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NEWSLETTER

PRESIDENT'S COLUMN

A COMMITMENT TO FURTHER EXCELLENCE



It is a historic chapter in ISHBT's continuous quest to achieve excellence in the field of haematology and spreading the knowledge about this very important discipline, among the

haematologists, medical fraternity and general public.

The first newsletter of ISHBT with the title 'The Hematology Indica' has been published. Congratulate to all the Hon'ble members of ISHBT for making this dream possible.

The newsletter will be a compendium of all activities of the ISHBT and its affiliated state and regional chapters across the country. From news to happenings, to information and technological advances, research and development, the newsletter will feature every aspect of haematology in India.

This news bulletin which I am sure will be printed on regular basis will update all our members with latest in haematology.

I WISH TO TAKE THIS OPPORTUNITY TO DISCUSS AND ADDRESS FEW CURRENT ISSUES RELATED TO OUR SOCIETY.

- All the members should be truly committed to the association and try to increase the membership and should reach at least 5000 (Current total No. < 2000)
- State chapters to be created in every state and should be functional with affiliation/coordination of ISHBT.
- Regular CME/Workshops should be conducted to familiarize/popularize haematology among doctors, public and administrators.
- Postgraduates should be mentored and encouraged to take haematology as career.
- Research activities and collaboration among various institutions
- Strong advocacy at Government and different level to create adequate infrastructure, funding allocation and proper distribution.
- Creating Uniform Protocol for various common diseases: This will protect our members and simultaneously generate huge data for research purposes. In addition this will enhance the importance and acceptance of ISHBT in the medical fraternity.
- Opening of DM courses in New Institutions:

This will be help in creating qualified haematologists to meet the dearth in specialists in our country at present.

- Colleagues with Pathology background: Our colleagues with MD Pathology are highly talented, motivated and constitute a big chunk of ISHBT. Many colleagues have established themselves as successful practitioners at state and national level both in clinical and laboratory pathology. Candidates having MD Pathology should be eligible to take up DM course. Those having DM (Haemato Pathology) should be preferably inducted in Clinical Hematology department to manage the departmental haematology laboratory which is so essential for better haematological services.

- Functioning of ISHBT: It is already time to change the function of society on the lines of ASH or EHA pattern. This includes centrally controlled management of all activities including annual conferences, CME/workshops in various places. Corporate style of office functioning, electronic voting etc. Everything should be predictable and this change is very much essential for progressive growth of our Society.

NEW ACHIEVEMENT THIS YEAR:

- One ISHBT consensus documents for national haematology quiz has been prepared and uploaded in the website. The haematology quiz will be conducted as per this document across the country.
 - Introduction of ISHBT News Bulletin
 - Creation of Indian College of Haematology which will be operational soon.
 - Up gradation/update of website with electronic data generation of 1300 members
- Lastly I would sincerely request all of you to contribute the society in various ways and try to turn this society to vibrant one. My sincere thanks to all of you for your generous support extended to me.

With Best Regards
LONG LIVE ISHBT

(Dr. Rabindra Kumar Jena)
President, ISHBT
Secretary, EHG & Odisha Hematology

ISHBT The way forward

■ ALOK SRIVASTAVA
President-Elect (ISHBT)



and enhanced access to several recent advances, access to several newer diagnostic and therapeutic products remain limited. How does India partake in these developments and make them accessible in India?

As the Indian Society for Haematology and Blood Transfusion completes nearly 50 years of its existence, it is good to recall its achievements and plan for the way forward. It has been and remains the only national scientific society to bring together all aspects of haematology - adult and pediatric, benign and malignant diseases from both laboratory and clinical aspects as well as transfusion medicine.

The annual meeting of the society provides the major opportunity for all those involved with the field to come together and discuss the latest advances and their impact on our practices. Over the last 20 years, we have also initiated formal training programs in haematology in the country starting with the DM in Haematology from 1998 and more recently the DipNB program which are helping to increase the number of haematologists and add to the workforce that is required to fulfil the needs of patients with haematological diseases in the country. Original research carried out in the country has helped shape practice in certain areas within India and in the world.

Our field is also rapidly evolving in the world, particularly in recent years, with major impact of the advances in molecular and cellular biology translating to advanced genomic diagnostics and transformative targeted molecular and cellular therapies. A few gene therapy products have already been licensed and several more are on the horizon - many of which are for critical haematological diseases which had inadequate or no effective therapies in the past.

We also have several challenges. For the size of the population in the country, the total of haematologists are still too few. There are also not enough institutions investing in creating departments and positions for more haematologists. Many physicians and paediatricians interested in the subject or just out of a call of duty towards their patients are helping to fill these gaps. Even though a robust pharmaceutical industry in the country

THAT IS THE CHALLENGE THAT WE NEED TO ADDRESS. OVER THE LAST SEVERAL YEARS, SEVERAL INITIATIVES HAVE BEEN DISCUSSED WITHIN THE EXECUTIVE COMMITTEE OF ISHBT. THEY INCLUDE THE FOLLOWING:

- Development of a strategic plan to increase awareness of the subject among post graduates students and membership of all those interested in and practicing any aspect of haematology.
 - Increased numbers of CME programs for all aspects of haematology practice in different parts of the country.
 - Professional management of the Society through staff appointed to run its office and the programs.
 - An annual scientific meeting organized by the Society through professional conference organizers at locations appropriate for such national meetings with predictable calendar dates and structure of the program.
 - Engagement with potential sponsors to convey these planned transformations and have their continued support for programs of the society.
- The task is not as difficult as it may seem because there are several examples of such successful models in the world. We need to study them and adapt those methods to suit our circumstances for achieving our goals. But we must have continuity of thought and plans as well as institutional memory and commitment to achieve them.

I want to take this opportunity to thank the Society for giving me the privilege to be part of the executive committee for the last few years and the President-Elect for this year. I invite everyone to be more engaged with critiques and suggestions for the Society.

There is too much to be done and there are resources available, if only we can channel them appropriately for the national good. We owe it to ourselves and to the generations to come.

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NEWS

INDIA CREATES BENCHMARK Innovative HOPE Asia 2019 at Kolkata draws EHA applause

THE European Hematology Association (EHA) in association with Indian Society of Haematology and Blood Transfusion (ISHBT) organised the first edition of the Highlights of Past EHA (HOPE) Asia 2019 at Kolkata from August 23 to 25, 2019.

Along with EHA and ISHBT, Eastern Haematology Group (EHG) also actively played its part for successful organisation of HOPE Asia 2019 where about 30 international speakers, who are accomplished experts in their own right, shared their knowledge with haematologists, practicing and upcoming, post graduate students and medical practitioners from various fields.

More than 700 hematologists from India and outside interacted with each other to enhance their domain knowledge.

The idea behind organizing HOPE Asia 2019 was to brush up the education acquired in the field of haematology especially diagnosis and treatment for blood diseases, clinical and translational research in haema-



tological disorders, emerging innovations and technology, diagnostic tools and risk-assessment strategies in haematology and its sub-specialties.

The highlights of the conference was presentation of rare cases of blood disorders by haematology practitioners in different technical sessions and subsequently, experts including foreign hematologists suggesting the line of treatment and answering tricky questions.

The EHA and ISHBT discussed whole range of issues concerning to collaboration at the



leadership meeting towards closing hours of conference. It was decided to offer clinical fellowship to Indian haematologists in advance training in haematology, both in laboratory and clinical field. Beside, EHA called upon young Indian haematologists to become

member of EHA by paying 20 Euros. EHA has 5062 members in 2018 and Asia constitutes 10% of total members.

EHA Executive Director EHA Carin Smand, EHA organizing chair Prof Shai Izraeli, Prof Gianluca Gaidano and Prof Gert Ossenkoppele, ISHBT chairperson Prof Rabinendra Kumar Jena, scientific committee chair Deepak Kumar Mishra discussed extensively on acute leukemias, chronic leukemias, multiple myeloma, bleeding and thrombosis, myelodysplastic syndromes and myeloproliferative neoplasms aplastic anemia and thalassemias.

The hugely successful HOPE Asia 2019, organised in a grand and innovative manner, under the leadership of organising secretary Dr Tuphan Kanti Dolai drew great appreciation from the EHA.



11TH INTERNATIONAL CME & ANNUAL CONFERENCE of Odisha Haematology held

THE Odisha Haematology held its 11th International CME and Annual Conference and SUM annual CME on Laboratory Haematology in Temple City of Bhubaneswar from September 6 to 8 to discuss blood disorders and diseases, share ideas on the latest advances in the diagnosis and patient care management.

More than 300 doctors from Odisha, West Bengal, Jharkhand, Delhi, Bihar, North-East and central India participated in the event where they talked about the importance of hematology in the field of medical science.

On the eve of conference, the second Sum Annual CME on Laboratory Haematology was also organized on campus of Institute of Medical Sciences of SOA University.

Hon'ble Governor of Odisha, His Excellency Ganeshi Lal, who inaugurated the event, hailed doctors for their selfless and determined service to the people and society.

Topics such as survival trends in Thalassemia, control of hemoglobinopathy in India and its relevance of Odisha model and pain phenotypes and implications in management of sickle cell diseases were discussed in detail. Post graduate students were encouraged to participate in discussions.

Professor RK Jena, President of ISHBT



and Secretary of Odisha Haematology, said haematological diseases such as anemia, thalassemia, sickle cell disease, hemoglobinopathies, platelet disorders and haematological cancers like leukemia, myeloma and lymphoma and combined together will definitely outnumber the number of other diseases humans suffer at present.

Prof Niranjan Tripathy, President of Odisha Haematology, Dr. Gitanjali Batmanabane, Director of AIIMS, Bhubaneswar, Amit Banerjee, Vice Chancellor of SOA University, H. P. Pati, Professor Haematology, AIIMS Delhi and Dr. Priyanka Samal, Head of Haematology of SOA University spoke on the occasion.



INTEGRATED strategies to improve SCD outcomes

■ **KALPNA GUPTA**
University of Minnesota
Medical School, USA



LINUS Pauling first described Sickle Cell Disease (SCD) as a molecular disorder in 1949. Over half a century later, SCD not only remains a scientific enigma but also afflicts millions of people worldwide.

The SCD is an autosomal recessive disorder caused by a point mutation in the beta-globin gene, resulting in sickle hemoglobin (HbS). Under low oxygen HbS polymerizes to form rigid fibers and confers a sickle shape to the RBCs. Sickle RBC show reduced flexibility resulting in erythrocyte membrane damage and hemolysis. The ensuing disease is characterized by hemolytic anemia and inflammation. Sickle RBC lead to the pathogenesis of number of organ-specific complications with enormous phenotypic variability.

Sickle RBC cluster together, occluding the blood vessels and impairing oxygen supply to the limbs and other organs, resulting in cumulative organ damage and acute painful episodes called "crises". Micro- and macro-occlusions cause ischemic injury to virtually every organ/tissue including but not limited to the brain, heart, lungs, spleen, kidneys, bones, muscle, nerves, penis and retina. Recurrent episodes of crises and pain lead to increased hospitalization, morbidity and mortality, resulting in reduced lifespan of SCD patients.

A hallmark of SCD is intense pain that can start during infancy and increases in severity throughout life, reaching levels considered higher than labor pain during pregnancy. SCD is accompanied by acute painful episodes ("crises") superimposed on chronic pain. The pathophysiology of SCD is compounded by inflammation, vasculopathy, ischemia-reperfusion injury, organ damage and neuropathy, each of which may contribute to pain. For example, behaviorally, "crises" result in acute episodes of severe pain that appears with each consecutive vaso-occlusive event, whereas ensuing tissue and/or bone damage may lead to persistent pain.

In addition, inflammation in SCD may potentiate both episodic and persistent pain. Clinical studies using self-reported assessment of symptoms in patient diaries show marked variability in pain presentation, apparently due to diverse factors including geographical location, sex, age and temperature, demonstrating the complexity of pain in SCD.

Opioids remain the mainstay for pain in SCD, which have liabilities of their own, and fear of addiction further obstructs their use even when needed. Therefore, integrative strategies are required that can improve the health and survival as well as improve symptom management in SCD. Some of these integrative strategies include diet modulation, mind-body exercises and acupuncture, which are cost-effective and user-friendly for resource limited settings with relatively large populations of SCD patients.

IMPORTANCE OF POST Transplant Survivorship Care

■ **LINDA BURNS**
University of Minnesota Medical School, USA
Past President, American Society of Hematology



SCIENTIFIC advances in hematopoietic cell transplantation (HCT) have led to an ever-increasing number of recipients who survive free of the disease for which they underwent transplant. Complications occurring ≥ 1 -year post treatment can affect any organ system and have a wide spectrum

in time to onset, severity, and potential for lethality.

Recognising the need to understand late complications, in 2016 the United States National Institutes of Health (NIH) sponsored the HCT late effects initiative to formulate recommendations for future research in the field. Six major areas were selected by experts for in-depth study within working groups, including research methodology and study design, subsequent neoplasms, patient centered outcomes, immune dysregulation and pathobiology, cardiovascular disease and associated risk factors, and healthcare delivery. 1-7 Survivorship care delivery was also identified by the National Marrow Donor Program/Be The Match, Patient Centered Outcomes Initiative as an area in which research is needed. 8 Supported by the Patient Centered Outcome Research Institute, like the NIH Initiative, the overall goal was to prioritize a research agenda in survivorship. However, this initiative differed significantly in that it engaged volunteers representing all major stakeholder groups, including patients and caregivers.

The overwhelming success of these initiatives and mounting interest in survivorship issues within the HCT community spurred establishment of the American Society for Transplantation and Cellular Therapy Survivorship Special Interest Group (SIG). 9 The SIG provides an international forum for the exchange of ideas, educational initiatives, research agenda setting, collaborative research and dissemination on issues of importance surrounding survivorship. The SIG also sponsors an online community and provides links to educational resources on survivorship topics. Importantly, the SIG includes patients/caregivers and their advocates to ascertain that the patient/caregiver voice is represented.

An example of research in an identified priority area is the demonstration of a strong effect of the dose of total body irradiation and dose fractionation on the risk of subsequent neoplasms after allogeneic HCT. 10 Another example is that providing patients with a survivorship care plan individualized by risk features, such as exposure to total body irradiation and graft-versus-host disease, was associated with reduced distress and improved mental domain of quality of life. 11

Scientific advances in HCT must include advances in prevention and management of late complications. With major initiatives having provided roadmaps for research in survivorship and engagement of a global community, there is optimism that significant progress will be made in this important field.

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MARK YOUR
CALENDAR



HAEMATOCON
2019

TAJ PALACE
NEW DELHI
NOVEMBER
7-9, 2019

THE 60th Annual conference of Indian Society of Hematology and Blood Transfusion (HAEMATOCON 2019) will be held at the Taj Palace, New Delhi, India from November 7 to 9, 2019.

Department of Haematology, AIIMS, New Delhi, will be hosting the conference during which various clinical and laboratory workshops will be held at different hospitals in Delhi and National Capital Region.

More than 75 renowned faculty and eminent speakers handpicked from India and abroad will share their experience in topics such as acute and chronic leukaemia, chronic

lymphoproliferative and myeloproliferative disorders, lymphoma and myeloma, and stem cell transplantation, etc..

The scientific programme has been designed to include diagnostic as well as therapeutic haematology, and will attract clinical haematologists, haematopathologists, medical oncologists, pathologists, paediatricians as well as physicians managing such disorders.

The conference is also an opportunity to meet colleagues, build consensus and forge new avenues of collaboration. Additional opportunities will also be available to interact with the experts during the period of this conference.

HAEMATOCON
2020

KOLKATA
NOVEMBER 6-10, 2020
BY

EASTERN HEMATOLOGY GROUP

ORGANISING SECRETARY
PROF. MAITREYEE BHATTACHARYA
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NEWS

NESHCON 2019 Sharing of Knowledge and Enhancing Skills

THE North East Chapter of ISHBT (NEISHBTM) and Department of Clinical Haematology, Gauhati Medical College and Hospital, organized its annual conference NESHCON 2019 at Kaziranga, Assam from September 20 to 22, 2019 in association with the department of Medicine, Jorhat Medical College & Hospital.

Eminent faculties from across India and the entire North-east participated in the conference and shared their knowledge regarding the latest in hematological advancement, guidelines and follow-ups. It was an excellent forum for young minds specifically the upcoming hematologists and postgraduate students from various institutions of the North-east and to enhance their skills. Oral pa-

pers, posters and case presentations by them were informative and provided a learning experience.

The program commenced with a symposium on thrombocytopenia where students and faculties of different medical colleges discussed different cases on thrombocytopenia.

During the inaugural function on September 21, renowned haematopathologist, AllMS New Delhi, Prof. HP Pati along with prominent and popular physician of the area Dr NN Goswami were felicitated for their contribution to the field of medicine and were presented citations. Dr DN Das Memorial oration was awarded to teacher par excellence Prof. MB Agarwal.

The scientific agenda was prepared keeping in mind of the need of the students and practicing physicians. Faculties from other specialties like pathology, internal medicine, pediatrics, gastroenterology, nephrology, radiology, nuclear medicine, rheumatology, and obstetrics and gynecology took part in active interactive sessions.

The Zonal level Quiz of 60th annual conference of ISHBT (Haematocon 2019) was held with the team from NEIGRIHMS, Meghalaya emerging winner and qualifying for the national level Final round to be held in Delhi with Haematocon 2019 in November.

A Health camp was organized in association with Assam Medical College Alumni Association and Academic Forum in Kaziranga National Park for the forest guards and their family members. On the day of finale, the podium was shared by CML patient for interaction with the experts to mark the occasion of the World CML Day on September 22.



BIRTH CENTENARY OF Prof JB Chatterjea observed



TO commemorate birth centenary Prof J B Chatterjea, the leading luminary of Haematology in the country, Bengal Society of Haematology organized the third International Annual Conference from February 16 to 17, 2019.

The Centenary Celebration Committee of Bengal Society of Haematology said the Calcutta School of Tropical Medicine was a pioneer of Haematology in India and Prof. J. B. Chatterjea, the doyen of Tropical Haematology, expanded the horizon of Haematology in India.

Prof Chatterjea, who was born on February 16, 1919, had earned his name for his path breaking work in Nutritional Anaemia and HbE Diseases.

Fifty national and international speakers discussed various aspects of haematological diseases in the conference themed 'From the Bench to Bedside' at Biswa Bangla Convention Centre in Kolkata. The conference divided into 12 sessions focussed on haemoglobinopathy, iron deficiency anaemia, acute leukemia, lymphoma and myeloma. About 350 delegates from across the country participated in the conference.

Post graduate students were provided complimentary registration and accommodation for the conference. Taking advantage of the facilitation, students were seen discussing the subjects with experts.

VARANASI Haematology Group formed

THE Varanasi Haematology Group (VHG) was formed this year to promote and propagate haematology discipline in Uttar Pradesh and other adjoining states. The association aims to work to update the knowledge of haematologists on recent advances in diagnosis, treatment and management of diseases and enhance their skills in the field.

The Executive Committee includes : Patron - Prof.VP Singh, President - Prof. VijaiTilak, Secretary - Dr.Nilesh Kumar, Joint Secretary - Dr.SandeepNautiyal, Scientific Secretary -Dr. Deepa Rani and Treasurer - Prof.VijaiTilak.

Dr.Anoop Srivastava, Dr.Sangeeta Kumar, Dr.Priyanka Aggarwal, Dr.Anju Bharti, Dr.Akhtar Ali, Dr.Ranjan Bhatnagar, Mr.Praveen Mishra, CA, Dr.Ankita Patel, Dr.S.D.Singh, Dr.Ritu Ragni and Dr.SK Singh have been selected as Executive members.

The Advisory has been constituted with Prof.KK Gupta, Prof.MadhukarRai and Prof.Vineeta Gupta while Ms Nikita Ajwani is the spokesperson.

The VHG has set up a Quiz Team - to undertake selection of College Level, State Level, Zonal Level & National Level Teams for Annual Hematology Quiz conducted under the aegis of ISHBT. Dr.Ranjan Bhatnagar-Medicine, Dr.Priyanka Aggarwal-Pediatrics along with Dr.Deepa Rani, Dr.Anju Bharti & Dr.Ankur Singh -Pathology are its members.

The VHG aims to regularly organize academic meets so that everyone remains updated with the old but classic & also with the new advances in the field. To provide a common forum for healthy exchange of ideas & to form collaborative group.

The VHG is ready to set to host the National Hematology Conference-2020 on February 22-23, 2020.

3RD ANNUAL CONFERENCE Haematology Foundation of Bihar

THE Third Annual Conference of Haematology Foundation of Bihar was organised in Patna on August 3-4, 2019.

More than 200 delegates from all over Bihar, Jharkhand and adjoining states took part in the two-day conference that aimed at bringing latest advances in the field to the doctors of the region. It also brought renowned experts and faculties from across the country to share their knowledge and guide the budding haematologists and post graduate students.

The conference was inaugurated by renowned physician Padma Shri Prof SN Arya, Padma Shri Prof Vijay Prakash, Padma Shri Dr JK Singh in the presence of ISHBT President Dr RK Jena, Chief Editor IJHBT Prof HP Pati, Director IGMS Patna Dr NR Biswas and Director Mahavir Cancer Sansthan Dr BB Sanyal.

The eminent guests emphasised on taking latest haematology treatment and care to the doorsteps of the patients and ensuring best possible services in the hospitals. They laid emphasis on setting up separate Haematology departments in different institutes of Bihar.

The conference covered common haematology topics like CMPN, Blood Transfusion, Pediatric Anemia, ITP, Thalassemia including Bone Marrow Transplant and Graft versus host disease. 'Stress Among Medical Professional Is An Issue And Presentation' by Dr Snehal Deshpande from Shri Ram Chandra Mission was an eye opener for all and appreciated by delegates and faculties.

The conference also featured oral and poster presentation and quiz for residents, which was well appreciated.

GLOBAL AGENDA FOR SICKLE CELL DISEASE India has a leading role to play

ISHBT, CONSTITUTED BY MOST OF THE LEADING EXPERTS IN HEMATOLOGY (CLINICAL AND LABORATORY), BLOOD TRANSFUSION MEDICINE AND HEMATOPOIETIC STEM CELL TRANSPLANTATION IN INDIA, HAS THE MANDATE TO LEAD EFFORTS TO FURTHER RESEARCH AND EDUCATION IN HEMOGLOBINOPATHIES AND ADVANCE THE CLINICAL CARE OF PATIENTS WITH SCD AND THALASSEMIA

■ **ISAAC ODAME**
Medical Director, Global Sickle Cell Disease Network

SICKLE cell disease (SCD) is one of the most common monogenetic diseases worldwide. India ranks among the top three countries that shoulder the heaviest disease burden globally. Notably, most of the patients with SCD in India are rural dwellers. To ensure universal health coverage for people with this life-long disease would require strategies that integrate SCD diagnosis and treatment into primary healthcare. Well-structured referral systems to link primary care with first or second-level referral hospitals need to be in place. There is overwhelming evidence that newborn/neonatal screening when linked with parental education, and enrolment in a comprehensive care program that delivers a package of simple interventions, effectively reduces SCD-related morbidity and early mortality. Hydroxyurea

therapy has proven to be an effective disease-modifying therapy for SCD in resource-limited settings. Point-of-care (POC) diagnostic tools are emerging, making it easier to diagnose patients with SCD wherever they seek care. A system-wide approach, involving Federal and State Governments, need to be developed so that no patient with SCD is left behind. We need to reach every patient with the simple life-saving and disability-preventing interventions that are available and that we know work.

In recognition of the potential role India could play in implementing transformative SCD programs, serving as a model for other low and middle-income countries (LMICs), particularly in Africa, the Global Sickle Cell Disease Network and Odisha Haematology, supported by the Indian Council of Medical Research and the Governments of India, Odisha, Maharashtra, Gujarat, Madhya Pradesh and Chhattisgarh held the 3rd Global Con-



gress on Sickle Cell Disease in Bhubaneswar in February 2017. Attended by more than 700 participants, including patients, advocates, clinicians and researchers from 34 countries, the Congress, themed: "Breaking the Barriers", defined priorities for SCD care, research and education in resource-limited settings and culturally diverse environments globally. Many of the clinicians and researchers in attendance were members of the ISHBT. The need to break the diagnostic barrier by employing emerging POC diagnostic tools was emphasized. Symposia focused on the standardization and wider use of hydroxyurea as disease-modifying therapy and curative approaches such as hematopoietic stem cell transplantation.

ISHBT, constituted by most of the leading experts in hematology (clinical and laboratory), blood transfusion medicine and hematopoietic stem cell transplantation in India, has the mandate to lead efforts to

further research and education in hemoglobinopathies and advance the clinical care of patients with SCD and thalassemia. To accomplish this goal, hematologists need to partner with a broad range of other healthcare professionals, including general physicians, internists, pediatricians and nurses to ensure that patients receive optimal care closest to where they live within primary care and first-referral level hospital settings. Health policy-makers within Ministries of Health need to be equipped with evidence-based information generated through sound clinical and laboratory research to be able to develop strategies that can be translated into effective interventions for patients with SCD at all levels of healthcare. ISHBT is well-positioned to play a leading role in advancing the SCD agenda in India. By so doing, India will be setting the pace as a model of excellence for many other LMICs, thereby helping transform the treatment and care of people with SCD worldwide, who predominantly live in low-resource settings.

LACUNAE IN CONTROL OF Thalassemia & Sickle Cell Disease in India

■ **PROF. H. P. PATI**
Dept Hematology, AIIMS, N Delhi



THALASSEMIA and sickle cell disease (SCD) are common hemoglobinopathy in India. Magnitude of hemoglobinopathy in different population has been delineated through pioneering work by individual workers, hematology institutions and ICMR center (NIH) at

Mumbai. β -thal Carrier (BTT) frequency considerably high frequency among the Sindhi (9.3%), Gujaratis, Punjabis, Bhanusahis, Jains, Kutchis, Lohanas, Gaur, Mahar, Koli, and Saraswats (5 to 17) including in tribal population.

Odisha, Madhya Pradesh, Chhattisgarh showed an overall Hb S trait of 24.4%. Among Scheduled castes of same population, Hb S carrier was also high as 4.4% to 37.9%. Similarly Gujarat also showed high sickle cell trait among tribal population. Even general population also showed high sickle cell gene frequency [Chaudhary 15.6%; Parmar 10.4%] as well as in SC populations like Solanki 9.2%, Chauhan 9.4%.

DISEASE CONTROL PROGRAM

At present and life expectancy in Thalassemia Majority patients have improved from 25 years when poorly managed to about 60 years in well managed patients and many women are becoming mothers. SCD needs proactive management from birth! 80% SCD children die by 5 yr age compared to <1% when preventive strategies are available. The preventive measures include Oral antibiotics prophylaxis + specific immunizations and frequent hospitalization as and when needed.

The success story of Greece and Cyprus are due to primarily mandatory premarital screening for hemoglobinopathies and their churches played a vital role in it. Many other countries, China (1992), UAE, Turkey, Iran, Bahrain, Saudi Arabia (2004), Pakistan, Europe, Singapore, Canada, Indonesia and Maldives have implemented it. Couples with this knowledge are more likely to avoid their high-risk marriages. In Saudi Arabia it resulted in 5-fold voluntary cancellation of marriage proposals among at-risk couples.

CHALLENGES

Ministry of Health & Family Welfare has submitted draft Policy for Prevention & Control of Hemoglobinopathies - Thalassemia, Sickle Cell Disease & variant Hemoglobins In India [Sept 2018]; that includes Carrier screening at high-school level Class VIII and above, Pre-marital screening with non-directive genetic counseling and establishment of centres of excellence in each state (bone marrow transplant unit and a prenatal diagnostic center; and training to health Professionals). It also envisages optimal treatment facility with establishing day care centers for transfusions, optimal iron chelation and monitoring and Hb HPLC and facility for iron studies at each district hospital. There will be also newborn sickle cell screening program in high prevalence area. Challenges are many at each level of recommendations made. Awareness about β -thalassemia among pregnant women in 6 states [in Jai Vigyan programme in Bangalore, Vadodara, Mumbai, Dibrugarh and Ludhiana] have shown to be very low (0.2% to 4.8%). Trained paediatricians at each district hospital, Regular supply of Chelators, vaccines, antibiotics, ferritin kits, HPLC reagents is essential and challenge. The sooner India implement this the better would be in tackling hemoglobinopathy problem.

WHAT'S NEW IN Treatment of AML in 2019?

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AML which makes up 32% of all adult leukemias used to be a simple disease, because for 40 years we were using standard induction therapy with two drugs, and that's how we treated patients. One is cytarabine (Cytosar-U) and another is anthracycline which form standard care.

Recently we acquired a lot of mutational data and there has been great progress in understanding the gene changes that often occur in AML which helps develop new therapy strategy against AML.

In past four decades, there was no development of drugs in tackling AML and then in last year, four new drugs have been approved in different settings, so it's - when it rains it pours.

One of them is Midostaurin, FLT3 inhibitor. FLT3 mutation is a high risk mutation seen in about one-third of patients with AML.

The second one is Ivosidenib another mutational target called IDH which is seen in 15-20 % of patients with AML. The third drug that has been approved is CPX against secondary AML.

The fourth drug that got approval is an immune therapy, Gemtuzumab ozogamicin which targets CD33.

Besides, there are two to three other exciting drugs including Venetoclax which is a Bcl-2 inhibitor. So therapeutic armamentarium of AML now includes novel cytotoxic drugs, drugs targeting recurrent oncogenes or functional vulnerabilities of leukemic cells.

NEWS

2019- A YEAR OF ACTIVITIES OF Mumbai Hematology Group



MUMBAI Hematology Group (MHG) is taking pro-active steps for development of haematological sciences in western India.

The 2019 has been a productive year for the group. As many as 18 events have already been organized in the current year. The MHG group roped in international speakers to enlighten hematologists and students about the fast developing discipline.

The year's educative programme began with Dr Annemarie Fogerty from Boston, USA as international faculty giving a talk on thrombophilia and pregnancy on January 5. Dr. Fogerty explained scientific updates related maternal thrombocytopenia.

During three days from January 25 to 27, the MHG invited 12 international faculty and experts to make presentations on various topics.

The 42nd Annual Conference of MHG on

March 16 and 17 witnessed Dr Laura C Michaelis, USA, Dr HC Hasselbalch, Denmark and Dr Dipti Talaulikar, Australia elucidating on haematological diseases.

The conference was followed by an update on ITP and TPO-RA on April 5, Seventh thalassemia luncheon symposium on April 27 with Dr Sylvia Titi Singer from California, USA, and master class in lymphoma with Dr Peter Johnson from UK as the international guest faculty May 19.

A joint meeting between Mumbai Hematology Group and Mumbai Nephrology Group was held on myeloma for nephrologists on May 26.

Dr Anita Hill from UK as the international guest speaker on pathogenesis and diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) updated haematologists on June 8. She



also spoke on management of PNH on June 9.

The third academy of clinical experts (ACE) - 2019 was held from July 12 to 14 of July 2019 during which six international guest speakers spoke.



NEXT GENERATION FLOWCYTOMETRY (NGF)

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FLOWCYTOMETRY is an enticing tool for simultaneous detection of multiple parameters in a single cell. In the past six decades this technique has evolved and has become a powerful and mandatory tool in diagnosis and classification of most of the hematological malignancies. Flowcytometry is one of the most widely used techniques for the Measurable Residual Disease (MRD) assessment.

The Coulter principle - based impedance counters and the cell sorters are the forerunners of today's modern flowcytometer. With the discovery of monoclonal antibodies in mid 80s flowcytometry found a new role in the clinical laboratories aiding in making clinical decisions. As the knowledge of various hematological malignancies advanced so did the utility of flowcytometry. Along with morphology it forms an integral part of diagnostic workup in the hematolymphoid malignancies.

The conventional flowcytometric methods or the first generation flowcytometry for measurable residual disease (MRD) detection is based on the use of 4-6 colours and has been implemented in first decade of this century. With the advances in optics, multicolor flowcytometry (up to 33 colours have been reported) has increased the sensitivity of the technique. Moreover high throughput hardware and high end software has made analysis of the data much simpler and sensitive. However, there are concerns over standardization, validation and spillovers with use of such sophisticated instruments. NGF addresses these issues by using various modifications in the conventional techniques.

Post treatment MRD is the most important prognostic predictor in various hematological malignancies. Molecular techniques provide a more sensitive MRD assessment than the conventional flowcytometric methods. Keeping up pace with molecular developments, Next Generation Flowcytometry (NGF) provides a sensitive, reproducible, quick and dependable method for MRD assessment.

EuroFlow consortium has efficiently designed and validated NGF in MRD monitoring specially for Multiple Myeloma (MM) and Acute



Leukemia. The use of validated standard operating procedures, acquisition of more events, designing innovative software tools and availability of high throughput analyzing workstations are the basis of NGF. With newer assessment criterion applied in Multiple Myeloma monitoring, NGF has become the modality of assessment wherein the undetectable cases (by convention flowcytometry) are now being picked up with NGF. This method is also being validated for monitoring plasma cell neoplasms by quantifying the circulating plasma cells in the peripheral blood.

The mainstay of NGF-MRD depends on analyzing maximum number of cells to increase the sensitivity of the test. This includes bulk lysis, followed by staining and then washing as a standard protocol for sample preparation. Moreover, optimized antibody panel designing and automated cell gating maximizes the assessment of cells of interest. There is published evidence to show that use of NGF-MRD offers comparable results to molecular methods of MRD detection and are more sensitive than the conventional MRD techniques.

Another platform of NGF uses the principle of mass cytometry in which the antibody is

coupled with metal isotopes thus enabling detection of multiple parameters without the disadvantage of spectral overlap. This platform has uses in the research applications in immunology, oncology and hematology but it has yet to find its place in the clinical setup.

NGF is a highly sensitive, rapid, relatively simpler and reproducible method which has advantage over molecular methods in MRD detection. With NGF, monitoring of patients has become more relevant in determining the outcomes of patients with malignancies.

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RELEVANCE OF NGS IN Hematology-Oncology

NGS IS DRIVING DISCOVERY AND ENABLING THE FUTURE OF PERSONALIZED MEDICINE. NGS PROVIDES A BROAD RANGE OF APPLICATIONS, INCLUDING I. GENE EXPRESSION PROFILING, II. CHROMOSOME ENUMERATION, III. DETECTION OF EPIGENETIC CHANGES, AND IV. MOLECULAR ANALYSIS. NEXT GENERATION SEQUENCING WAS FIRSTLY APPLIED TO GENOMICS RESEARCH, MAINLY TO DETECT VARIANTS IN DNA SEQUENCE IN TERMS OF SINGLE NUCLEOTIDE VARIATIONS (SNVS), INSERTION-DELETIONS (INDELS), STRUCTURAL VARIATIONS (SVS), AND COPY NUMBER ALTERATIONS (CNAS)

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MANY decades of research has shown that accumulation of molecular alterations is the key element of tumorigenesis, determining the acquisition of the malignant phenotype. Genes involved in oncogenesis are classified as 'oncogenes' and 'oncosuppressors'. Mutations of oncogenes (gain of function) or oncosuppressors (loss of function) can be genetically inherited (germline), but these are mostly acquired and caused by DNA replication errors and/or exposure to carcinogens.

The identification of specific driver genomic alterations has led to the development of targeted therapies, more effective and less toxic compared to standard chemotherapies. Trastuzumab (approved in 1998) and imatinib (approved in 2001) were the first two drugs to show the potential of targeted therapy, followed by many molecules nowadays approved for the treatment of several types of cancers. Presently, both imatinib and trastuzumab are enlisted as 'essential medicines' by WHO, for the treatment of CML and breast cancer.

Since 2000s patients can be stratified according to their tumor mutational profile, tailoring therapies according to the genetic signature. However, genetic testing was aimed at those few mutations known to be targetable in each specific tumor type, thus limiting the information acquired in a strict disease-oriented manner. In order to better understand the relevance of cancer mutations

across different tumor types and easily identify new actionable targets, a reference 'normal' genome sequence was needed to compare with the abnormal ones. This feature was provided in 2003 by The Human Genome Project, using the Sanger sequencing technique to determine the exact sequence of nucleotide base pairs of the human genome. Large-scale cancer sequencing projects, such as the American TCGA (The Cancer Genome Atlas) and the British Cancer Genome Project gave birth to the 'genomic era' of cancer research, thereby promoting the progressive evolution of sequencing methods.

Next-generation sequencing (NGS) is a high-throughput methodology that enables rapid sequencing of the base pairs in DNA or RNA samples. NGS provides a broad range of applications, including i. Gene expression profiling, ii. Chromosome enumeration, iii. Detection of epigenetic changes, and iv. Molecular analysis. NGS is driving discovery and enabling the future of personalized medicine.

NGS process involves 3 phases: library preparation (amplification), sequencing and data analysis. The large amount of raw data generated is inserted into bioinformatics workflows in order to convert these nucleotide sequences into meaningful biological results. A typical NGS data analysis pipeline can be divided into four main operations: base calling, read alignment, variant identification (SNVs, indels, CNAs, SVs), and variant annotation.

Next generation sequencing was firstly applied to genomics research, mainly to detect variants in DNA sequence in terms of single nucleotide variations (SNVs), insertion-deletions



(indels), structural variations (SVs), and copy number alterations (CNAs).

NGS methodology applied to an entire genome is called 'whole genome sequencing', in which both coding and non-coding regions are sequenced. WGS generates huge amounts of data per sample, but usually has low depth coverage. A typical WGS experiment detects most germline variants in human genome, but is inadequate to identify all rare somatic mutations present in cancer genomes.

'Whole exome sequencing' is instead specifically designed to sequence only coding DNA. By sequencing only 2% of a genome, a single region can be read much more time, ensuring a coverage of 100X with a cheaper and faster process. WES is therefore more suitable to analyse cancer genome.

An even more selective genome analysis is provided by 'targeted sequencing', in which specific regions of interest are isolated and sequenced. Many gene panels have been designed specifically for this purpose, allowing to focus time and resources on selected genes usually sequenced with a 500-1000X coverage.

Transcriptomics studies have a pivotal role in cancer research, providing information of what transcribes in neoplastic cells after DNA transcription. RNA-sequencing (RNA-seq), a relatively new application of NGS, is gradually replacing microarrays as favoured technology for transcripts analysis. Differently from arrays, RNA-seq is not designed as a targeted test and does not require species- or transcript- specific probes. It can be used both to quantify gene expression and to detect novel tran-

scripts, gene fusions, SNV and indels at the same time.

FEW EXAMPLES WHERE NGS HAS BEEN USED

- Driver mutations in JAK2, CALR, or MPL genes are the hallmark of BCR-ABL1-negative myeloproliferative neoplasms (MPNs), which are useful for diagnostic, prognostic and therapeutic approaches. Recently, the allele burden quantification of these driver mutations has become a useful tool, both for prognostication and efficacy evaluation of therapies. Both driver and sub-clonal mutations (like ASXL1 mutation) are now taken into consideration in new prognostic scoring systems and may be better investigated using NGS technology.
- Molecular mutations in genes including NPM1, CEBPA, FLT3, IDH1/2, TP53, RUNX1, and ASXL1 provide important prognostic and/or therapeutic information in AML, including best treatment strategies, transplant recommendations, and significance of MRD detection. Mutational analysis has led to the recognition of new entities including hereditary leukemia syndromes and clonal hematopoiesis of indeterminate potential (CHIP). FLT3 and IDH1/2 mutations are the focus of targeted therapies in the treatment of AML.
- The diagnostic utility of somatic mutations in the context of cytopenias is unclear as clonal hematopoiesis can be found in healthy individuals, patients with aplastic anemia (AA), clonal cytopenia of undetermined significance (CCUS) and myelodysplastic syndrome (MDS). In a cohort of 207

well-characterized cytopenic patients analysed, TET2, SF3B1, ASXL1, and TP53 were the most commonly mutated genes (frequency >10%). When applying VAF cutoffs (>20% for 1 and >10% for >2 somatic mutations), targeted gene panel sequencing improves the diagnostic approach and accuracy for unexplained cytopenias.

- A step-wise approach is required for diagnostic workup of inherited benign and malignant haematological disorders. Numerous causative genes are implicated in these conditions, therefore a gene-by-gene approach by Sanger sequencing is very time consuming, expensive and labour intensive. Targeted re-sequencing can be extremely useful in explaining these cases.

Advances in the molecular characterization of haematological malignancies have improved the understanding of leukemogenesis and risk stratification, improved disease monitoring techniques and optimized therapeutic strategies. Being such a powerful technology, the role of NGS is likely to expand in future, in the study of both malignant and benign disorders.

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HYPERFIBRINOLYSIS IN LIVER DISEASE causes, effects and management

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LIVER is an organ which produces proteins involved in fibrinolytic pathway, such as plasminogen, fibrinogen, TPA, alpha 2 antiplasmin, plasminogen activator inhibitor and

TAFI.

In liver disease, fibrinolysis may be primary due to liver disease induced defects in levels of above proteins or secondary to DIC.

The latter is more commonly seen, in about 30% of cirrhotic patients, and can be diagnosed using the ISTH score for DIC. However, for diagnosis of



primary fibrinolysis, tests like euglobulin clot lysis time, TEG and ROTEM may be used. Role of low TAFI levels in liver cirrhosis induced fibrinolysis is emerging but controversial. TAFI levels can dip to 47% in cirrhosis and upto 26% in acute liver failure. However it is postulated that they may not actually cause fibrinolysis, possibly

due to compensatory reduction in profibrinolytics too. It is also postulated that ascitic fluid may reenter the circulation via thoracic duct and contribute to fibrinolysis. Hyperfibrinolysis, along with hepatic coagulopathy, is often an important cause of bleeding in liver disease. Use of antifibrinolytics like EACA, tranexamic acid has been proved useful in surgical procedures/hepatic transplant. However their use in variceal bleeds is controversial.

THE ESSENCE OF ISHBT quiz

■ M JOSEPH JOHN

CLINICAL Haematology undoubtedly is one of the fastest growing branches of medical science today which embodies the wonder and mystery of inter-relationships at the levels of physical, the physiological and molecular phenomenon of the human body in both its benign and malignant predispositions. This field also prompts active interaction between various specialities which transcend our limitations to overcome the bane of the medical profession "The Ego".

The word quiz encompasses the test of knowledge, a competition between teams as a form of entertainment. When the quiz was started in 2011, the intent was to encourage and stimulate young minds to take up this field for the increasing need in laboratory and clinical expertise. The team of "three" preferably from different areas of expertise was thus chosen to enable the students to prepare for the quiz over a period of time to learn dependency and trust on each other.

The emblem chosen was the tricolour while blood cells, red blood cells, and platelets symbolizing a 3 member team from any three specialities, Internal medicine, paediatrics, pathology and of late, transfusion medicine. This signifies the importance of multidisciplinary coherence which is paramount for haematology practice.

The delegation, independence and empowerment in the conduct of the quiz to various state level and zonal co-coordinators for relatively younger (in mind and age) members also enables the organization to spur leadership development for the future.

I believe that collaboration of great minds with a long term orientation will enable us to improve the existing health care situation. Let us together envision a brighter future for India.

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FETAL HAEMOGLOBIN Induction In Thalassaemia

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THALASSAEMIA is an inherited autosomal recessive genetic disorder associated with abnormal hemoglobin production. The phenotypic expression in beta thalassaemia varies to a large extent from mild anemia to severe anemia needing occasional or regular blood transfusions for surviving. Pathophysiology of thalassaemia primarily depends on the imbalance between alpha & beta globin chain. In cases of Beta thalassaemia excess alpha chain precipitates causing damage of RBC membrane which leads to ineffective erythropoiesis.

Fetal hemoglobin, (HbF) is a product of gamma globin gene that constitutes the major hemoglobin (Hb) during fetal life and is gradually switched to adult Hb (HbA) in infancy. The silencing of gamma globin genes or otherwise the persistence of HbF production is controlled by a variety of complex genetic conditions. Several loci and polymorphisms within beta globin gene cluster in chromosome 11 and outside [BCL11A, KLF1, MYB, BCL11A, etc.] to be associated with the level of HbF production along with the participation of various epigenetic mechanism and chromatin modifying activities [DNMT3, PRMT5, NuRD etc.] in controlling the event. Induction of fetal hemoglobin (HbF) synthesis becomes a promising therapeutic approach to ameliorate the globin chain imbalance and reduce the disease severity.

The available modalities of treatment in β -thalassaemia include blood transfusion and use of iron chelating agents. In recent years, the use of fetal hemoglobin (HbF) inducing drugs is regarded as the appropriate therapy for hemoglobinopathies. Insights into understanding of the molecular mechanisms controlling hemoglobin switching and, particularly, γ -globin gene expression have greatly contributed to the identification and study of chemical compounds able to induce HbF synthesis.

Hydroxyurea has been found to increase HbF level and became one of the therapeutic agents for the management of patients with SCD and beta thalassaemia. The exact mechanisms by which hydroxyurea induces HbF production are not fully understood. There is good correlation between in vitro γ -mRNA fold increase and the in vivo HbF fold increase.

Study reported increase in HbF level varied extensively from 1% to 90% with an average of 20% & this was more in beta thalassaemia than in sickle cell disease [31]. Some of the studies have reported good correlation between rise of HbF and haemoglobin (Hb) while others did not [34]. In a study on HbE Beta thalassaemia patients we found a significant rise of HbF from baseline. However there was no correlation between rise of HbF & Hb [35]. Baseline HbF percentage, beta globin gene mutation, beta globin haplotypes & various polymorphism have been studied as a determinant of response to hydroxyurea therapy. Results are not very consistent and differs from studies to studies. Most consistent determinant was homozygous Xmn polymorphism which was associated with a favorable response. In a study done by us associated alpha gene deletion was found to be the most important determinant in cases of HbE beta thalassaemia.

Azacitidine and decitabine act as HDAC and DNA methyl transferase (DNMT) inhibitors that result in increased HbF. A recent study suggested that 5-azacytidine induction of HbF was not the result of global DNA demethylation or changes in differentiation kinetics, but rather may be due to a localized demethylation of the β -promoter, although other results suggest that posttranscriptional regulation could also play an important role.

Decitabine (5-aza-2'-deoxycytidine) was also shown to demethylate and reactivate the expression of the γ -globin gene. In a pilot study in 2011 Nancy et al showed that Decitabine increased HbF & Hb level in 5 thalassaemia intermedia patients. Recently in a study done by us thirty patients of HbE/ β -thalassaemia (age > 18 years) both transfusion-dependent (TDT) and non-transfusion-dependent it was found that We found that Decitabine was effective in increasing Hb% and HbF level in HbE Beta thalassaemia patients. The effect was sustained even 6 months after withdrawal of the drug.

THALIDOMIDE

Thalidomide a drug known for its immunomodulating and antiangiogenic properties for multiple myeloma is effective in HbF induction [63]. The exact mechanism of action of this drug is still unknown. However, it may be due to suppression of NF- κ B induction by Tumor Necrosis Factor (TNF- α), Vascular Endothelial Growth Factor (VEGF) and prostaglandin E2 synthesis (PG-E2) associated with increased release of reactive oxygen species (ROS). Three cases of beta thalassaemia was reported to have significant increase in fetal haemoglobin as well as haemoglobin F with Thalidomide.

COMBINATION THERAPY

A better effect was obtained when HU was combined with butyrate and Erythropoietin than hydroxyurea alone. However later studies did not show consistent results.

FUTURE DIRECTIONS

In a recent study microarray analysis showed aberrant expression of mRNAs and miRNAs in the high-HbF group compared with the control group. In other studies, cytokines like stem cell factor (SCF) and transforming growth factor-beta (TGF- β) have been shown to have HbF induction potential. Another study reports the synergistic effect of SCF, TGF- β and erythropoietin (EPO) in fetal hemoglobin expression induction in erythroid progenitor cells in vitro shows molecular and/or epigenetic mechanisms of some other drugs in HbF induction, which have been recently studied.

Therapeutic HbF induction in beta -thalassaemia patients by using the available agents have been ongoing for over 3 decades, however recent understanding of molecular basis suggest that there is great promise and more-effective targeted therapies to induce HbF can be developed. The lessons from prior trials in this field can serve as a guide for these future efforts.

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