the jeopardies of the profession, doctors in India are daily exposed to a lot of other hardships like medico-legal problems, economic hardship, lack of employment and the ever-present risk of physical violence. All of these insecurities destroy the morale of the workforce and naturally lead to inferior quality patient care. In many places, aged doctors are working in Covid wards despite having co-morbidities, thereby exposing them to high level of biohazard.

In India, the general practitioners have to work in small chambers with almost no mechanism of biohazard protection. Due to the unorganized structure of medical practice in India, such GPs (who are at the lowest rung of power) are in no position to negotiate for a safer working environment from the businessmen (Owners of health facilities). These doctors are thus, at high risk of contracting the infection and in fact, among the dead doctors in India, the largest proportion is GPs and that too, mostly those over 60.

Thus, at this juncture, the policy makers and common people have to realize that safety at the workplace in terms of physical, mental and economic wellbeing is a **fundamental right** of the health workers of this country. Unless this is implemented, a good health system can never be possible.

Further reading :

Shaw A et al. No patient safety without Health Worker safety. *The Lancet* 2020; [Online first]

Ads from the Past

Medical therapies for “Female problems”

Rudrajit Paul, Jayati Mondal

In the early days of medical science, almost all the physicians were male. Thus, in those days, most symptoms and signs of female patients were clubbed together as “female problems”. Physicians were used to analyzing all medical problems from the point of view of male physiology and anything that did not fit the pattern in female patients were brushed aside with the moniker of “feminine”. Thus, there were very few scientific discussions on gynecological or obstetrical maladies.

The drug development and marketing of that era also represented this mindset, as the examples below (published in JIMA between 1940 and 1944) will show.



Figure 1

This is a vaginal tablet containing acetarsol. This was an arsenical compound with probable anti-protozoal action. As seen here, it was marketed for leucorrhoea. However, arsenicals have a lot of side effects. There was local dermatitis/mucositis and also systemic toxicity. Such arsenical compounds were marketed under different names in different countries. For example, in the USA, there was “Powdex-Formula 21”. Sometimes, salicylate or zinc oxide was added to acetarsol. After the discovery of modern antibiotics, this compound fell into disuse. However, after the emergence of metronidazole-resistant *Trichomonas*, some modern doctors have again done studies with arsenical pessaries.

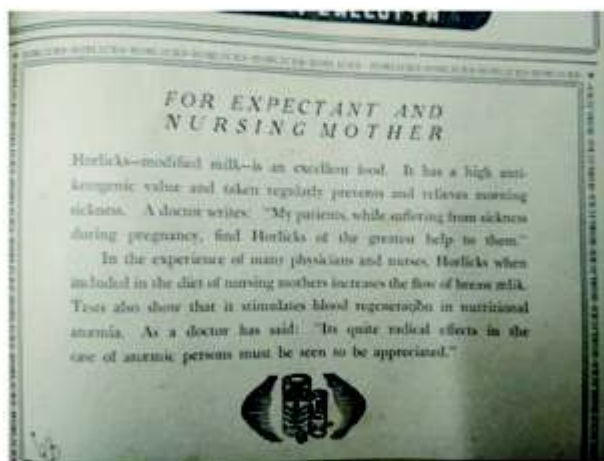


Figure 2

Figure 2 shows the marketing of a food supplement for pregnant and lactating women. Food supplement is not needed for pregnant women if they are having a balanced diet. But such advertisements are common and often mislead the consumers. Such supplements are widely marketed today.

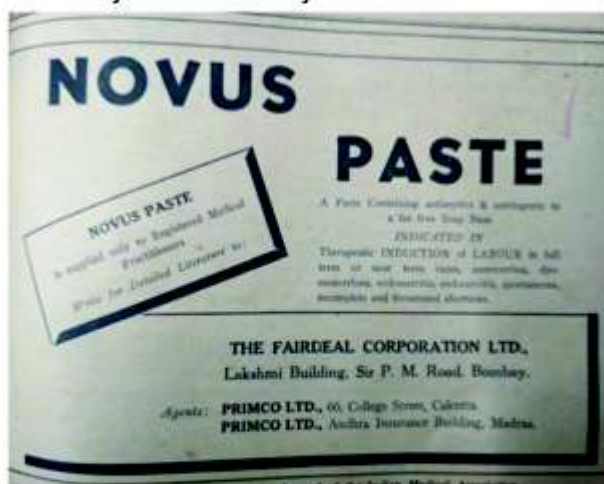


Figure 3

Figure 3 was a proprietary vaginal paste, which was marketed for all sorts of conditions from induction of labour to amenorrhoea. Naturally, one single cure for all gynecological problems is likely to be a sham

therapy. But as discussed in the introductory paragraph, in a male dominated medical system, this tendency to club all "female" problems together was quite common.



Figure 4

Figures 4 and 5 show different variations of the same medicine. Ashoka plant extract mixed with vitamins was thought to be effective for "female" problems. Many famous doctors of that era prescribed this medicine. While the previous three medicines are not available now, this Ashoka compound is still marketed in India and used by many consumers. In India, the people



Figure 5

tend to have blind faith in "natural" remedies and such questionable medicines are widely consumed.

The plant, Ashoka has long been venerated in India. It finds its mention in many ayurvedic texts. It has long been used for menorrhagia by indigenous healers. The bark and seeds of the plant are used. However, there is very little scientific evidence of efficacy of this plant extract for any disease. Persistent use of Ashoka plant extract for menorrhagia in lieu of proper scientific medicine is harmful and will lead to severe anemia.

What is the 5x5 model ?

Non-communicable diseases (NCD) are rising in prevalence all over the world. For comprehensive discussion on this topic, the WHO has identified some priority areas for immediate action. This idea is enshrined in the 5x5 model. There are five diseases and five risk factors which are to be targeted for intervention.

The five diseases are : Cardiovascular disease, Cancer, Diabetes, Chronic respiratory disease, Mental ill-health

The five risk factors are : Tobacco, harmful use of alcohol, unhealthy diet, physical inactivity and air pollution

Drug Corner

Ivermectin in COVID 19 — Promises and Prospects

Shambo Samrat Samajdar¹, Santanu K Tripathi², Jyotirmoy Paul³, Bibhuti Saha⁴

Age old anthelmintic drug ivermectin is showing some promises in the management of COVID 19 patients. In vitro study suggests anti SARS CoV2 viral role of ivermectin but there is some controversy regarding dose selection. Ivermectin has immunomodulatory role which may be responsible for its beneficial effects. Though it is not included in Interim COVID 19 management guideline by GOI, but several states like West Bengal, Bihar, UP, Assam have included it in state COVID 19 management guideline. It is important to be vigilant and more focused to prospectively observe the outcome in COVID 19 patients.

[J Indian Med Assoc 2020; 118(10): 86-9]

Key words : COVID 19, Ivermectin.

“The most fruitful basis for the discovery of a new drug is to start with an old drug.”

— Sir James Whyte Black,
Winner of the 1988 Nobel Prize in Medicine¹

Due to rapid increase in number of cases and geopolitical issues we cannot afford regular time duration for new drug development which is generally 12-18 years. Even after that we have to be cautious regarding the safety concerns for new drugs. This compressed timeline for drug development generally has directed us to revisit the Nobel Prize winner pharmacologist Professor James Whyte Black's advice on drug discovery, which is mentioned above. COVID 19 therapeutics starting from hydroxychloroquine, remdesivir, favipiravir, doxycycline to tocilizumab is used by applying the same principle of drug repurposing. Drug repurposing (also called drug reprofiling, repositioning or re tasking) is a developmental blueprint for selecting new indications for approved or investigational drugs other than original medical indication². Ivermectin, indicated for strongyloidiasis of the intestinal tract and onchocerciasis; is used in COVID 19 patients following the principle of 'drug repurposing'.

As an anthelmintic drug, its mechanism of action is mainly the selective opening of glutamate-gated and

Editor's Comment :

- Ivermectin shows some promises in in-vitro studies that it inhibits SARS-CoV 2 viral entry in host nucleus.
- It has immunomodulatory role which may produce benefits in preventing inflammation cascade of COVID 19.
- Dose of ivermectin use both prophylactic and therapeutic indication creates some controversy. We need to focus on prospective studies to have the final call.

Gamma aminobutyric acid (GABA)-gated chloride channels in invertebrates, which leads to increased inward movement of chloride ions. There would be subsequent motor paralysis in parasites³. Ivermectin has shown antiviral potential against human and animal viruses like parvoviruses in a freshwater crayfish (*Cherax quadricarinatus*) model⁴, RNA viruses, like influenza A virus⁵, Venezuelan equine encephalitis virus⁶, West Nile virus⁷, porcine reproductive and respiratory syndrome virus⁸, Newcastle disease virus⁹, chikungunya virus¹⁰, human immunodeficiency virus (HIV-1)¹¹, Zika virus¹², yellow fever virus, dengue virus, Japanese encephalitis virus, and tick-borne encephalitis virus¹³. On this background there was a ray of hope initially whether ivermectin can show anti SARS-CoV2 viral effects. One in-vitro study done on Vero-hSLAM cells, which were treated with ivermectin after 2 hours of SARS-CoV-2 infection and result was promising as there was decrease in ~5000-fold reduction in viral RNA after 48 hours. The proposed mechanism is as there is attachment of ivermectin to the Impα/β1 heterodimer, which causes destabilization and prevention of Impα/β1 binding to SARS CoV2 viral proteins. This leads to prevention of viral proteins from entering the nucleus which causes thereby inhibition of antiviral responses. Fig 1 depicts the anti-viral mechanism of ivermectin¹⁴. In Vitro evidences with

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ivermectin need to be evaluated with in vivo studies and well-designed clinical research. One study had shown that therapy with ivermectin at a dose of 150 µg/kg associated with a reduced mortality rate and lesser healthcare resource use¹⁵. There is a hypothesis that combination of hydroxychloroquine and ivermectin can produce a synergistic inhibitory effect on SARS-CoV-2. Mechanism wise hydroxychloroquine inhibits the entrance of SARS-CoV-2 into the host cells, whereas ivermectin prevents viral protein entrance into host nucleus and inhibits viral replication¹⁶.

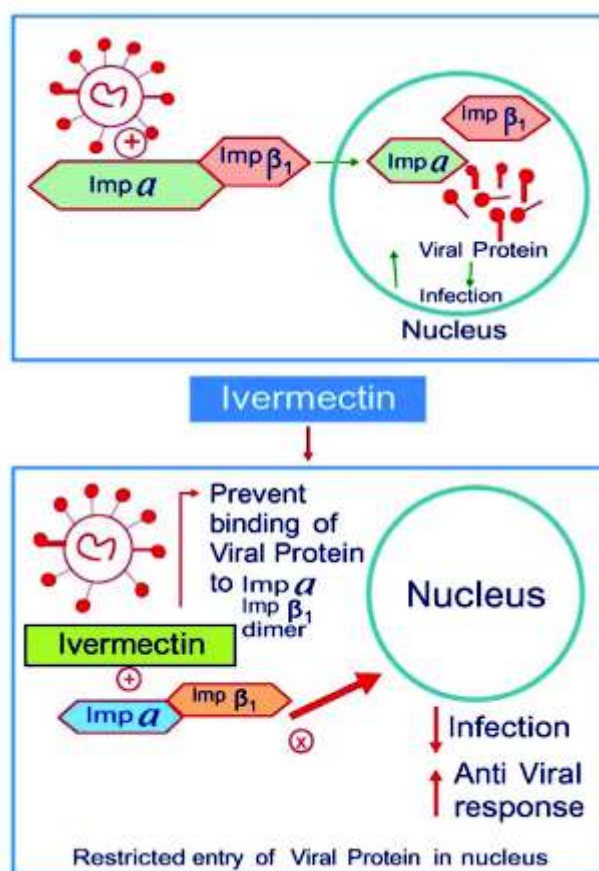


Figure 1 : Antiviral action of Ivermectin

Dose selection of ivermectin and controversy :

Single dose of ivermectin (200 µg/kg) produces plasma level of 0.0327 µM [CI 0.0228, 0.0429] and if we convert it into lung concentration it would be 0.0873 µM [CI 0.0609 - 0.115]. Predicted lung concentration is calculated based on reported lung:plasma ratio of 2.67 in cattle¹⁷. 120 mg single dose of ivermectin can produce 0.307 µM [CI - 0.204-0.449] plasma level and 0.820 µM [CI 0.545 - 1.20] lung concentration¹⁸. IC₅₀ reported by Caly et al. for SARS CoV2 is 2 µM, which is much lower than

predicted ivermectin concentration even with 120 mg weekly dose of ivermectin¹⁴. It is important to consider that as there is more day to day clinical experiences are in favor of ivermectin use, lung tissue concentration may be not correlating with concentrations at the site of action. There may a few doubts on the IC₅₀ value, distribution into or retention in the lung tissue of humans which may be greater than in cattle, or that accumulation in lung tissue is much greater (>20-fold) than expected after repeat dosing¹⁹. Selective concentration around 3 times the plasma concentration and sequestration in the pulmonary tissue with a long residence time are features for ivermectin²⁰.

Though it is not included GOI guideline but a few states of India is recommending ivermectin in their protocol. Assam government recommends ivermectin 12 mg 1 tab twice daily for 5 days along with doxycycline 100 mg twice daily for 5 days. Bihar and UP government recommend ivermectin 12 mg once daily for 3 days. These states recommend using ivermectin 2 hours after meal. West Bengal government recommends ivermectin 12 mg once daily with fatty meal and doxycycline 100 mg 1 tab twice daily for 7 days in mild symptomatic COVID 19 patients. It is important to consider ivermectin after fatty meal as it increases systemic bioavailability, whereas label suggests taking it 2 hour after meal. When the indication is to have anthelmintic action then it is important to reduce systemic absorption but anti SARS CoV 2 action demands increase systemic absorption hence it should be taken just after taking fatty meal.

Immunomodulation by ivermectin :

Ivermectin has an immunomodulatory profile that alters the function of T-lymphocytes and changes the lymphocyte count²¹. This drug reduces the production of several cytokines, such as TNF-α, IL-1ss, IL6, IL-4, IL-13 and IL5^{22,23}. By inhibiting a group of inflammatory cytokines which have an immense role in the development of the "cytokines storm", ivermectin reduces the complications of COVID-19. It also has effects on binding of viral spike protein to CD-147 receptors on blood cells and vascular endothelium which prevent haemagglutination and thrombogenesis. Beneficial effect of ivermectin is generally may be due to this immunomodulatory effects considering difficulty in reaching concentration for its anti SARS COV2 viral effect.

Future route of ivermectin delivery for its anti-viral effect :

Inhaled treatment with ivermectin can address the issue of less availability of ivermectin into pulmonary tissues. It is important to explore its feasibility. Inhaled therapy would allow for higher concentrations at the

site of action while limiting the systemic exposure. Further studies of the safety and tolerability in animal model and human are required to have success in this new route of ivermectin selection. This would also explore the anti-viral property of ivermectin. One in vivo study on inhaled ivermectin in Sprague Dawley rats is published. The study had shown that no-observed-adverse-effect level (NOAEL) after 28 days of inhaled ivermectin was identified to be 380 mg/m³, which would be a potent anti-viral dose²⁴. Need to explore its safety in higher animal and then in human before making final comment and initiating clinical trials.

Clinical Pharmacokinetics :

Food and a fatty meal increases absorption of ivermectin. As it is Lipophilic in nature, widely distributed, high Volume of distribution needs a large loading dose. It has high protein (albumin) binding affinity; does not cross BBB (blood brain barrier) unless in inflammation. The BBB is weakened with raised endothelial permeability in the hyper-inflammatory state of severe Covid-19. This may cause ivermectin leak into the CNS, potentially causing harm. So need to be vigilant regarding high dose of ivermectin and its CNS adverse effects. It is mainly metabolized in the liver and excreted exclusively in feces over an estimated 12 days. Elimination $t_{1/2}$ of ivermectin is 18 hours. T_{max} is generally 6 hours and mean residence time in body is around 4 days³.

Drug Interactions :

Post-marketing surveillance studies show some evidences of increased INR (International Normalized Ratio) rarely reported when ivermectin was co-administered with warfarin. Ivermectin is primarily metabolized by CYP3A4 enzyme. Medicines that are potent CYP3A4 inhibitors like clarithromycin, diltiazem, erythromycin, itraconazole, ketoconazole, ritonavir, and verapamil can increase the systemic availability of itraconazole, may potentiate its anti SARS CoV2 effect but need to be cautious regarding safety issues with ivermectin. CYP3A4 activity is induced via the pregnane X receptor (PXR), the constitutive androstane receptor (CAR), peroxisome proliferator-activated receptor (PPAR α) and probably the *glucocorticoid receptor (GR)*. Use of concomitant phenobarbital, phenytoin and rifampicin, glucocorticoids induce CYP3A4, may theoretically reduce ivermectin concentration and residence duration in body but need to explore its clinical significance. Grapefruit is a potent inhibitor of intestinal CYP3A4 that has been proposed to increase the concentration of ivermectin in circulation.

Adverse effects :

Generally it is a well-tolerated drug. But as we are using higher than labelled dose need to be vigilant on the following adverse effects like asthenia/fatigue, abdominal pain, anorexia, constipation, diarrhea, nausea, vomiting, dizziness, somnolence, vertigo, tremor, pruritus, rash, and urticarial. One safety pharmacokinetics study suggests that ivermectin was generally well tolerated. There was no evidence of associated CNS toxicity for doses up to 10 times the highest FDA approved dose of 200 μ g/kg. [25]

Clinical Evidences :

1. USA STUDY I : Printed in Medscape (Jul 15, 2020) Study was done at four Florida hospitals. Ivermectin arm had showed significantly lower mortality rates compared with usual care (15% *versus* 25.2%; $P < 0.03$). It was a retrospective cohort study in 280 hospitalized patients with confirmed SARSCoV-2 infection. There were 75 patients with severe pulmonary disease. The mortality rate was also lower in ivermectin treated group compared to usual care (38.8% *versus* 80.7%; $P < 0.001$). There is no significant difference in rate of successful extubation^{26,27}.

2. 1,300 early stage COVID-19 patients were treated with ivermectin in Dominican Republic. Treatment was initiated with standard dose of 100 - 200 mcg/kg. Dose was increased upto 400 mcg/kg. 99% of the patient population was cured. Average duration of full infection decreased from 21 days to 10 days. Only mild gastro intestinal adverse effects like heart burn and diarrhea were reported²⁸.

3. RCT involving mild to moderate degree of COVID-19 patients was conducted in Bangladesh. In one group around 60 patients were given ivermectin 200 mcg/kg single dose and Doxycycline 100mg twice daily for 10 days. Another group of 56 patients were administered HCQ 400 mg 1st day, then 200mg twice daily for 9 days along with azithromycin 500mg daily for 5 Days. Recovery rate was 100% *versus* 96.36%, mean symptomatic recovery duration was 5.93 days *versus* 6.99 days, negative PCR was achieved on 8.93 days *versus* 9.33 days in favour of ivermectin doxycycline group. 5th day gaining symptomatic recovery, 55.10% in ivermectin doxycycline arm compared to 23.8% of patients on HCQ azithromycin arm. Adverse events were lesser in ivermectin doxycycline arm compared to HCQ azithromycin arm 31.67% *versus* 46.43%²⁹.

Conclusion :

It spurred huge enthusiasm with off-label use of ivermectin for Covid-19 Prevention and treatment. Anecdotal evidences show some ray of hope with it. More than 450 publications have since been cited but

robust evidences yet to be reported from well powered RCTs. Nonetheless, it's off-label and compassionate use in Covid-19 requires careful risk-benefit considerations with due diligence and critical review. Should we wait until hard evidence from well powered RCTs, or can we start cautious and guarded 'experimental' use of an old, time-tested, well-tolerated drug for based on mechanistic reasoning and some empiric preliminary evidence as available till date?

There are lots of controversies and arguments counter-arguments with dose and regime of ivermectin usage in COVID 19. We just resolved to start a cautious and guarded 'experimental' use of an old, time-tested, well-tolerated drug for based on mechanistic reasoning and some empiric preliminary evidence as available till date.

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Mediquiz

Series - 9

Coronavirus trials



Rudrajit Paul
Quiz Master

1. Which of the following was studied in the recently published COALITION II trial (Lancet)?

- a. Addition of hydroxychloroquine to standard therapy
- b. Addition of azithromycin to standard therapy
- c. Addition of Remdesivir to standard therapy
- d. The new Covid-19 vaccine

2. The RECOVERY trial (NEJM) tested a particular treatment strategy for Covid-19 infection. What was this strategy?

- a. Tocilizumab
- b. Ciprofloxacin
- c. Dexamethasone
- d. Ivermectin

3. On August 21, 2020, Spinner et al published the results of a trial in JAMA about a Covid-19 therapy. What did this trial study?

- a. Remdesivir
- b. Favipiravir
- c. Ivermectin
- d. Lopinavir

4. The SOLIDARITY trial was launched by the WHO and its partners to test therapies for Covid-19. What is the fate of the trial as of now (September 2020)?

- a. The hydroxychloroquine and Lopinavir arms stopped, rest continuing
- b. Hydroxychloroquine arm stopped, rest continuing
- c. All arms are under study
- d. Only the Vaccine arm is still active

5. Which if the following is NOT a therapy studied in the on-going DISCOVERY trial?

- a. Remdesivir
- b. Hydroxychloroquine
- c. Ivermectin
- d. Interferon β

6. Which country is hosting the COLCORONA study and which drug is tested in it?

- a. USA, prednisolone
- b. UK, Remdesivir
- c. Canada, anti-IL-6 therapy
- d. Canada, Colchicine

7. The Oxford vaccine is currently the most promising candidate undergoing trial for a successful Covid-19 vaccine. What is the chemical nature of this vaccine?

- a. Recombinant Covid-19 virus particles
- b. Adenovirus vector expressing Covid-19 spike protein
- c. Covid-19 surface antigen
- d. Inactivated Covid-19 virus

(Answer : next page)

Answer : Mediquiz**Answers : -****1. B**

This Brazilian trial tested Azithromycin in addition to the standard of care in Covid-19 patients. The Azithromycin was given in a dose of 500 mg OD for 10 days. The primary end point was the clinical status on day 15 after randomization. This trial showed that **there was no significant effect of the addition of azithromycin.**

2. C

This trial, which was conducted in the UK, coordinated by the University of Oxford, published the first results regarding the use of steroids in Covid-19. The dose of Dexamethasone used was 6 mg OD for 10 days. The trial found that there was "lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support" (NEJM July 17, 2020)

3. A

This was a Phase-3 trial of Remdesivir 5 day vs 10 day in Covid-19 infection. This was a multi-centre study. The dose of Remdesivir was 200 mg on Day 1 followed by 100 mg/day. Clinical status of day 11 was the end point. Mortality was not studied. Remdesivir 5-Day therapy was better than standard care in improving clinical status. But the 10-day therapy had no advantage.

4. A

On 6th July, 2020, the WHO posted an update on its website discontinuing the HCQS and lopinavir arms of this trial. These two drugs have been shown to have no effect on Covid-19 patients. The other arms of the trial will continue and even new arms may be added.

5. C

The DISCOVERY trial is a trial coordinated in France. This is supposed to be a prolonged study to test various therapeutic options in Covid-19 patients. Lopinavir/Ritonavir and Hydroxychloroquine arms have been discontinued. The primary end point is clinical status on day 15.

6. D

This study has recently been started in Montreal, Canada. It will test the efficacy of Colchicine to prevent lung complications in Covid-19.

7. B

This is the chemical nature of this candidate vaccine, as discussed in the Lancet publication on August 15, 2020. The Phases 1/2 have been completed. Volunteers are being given 5×10^{10} viral particles per shot.

Famous quotes:

- The prime goal is to alleviate suffering, and not to prolong life. And if your treatment does not alleviate suffering, but only prolongs life, that treatment should be stopped. Dr Christian Barnard (the world's first heart transplant surgeon)
- In practical life we observe that the best practical discoveries are obtained during the execution of practical work and that long academic discussions are apt to lead to nothing but academic profit. Dr Ronald Ross (Nobel Laureate in Medicine, 1902)

Letters to the Editor

[The Editor is not responsible for the views expressed by the correspondents]

JIMA, September, 2020

("Hypertensiologists"

— The Need and Necessity in India)

SIR, — The article ("Hypertensiologists" — The Need and Necessity in India) written by Dr A Muruganathan, a prolific author in medicine is apt, relevant and timely. Hypertension-specialists or "Hypertensionologists" as coined by the author is a rare breed in India and it is high time for the concept of the same to be propagated across the board. Various modalities of prevention of this dreaded co-morbidity have been covered. However, we have also to focus on the primordial prevention considering the fact that the prevalence of childhood obesity and hypertension is on increase in India. This can be achieved by educating and caring the hypertensive mothers, identifying the high-risk pre-hypertensive children and adopting the life style modifications even at the pre-school and school levels. The 'womb to tomb' approach will not only ensure the reduction of the prevalence of hypertension in India in future, but also the morbidity and mortality associated with hypertension.

MD, DM (Cardiology), FICP, FICC,
FCSI, FACC,
President, Cardiological Society of India

Mrinal Kanti Das

=====

SIR, — I totally agree with Dr Muruganathan's comments & remarks in this field.

Hypertension Prevalance is increasing in India, both Urban & Rural. Moreover Hypertension & Diabetes, Hypertension & Lipid abnormalities, or All 3 ie Hypertension, Diabetes & Dyslipidemia coexist in a significant number of patients.

Best Way to Control & Effectively treat hypertension is by diagnosing hypertension correctly by creating awareness.

So, there is a strong need of focussing this issue by developing a separate speciality for this. I totally agree with Dr Muruganathan's concept of creating "Hypertensionist & Hypertensionologist".

DM (Cardiology), MD (Med),
Emeritus Professor, Dr DY Patil
University School of Medicines, Navi Mumbai.
Head, Department of Cardiology,
KJ Somaiya Superspeciality Institute, Sion

Sadanand R Shetty

=====

SIR, — The article about "Hypertensiologist" concept for JIMA by Dr. Muruganathan is read by me with lot of interest and enthusiasm. As all of us know the awareness, diagnosis, treatment as well as patients with controlled by BP are the lowest in India. Hypertension is an independent, continuous, consistent and most dangerous risk factor for future CVD. It is always felt hypertension did not receive the attention it should receive when considered other risk factors such as Diabetes. In this scenario, the article by Dr. Muruganathan is in right direction with an innovative idea of increasing hypertension control, awareness as well as scientific management of hypertension by mooted the concept of Hypertension Specialists who are "Hypertensiologists".

Adjunct Professor,
Dr MGR Medical University, Tamilnadu;
Senior consultant cardiologist, Tamilnadu;
Ramakrishna Medical Centre,
Apollo Speciality Hospital, Trichy

M Chenniappan

Dear Hony Editor, Greetings!

Hypertension the incidence, morbidity and mortality is more when compared to diabetes. We don't have many hypertension clinics, hypertension specialists, hypertensionist and hypertensionologist. The need of the hour to reduce the health and economic burden of hypertension of our country.

We have to promote members to take more interest and focus on hypertension so that the hypertension control in India which is only around 15 % now, can be improved.

We must also promote home blood pressure monitoring which will help more for blood pressure control.
Thank you.

With Best Regards

Let us pledge to "serve and care, search and share"

Dr A Muruganathan

MD, FICP, FRCP (Glasg & London), FRCP Ireland (Hon), FACP (USA & Philippines)
Tirupur 641601, Tamilnadu

Diagnostic criteria (DSM-V):

- ❑ Five (or more) of the following symptoms have been present during the same **2-week period**; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure..
 - Depressed most of the day
 - Markedly diminished interest or pleasure in all, or almost all, activities
 - Significant weight loss when not dieting or weight gain or decrease or increase in appetite nearly every day
- Insomnia or hypersomnia nearly every day
- Psychomotor agitation or retardation
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt nearly every day
 - Diminished ability to think or concentrate, or indecisiveness
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
- ❑ The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- ❑ The episode is not attributable to the physiological effects of a substance or to another medical condition.
- ❑ The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
- ❑ There has never been a manic episode or a hypomanic episode.

Mostly

undiagnosed
disease

Globally more than
260 Million people
are suffering.

In India, around **50 million** people are
suffering.

Increases Suicide

DEPRESSION: THE SILENT KILLER

**Rudrajit Paul and
Jyotirmoy Pal**

Treatment:

ACUTE

- Psychotherapy
- Pharmacotherapy
- ECT
- Psycho-education

CHRONIC

Combination of
Psychotherapy and
Pharmacotherapy may
continue for life

Beware of **medicines that
can cause depression:** -

Glucocorticoid, Levodopa,
ART, Ethanol, Phenytoin

Conditions associated with Depression: Diabetes, Parkinson's Disease, Hypothyroidism, Addison's Ds etc

Two Feathers in the Cap of Team JIMA in 2019

JIMA goes SMART



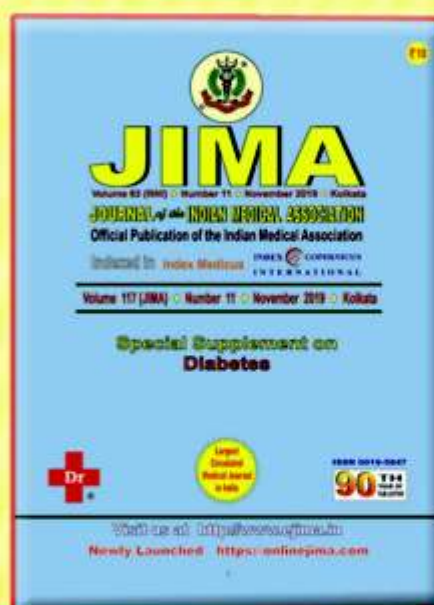
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**A Promising Anti-viral Therapy For
Prophylaxis & Treatment of COVID-19**

Scavista-12

Ivermectin Tablet 12mg

A Vista to Scavenge Effectively



**Antiviral
Journal
April, 2020**

Reveals

**The FDA-approved drug Ivermectin
inhibits the replication of SARS-CoV-2
in vitro¹**

Early Treatment with Ivermectin Helps to

Limit viral load

~5000 fold reduction in viral
RNA seen in 48 hours¹

Reduce disease progression

50% reduction in average
duration of infection²

Control person to person transmission

99.9% clearance of SARS-CoV-2¹

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1. Gali L. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020;173:104702. 2. <https://www.vitaldatanews.com/president-of-democratic-speciesity-largest-private-health-group-discusses-the-success-of-ivermectin-as-a-treatment-for-early-stage-coronavirus-the-7-day-treatment/>



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