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HALDANE MEMORIAL FUNCTION

104th BIRTH CENTENARY CELEBRATIONS

20th January, 1997 - 11.00 a.m. to 2.00 p.m.

PATHOLOGY CONFERENCE HALL

PARACLINICAL BUILDINGS
RANGARAYA MEDICAL COLLEGE, KAKINADA

Dr. P. MEERAKHAN

Professor of Human Genetics
University of Leiden, Netherlands &
a deciple of JBS Haldane

will deliver a guest lecture on
"ONCOGENES - COLORECTAL CANCER"

Oranised by

GODAVARI HUMAN GENETICS SOCIETY (REGD)

&

HALDANE MEMORIAL FOUNDATION (REGD)

KAKINADA, INDIA

J. B. S. HALDANE *A Tribute*

John Burdon Sanderson Haldane, popularly known by his initials as JBS, was born on 5th November, 1892 at Oxford. He is known all over the world as a scientist, famous for self experimentation and contributions in the field of Physiology, Biochemistry and Genetics. He wrote hundreds of articles of science in simple language for the layman. Quickness of grasp of knowledge and phenomenal memory made him intellectually precocious. Highly individualistic, he was a man of action and a brilliant teacher, but also controversial with authority and bureaucracy, he was a genius.

His father John Scot Haldane, F.R.S., studied medicine and was famous for his research on the physiology of respiration. His fundamental discovery was that the regulation of breathing is determined by the effect of tension of carbon dioxide in the blood on the respiratory center in the brain. He investigated into the causes of suffocation in coal mines and the effect of carbon monoxide after mine explosion. He became president of Institute of Mining Engineers without a degree in that speciality. He developed stage decompression in deep sea divers. JBS participated in many of the experiments conducted by his father, at a young age with considerable discomfort and hazard and once dived into the scottish sea from a 40 Ft. high cliff.

JBS taught the maths teacher at school and he stood first in Latin, Arithmetic, Geometry and translation and got armful of prizes at Eton school. At Oxford college he obtained first class in mathematics and classics. In his 8th year he helped his father with gas analysis apparatus and calculated the fraction of gases in the samples. He could read Latin, Greek, French and German. He used to say that no one can study mathematics intensively for more than five hours a day and remain sane. For relaxation he attended a senior course in zoology.

With his father he used to go deep into the coal mines. Once his father asked him to stand on fire damp and recite the speech of Mark Antony from Shakespeare's drama "Julius caesar". During the middle of this, he fell unconscious and soon recovered.

This experiment showed that fire damp consisting of methane is lighter than air. The same methane is present in coal mines and when the miners became dizzy they lay down on the floor of the mine and inhale the normal air which is heavier and thus recover.

He became famous for experiments on himself. He ate 1.5 Ozs of bicarbonate of soda which slowed his respiration. He drank dilute hydrochloric acid to see the effect of acid on respiration. He drank ammonium chloride solution and became sick & later he diluted it and found that 1 or 2 ounces make him short of breath. The compound gets converted to urea leaving the chloride ion in the body. Later this was used for treating tetany in children. He drank calcium chloride and large quantities of common salt. He inhaled carbon monoxide and showed that it competed with oxygen with an enzyme in the blood and the substance responsible was found in plants, insects and animals. Now that substance is called cytochrome oxidase.

He became a biochemist in 1921. At that time it was called "physiological chemistry". In 1923 Gowland Hopkins who got Nobel prize for his work on vitamins became professor of physiology at Cambridge and he offered readership to Haldane, second in command in the department. He knew a little physiology of breathing and learnt the subject just 6 weeks before he started teaching his pupils. The famous neurologist Dr. Lord Brain who was the author of a book on Neurology was student of JBS in the first batch, who stood first in his career. Haldane worked on enzymes for a decade which were thought as mysterious compounds at that time.

He started proving the use of mathematics in genetics. He said that reading genetics gives a satisfaction of reading a first class detective story and the story was true. A rediscovery of Mendal's work on genetics in the beginning of nineteenth century can be attributed independently to Haldane and two other scientists. The mechanics of inheritance were made clearer but also found to be complex, the solution to one problem produced innumerable riddles and many of these could be solved only by men of mathematical background and Haldane was one of them. The interaction of genes which occur very closely is called linkage and JBS was the first to publish linkage in

vertebrates. Briggs - Haldane relationship is a proof that reactions produced by enzymes obey the known laws of thermodynamics.

Haldane's law states that the crossing of several animal species produces an offspring when one sex is rare or absent and if present is sterile. It was found correct with one exception in 48 cases.

His most important work consists of 10 papers on Mathematical theory of natural selection during 1924-1934. It is an outstanding contribution. He estimated the frequency of dominant and recessive genes and explained how they change under various types of selection. His paper on the origin of life described a plausible mechanism of synthesis of organic matter from gases like ammonia, hydrogen, methane mixture and water. Oparin, a Russian scientist synthesized and is called Oparin-Haldane law.

In 1914 he was enlisted into army during the first world war. Due to an injury he returned to England and became instructor at bombing school. He went to Middle East during the war and after a thigh injury he was transferred to hospital at Poona and that was his first visit to India in 1917 where he stayed for a little over a year. Just before the II world war HMS Thetis submarine had sunk at Liverpool while on trial with loss of 99 lives. At the request of British Navy he exposed himself and his team of investigators to severe cold and high pressure which would be present in submarines in great depth. He immersed in melting ice, inhaling 6.5 percent carbon dioxide and exposed himself to 10 atmospheres of pressure and became unconscious.

JBS swam confidently through scientific seas for half a century, did so without any scientific degree or technical qualification. He learnt the hard way to write clearly, comprehensively and with economy. He visited India in 1952 and 1954 to give lectures at various institutes. On 24th July 1957 he left London by air and arrived in Calcutta 24 hrs later. The reasons of migrating to India might have been many. He forcefully condemned the morality and wisdom of the British attack on Suez. India was a virgin country with variety and beauty of animals and plants and the prospect of biological

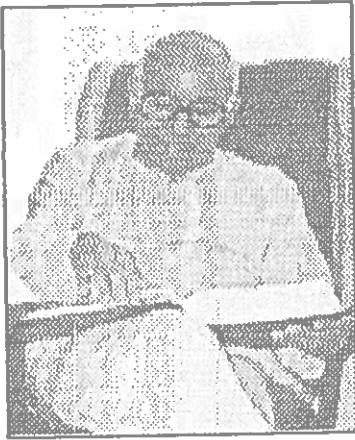
investigation that can be carried without expensive equipment but only requiring observation and stretching of the human mind. He was attracted to the Hindu Philosophy after the second world war and explosion of the Atom bomb. He believed that non-violence was both practically wise and morally compulsive.

He wore simple Indian clothes and became a vegetarian. He worked at Calcutta with the Indian Institute of Statistics and later with the CSIR. In 1962 he left for Bhubaneswar, on the invitation of the Chief Minister of Orissa.

He became Fellow of the Royal Society in 1932. He was awarded many Honorary doctorates. In 1961 President of the Italian Republic awarded the Feltrinelli prize in recognition of his being the best Biologist in the world. It turned out to be greater than the cash value of Nobel prize. He commented that he received a monstrous prize of Rs. 1,60,000/-.

JBS was given the Kimber Award by the U.S.National Academy of Science. During his visit to America he was diagnosed to be suffering from cancer of rectum and was operated in England. Before operation he gave a television interview to B.B.C. and recorded his own obituary. After operation he wrote the poem "Cancer is a funny thing". He died at Bhubaneswar on 1st Dec., 1964. He willed his body to Rangaraya Medical College, Kakinada. The postmortem was done by Professor of Pathology Dr. Rao R Paladugu who is now Professor of Pathology, University of Southern California at Los Angeles. His skeleton and organs in the anatomy and pathology museums of Rangaraya Medical College are his immortal remnants at Kakinada.

In India he gathered young men and brought out their talent and encouraged them in scientific research often with his funds. He used to remind his young colleagues of the principles of moral courage, scientific honesty, intellectual integrity underlining the importance of discovering new truths and spreading old ones. He thought it wrong in principle to attend events where he could neither learn nor teach. He was reluctant to be treated as V.I.P. and appear on public platform to utter pomposities.



Dr. P. MEERAKHAN

Professor of Human Genetics
University of Leiden, Netherlands

P. Meerakhan was born at Ambajeept in East Godavari District of Andhra Pradesh in 1935. He studied M.B.B.S. at Andhra Medical College, Visakhapatnam. In 1959 he attended a lecture delivered by JBS Haldane on "Physiology of high altitude and deep sea diving. He read the articles on science of JBS and collaborative studies of his junior colleague Dronamraju published in "HINDU". Meerakhan sent a congratulatory letter. Dronamraju met him at Visakhapatnam and explained that JBS is looking for a medically qualified man for research in Andhra Pradesh. As a house-surgeon, he gathered data on consanguinous marriages in persons admitted in tuberculosis wards in King George Hospital. With Dronamraju, he found 7% uncle-neice marriages and 16% first cousin marriages and a raised coefficient of inbreeding in case of Pulmonary tuberculosis. He was invited by JBS Haldane to visit the Indian Institute of statistics, Calcutta and stayed for 4 days with him. Later he joined the team of research workers at Calcutta. In 1961 he joined Andhra Pradesh Medical Service and requested for a posting in highly endemic area of Malaria at Polavaram, a place with a large percentage of tribal population living in hilly forest areas. JBS Haldane visited Italy and came across the survey work for malaria, thalassemia, G6PD deficiency and sickle cell disease being done by Siniscalco. He informed Meerakhan to obtain training in the work at Italy and offered full expenses for the trip and maintenance from his earnings. In spite of the hurdles and non responsiveness of the bureaucracy of the Government, Meerakhan wanted to resign the job and take the offer, luckily the Government granted him leave of absence. He went to Italy, worked with Professor Siniscalco and learned the technology at Naples and involved in field work at Sardinia. He rejoined his duties at Polavaram. JBS conceived a project for study of genetic abnormalities in the tribal and non tribal population at Polavaram. And obtained a huge grant from W.H.O. with Italian, Dutch & American supplements.

During 1963-64 Meerakhan's services were lent to join the research campaign. JBS also contributed his own money for the campaign, but could not join it due to failing health. Professor Marcello Siniscalco as team leader, Luigi Bernini, Leo Went,

Mario Rattazi, George Stamatoyannopoulos from Leiden visited Polavaram. Along with Meerakan, Ajit Ray and Sastry Mangipudi. JBS died on 1st December, 1964.

Meerakhan was invited to join the staff of department of Human Genetics, Leiden by Siniscalco in 1966. Meerakhan obtained his Ph.D. degree in 1971 under the guidance of professor Siniscalco, the subject of the thesis being "Enzyme studies in the interspecific somatic cell hybrids with special reference to mapping of Human X-chromosomes". Sendai virus is known to fuse chromosomes of one species with the other species producing genetic recombination in somatic cells. In hybrid cells some chromosomal loss occurs. Man-mouse, Man-chinese hamster hybrids are compared to human genetics and the fate of active and inactive X-chromosomes in human cell hybrids was recorded. Chromosomal and electrophoretic studies and autoradiography led to the characterization of three enzymes. They are HGPRT (Hypoxanthine guanine phospho ribosomal transferase) absence of which leads to gout, G6PD (Glucose 6-phosphate dehydrogenase) which is likely to produce resistance against malarial infection in man and PGK (Phospho glycerate kinase).

In 1969 Meerakhan collected blood samples in the tribal populations living on the east and west banks of the Godavari River at Polavaram. Fresh blood samples kept in ice were sent to Madras and air lifted to Amsterdam by KLM air service where they were analysed. Two new haemoglobin variants - Hb Rampa, named after Rampachodavaram and Hb Koya dora, named after the Koyadora tribe were discovered which are not found else where in the world. He is an authority on G6PD deficiency and contributed many publications to W.H.O.

In 1988 University of Leiden honoured him with professorship. In 1988-89 his team at Leiden have analysed blood samples collected in the field work in Andhra Pradesh by Dr. N.V.S. Nayudu who was invited to join the team. High percentage of Alpha thalassemia cases were recognised in tribals which are different from the Alpha thalassemia cases of South East Asia, which are more serious. Normally Alpha gene is duplicated, while triplication of Alpha gene was also identified in the tribal populations, the significance of which is still unknown. At present he is working on "Cancer producing genes, his work on colorectal cancer, from which JBS died, is internationally recognised.

ONCOGENES A BRIEF SUMMARY

Cancer in Human beings and also animals have genetic component in that there are chromosomal abnormalities, specific in particular types of cancer. The origin of cancer lies in particular genes, which are called oncogenes. Cancer lurks behind every door; heredity is an important factor and environment plays a precipitating role. Some families have the same type of cancer in generations like retinoblastoma or osteo sarcoma - eye and bone cancers. Some families have different types of cancer occurring with higher incidence in generations. Blood cancers were extensively studied with new techniques of cell culture, identification of chromosome number and their rearrangement.

Deletions, excess number, breaks and rearrangements of chromosomes as observed under the microscope reflect the fragile sites occur after the onset of malignant change in the gene. Deletions or extra number of chromosomes observed at birth may lead to increased incidence of cancer. Translocation of a part of chromosome occurs at cell division where genes jump from one site to another. Jumping genes were first identified by Barbara Mcklinton for which she was awarded Noble prize.

<u>BLOOD CANCER TYPE</u>	<u>GENE CHANGE & CHROMOSOME NUMBERS</u>
Chronic Myeloid Leukemia (CML)	t (9.22) translocation
Acute myeloid leukemia (AML)	t (9.22 or 8.21 or 11.17)
Acute lymphatic leukemia (ALL)	t (9.22; 1.15; 4.11, 8.14)
Chronic lymphatic leukemia (CLL)	12 (plus) increased 12

Balanced translocation was first observed in CML and is termed Philadelphia (Ph) chromosome, as it was first identified in Philadelphia, USA, which is seen in 90% of CML. and there is change of material in chromosomes 9 and 22; t (9.22) - shortened for brevity. Oncogene is present at the breakpoint of chromosome No. 9 and a shift of the same is a fundamental change before blood cancer develops. This change occurs in blood cells only and does not affect cells under the skin or muscle.

It is documented that 1 in 5 die of cancer in U.S.A. Ten lakhs of new cases are diagnosed in an year in U.S.A. which are serious; and another 5 lakhs are diagnoseed which are curable.

Cancer suppressor gene occurs in chromosome 13 and loss of the gene produces eye and bone cancer in children. Cancer in the large gut - colorectal cancer occurs in 1 lakh persons in U.S.A. with slightly higher incidence in females. Multiple (Uncountable) polyps are seen in the large gut at an young age and cent percent of them suffer from cancer before 50 years.

Cancer causing genes at one end and environmental factors (Smoking, Chemicals, Viruses, Drugs, Food, Ultraviolet rays, X-rays, and Electronics) at the other end and their interaction are responsible for cancer.

Cancer's Funny Thing

I wish I had the voice of Homer
To sing of rectal carcinoma
 which kills a lot more chaps, in fact,
Than were bumped off when Troy was sacked.

Yet, thanks to modern surgeons' skills,
It can be killed before it kills
Upon a scientific basis
In nineteen out of twenty cases

I noticed I was passing blood
(Only a few drops, not a flood),
So pausing on my homeward way
From Tallahassee to Bombay
I asked a doctor, now my friend,
To peer into my hinder end,
To prove or to disprove the rumor
That I had a malignant tumor

They pumped in Ba So4
Till I could really stand no more,
And when sufficient had been pressed in,
They photographed my large intestine.

In order to decide the issue
They next scraped out some bits of tissue.
(Before they did so, some good pal
Had knocked me out with pentothal,
whose action is extremely quick,
And does not leave me feeling sick)

The microscope returned the answer
That I had certainly, got cancer,
So I was wheeled to the theatre
Where holes were made to make me better.

One set is in my perineum
Where I can feel, but can' yet see 'em.
Another made me like a kipper
Or female prey of Jack the Ripper.

Through this incision, I don't doubt
The neoplasm was taken out,
Along with colon, and lymph nodes
Where cancer cells, might find abodes

A third much smaller hole is meant
To function as a ventral vent;
So now I am like two-faced Janus,
The only god who sees his anus
I'll swear, without the risk of perjury,
It was a snappy bit of surgery.

My rectum is a serious loss to me
But I've very neat colostomy,
 and hope as soon as I am able,
To make it keep a fixed time-table.

So do not wait for aches and pains
To have a surgeon mend your drains
If he says "Cancer" You're a dunce
Unless you have it out at once,
For if you wait it's sure to swell,
And may have progeny as well.

My final word, before I'm done,
Is "Cancer can be rather fun"
Thanks to the nurses and Nye Bevan
The NHS is quite like heaven
Provided one confronts the tumor
With a sufficient sense of humor.

I know that cancer often kills
But so do cars and sleeping pills;
And it can hurt one till one sweats
So can had teeth and unpaid debts.

A spot of laughter, I am sure,
Often accelerates one's cure
So left us patients do our bit
To help the surgeons make us fit.

-- J.B.S.HALDANE

HALDANE'S *Quotable Quotes*

- "Europe's greatest contribution is the scientific method. Dalton's atomic theory is still the basis of chemistry, but it is such a good theory that it disproves itself, and makes way for a nearer approach to absolute truth."
- "His mother used to tell that religion is suitable only to servants. He became completely immune to religion."
- As a rationalist he remarked that "diety is no more than a gaseous vertebrate."
- "You may call me crass materialist, but it seems to me more important that children should be taught such facts as the amount of oxygen we need etc. than they should know how often Henry VIII married or who won the battle of Agincourt."
- "Big fleas have little fleas
upon their backs to bite them;
The little ones have lesser ones,
And so ad infinitum – The bacillus is the flea of fleas."
- "When Darwin deduced the animal origin of man, a search began for a "missing link" between ourselves and apes.

The origin of life on the earth would have been as casual an affair as the evolution of monkeys to man.

To God making tenedncy is always with us, and only by a study of its past are we likely to be able to curb its development in the present."
- "The only tools of philosophers were words, and the art of using words correctly is called logic."
- "Today Science is important because it is applied, Modern industry began with printing in 1450."
- "Facts of nature must be spoken about naturally some are bawdy and controversial with aggressive outspokenness".
- "Hindu caste system is the greatest glorification of snobbery that the world has ever known".
- "Indian bereaucracy has spread out around research workers like all enveloping glue, incompetence is pretty well organised to protect itself".

GODAVARI HUMAN GENETICS SOCIETY (REGD)

KAKINADA

President : Dr. S. BANERJEA

Secretary : Dr. N.V.S.NAYUDU

Treasurer : Dr. A.V.K.RAJU

Godavari Human Genetics Society was established and Registered on 19th June 1992, with the objectives of promotion of knowledge in the field of Genetics and Genetically transmitted diseases in humans. It is active in organising academic programmes on Haldane's birth centenary every year with co-operation and involvement of the members. It has a strength of 50 Life members and 50 Annual Subscription members.

The following is the list of Life Members :

1. Dr. N.V.S. NAYUDU, M.D.
2. Dr. A.V.KRISHNAM RAJU, M.D.
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