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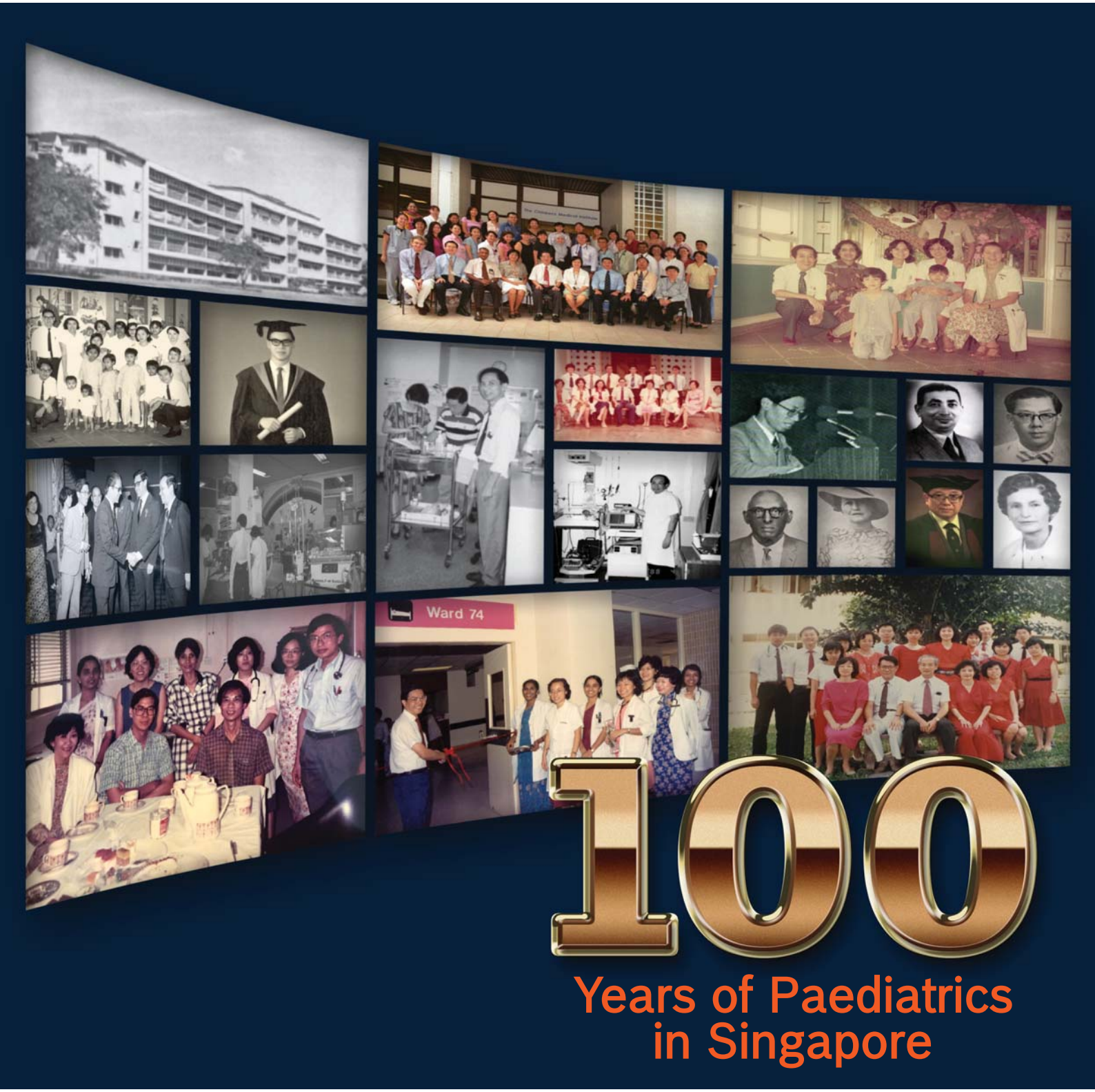

100 Years of Paediatrics in Singapore

SingHealth DukeNUS ACADEMIC MEDICAL CENTRE
PAEDIATRICS

The Journal of the Singapore Medical Association

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Preface

Professor Ivy Ng

Group Chief Executive Officer, Singapore Health Services Pte Ltd

It is with great pleasure that we celebrate the 100th year of Paediatrics in Singapore with this commemorative issue, with Professor Quak Seng Hock as the Guest Editor. In 1921, Paediatrics emerged as a standalone specialty in Singapore, and the first inpatient paediatric unit was opened at Singapore General Hospital (SGH). The first article in this special supplementary edition of the *Singapore Medical Journal* by Ng et al takes us through the evolution of paediatrics from 'Paeds East' and 'Paeds West' at the Mistri Wing in SGH to Alexandra Hospital (AH) and Tan Tock Seng Hospital (TTSH), and to the current departments in National University Hospital (NUH) and KK Women's and Children's Hospital (KKH). Neonatology was first established at KKH, Toa Payoh Hospital and AH before moving to the current departments in NUH, SGH and KKH. Paediatric surgery was formally introduced in 1981 at SGH, and Prof A Jacobsen takes us through the growth of this discipline. Another article by Prof Ho Lai Yun chronicles the 30 years of building a nationwide system aimed at early diagnosis and timely intervention for children with developmental issues.

There have been significant advances in child health in Singapore over the past century, and epidemiology, diagnostics and therapies for paediatric illnesses have evolved greatly over time. Growth has been recorded in every subspecialty, and this issue highlights some of the achievements and developments in the management of children with gastrointestinal and liver disorders, and provides interesting insights into the history and outcomes of our national paediatric liver transplantation programme. Newborn screening and genomics have also played an increasingly important role over the years by facilitating earlier detection of and appropriate therapy for congenital disorders.

All these advancements could not have been realised without the dedication and mentorship of the pioneering generations of paediatricians over the years. There have been many key figures in paediatrics who have paved the way and been the giants on whose shoulders we stand. It would be impossible to name all of them, but we hope that as you read through the articles in this special edition, you will take a moment to remember and honour the many mentors in paediatrics. We thank them for their selfless sacrifices and deep commitment to build the future.

As we celebrate 100 years of paediatrics in Singapore, we rejoice in the achievements and evolution of medical care for children and eagerly strive towards the impactful transformation of child health.

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From the 20th to the 21st century: the first 100 years of paediatrics in Singapore

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ABSTRACT In Singapore, paediatrics as a separate discipline was started in 1921 at Singapore General Hospital (SGH). From Mistri Wing to Alexandra Hospital (AH) and Tan Tock Seng Hospital (TTSH), paediatrics was started at National University Hospital (NUH) and the Children's Hospital at KK Women's and Children's Hospital (KKH) from 1997. After World War II, neonatology started in KKH, followed by Toa Payoh Hospital (TPH), AH, NUH and SGH. Neonates from TPH and AH were moved to KKH in 1990. Our pioneering giants include Dr Gopal Haridas, Professors Wong Hock Boon (First Paediatrics Professor), Tan Cheng Lim and Tan Kim Leong. Paediatrics in Singapore is resplendent with many achievements. Prof Wong identified the relationship of hyperbilirubinaemia/kernicterus with glucose-6-phosphate dehydrogenase (G6PD) deficiency and initiated G6PD deficiency screening. This has saved many lives and improved the overall health of children in Singapore. 100 years on, we stand firmly on the shoulders of our pioneering clinician giants as we face the paediatric millennial health needs of this new century.

Keywords: history, neonatology, paediatrics, Singapore

INTRODUCTION

The term 'paediatrics' is derived from two Greek words: παῖς/pais (or child) and ἰατρός/iatros (or doctor/healer). Having been in existence for only about 200 years, paediatrics is a relatively young discipline in the long passage of the history of medicine.[1-3] In 1802, the first paediatric hospital in the Western world, the 'Hôpital des Enfants Malades' (or the Hospital for Sick Children) opened on the site of a previous orphanage and cared for patients up to 15 years of age. Today, it exists as the paediatric division of the Necker-Enfants Malades Hospital, which was created following a merger with the Necker Hospital that was founded in 1778 for adults.[1,2] In the rest of Europe, the Charité in Berlin set up a separate paediatric pavilion in 1830 as did St. Petersburg in 1834 as well as Vienna and Breslau (now Wroclaw) in Poland, both in 1837. The Hospital for Sick Children was the first hospital in England to have inpatient paediatric care and opened with just 10 beds on Valentine's Day, 14 February 1852. It is now known more widely as Great Ormond Street Hospital (or GOSH). It was founded by Dr Charles West (1816–1898), who specialised in paediatrics and obstetrics. Sir Frederic Still (1868–1941) was the first full-time consultant and professor of paediatrics in the UK and is considered as the Father of British Paediatrics. Sir Still was also the inaugural president of the British Paediatric Association.[1,2,4]

In the US, the first hospital for children opened in Philadelphia in 1855, followed by the Boston Children's Hospital in 1869. Dr Abraham Jacobi, a German paediatrician who came to New York in 1853, is considered as the Father of Paediatrics in America.[1,2,5] In Canada, the Hospital for Sick Children (SickKids) was established in 1875 by Elizabeth McMaster, with Maggie, a three-year-old scalded child, as its first patient.

PAEDIATRICS AS A SEPARATE DISCIPLINE IN SINGAPORE'S EARLY YEARS

"*The emergence of paediatrics as a special branch of medicine in Singapore can probably date back to the year 1921*", wrote Dr Constance Elaine Field in a paper entitled 'The development of paediatrics in Singapore' in 1962.[6-10] In 1921, the Singapore General Hospital (SGH, previously known as 'General Hospital' and 'Outram Road General Hospital') started providing inpatient medical care for children.

An editorial in the *Malayan Medical Journal* in 1936 states, *"A reluctance to bring children to the practitioner of Western medicine has held up the study of paediatrics in this region*". This indicated the need for dedicated champions to apply Western paediatric medicine into the local community. In 1921, paediatric inpatient care at SGH was led by Dr Sarah Mary O'Flynn (later Lady Winstedt), Dr Richard Brunel-Hawes (later Sir RB Hawes) and Ms Ida Simmons, the Public Health Matron. They were also responsible for the successful setting up of the fledgling Maternal and Child Welfare services in colonial Singapore. Thus, 100 years ago and 100 years following the birth of SGH in 1821, paediatrics came into its own in Singapore, when children were admitted to SGH for inpatient care.

Professor Richard Brunel Hawes was Professor Gordon Arthur Ransome's senior and was, as the late great Professor Seah Cheng Siang puts it, "*an excellent clinician of the old type; he could smell diseases as it were*".[11] Prof Hawes was responsible to teach medical students in paediatrics and was appointed Head of the Department of Medicine at Tan Tock Seng Hospital (TTSH) in 1938. He guided and influenced Dr Gopal Haridas to take a special interest in paediatrics and child health when Dr Haridas was a tutor of medicine at TTSH from 1929 to 1932.

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FATHER OF SINGAPORE PAEDIATRICS AND THE HARIDAS MEMORIAL LECTURE

Dr Gopal Haridas is the first Father of Paediatrics in Singapore. He was the first local hospital doctor to obtain the MRCP in 1933 after a period of postgraduate training at Great Ormond Street in Medicine and Children's Diseases and was subsequently appointed part-time lecturer in Paediatrics. Dr Haridas later took charge of the two wards at SGH that were set aside for children, namely Wards 12 and 13, located at Level 2 in the Stanley Block. Formerly known as the 'Middle Block', it was used to house the second- and third-class female wards and was named after Dr Cuthbert Arthur Stanley, who was tortured to death by the Japanese in the 1940s. It was demolished in the 1970s and replaced by Block 8 at SGH.[12]

Infections and malnutrition accounted for a large number of cases that required admission to SGH (Box 1). In infantile beri beri, the babies would cry with a dysphonic type of sound due to oedema of the glottis, show congestive cardiac failure and, often, a peripheral neuropathy, and would often die very shortly after admission unless diagnosed and administered thiamine intramuscularly or intravenously.[13] As Prof Wong wrote, "*Dr Haridas was instrumental in describing the syndrome, making it well-known to doctors in Singapore at that time*".

Dr Cicely Williams succeeded Dr Haridas in 1936, following his promotion to Chief Medical Officer at TTSH. Dr Haridas continued to serve as a paediatrician and part-time lecturer. During the Japanese Occupation, TTSH and the then Kandang Kerbau Hospital (KK Hospital) functioned as the Japanese Civil General Hospital. The latter was called 'Chuo Byoin' (Central Hospital) by the Japanese and had 12 children's beds. KK Hospital's maternity service was scaled down to one ward. It was manned by local and Japanese staff, with Dr Benjamin Sheares as the Deputy Medical Superintendent.[14] The Japanese commandeered SGH for their own casualties, and it became the main surgical centre for the Japanese army and navy in Southeast Asia.[14,15]

Dr Haridas resumed headship of paediatrics after the war in 1945 until he retired in 1954. The Haridas Memorial Lecture Fund was set up in memory of the 'Father of Paediatrics' in Singapore after he passed away in 1964. The first Haridas Memorial Lecture was delivered by Professor Wong Hock Boon in 1966 and was entitled 'Haemoglobinopathies in Singapore'. Through the years, the distinguished Haridas Memorial speakers have included Drs Tan Kwang-Hoh, Freda Paul, Gary Tan SG, Loh Tee Fun, Chan Kim Yong, Tan Kim Leong (who spoke at two memorial lectures), William Yip, Eric Aiyathurai, Ho Ting Fei, Tan Siok Hoon, John Tay, Lee Wei Ling and Loke Kah Yin. The topics covered were kernicterus and cerebral palsy, mental retardation in Singapore, recent trends in infantile gastroenteritis, congenital heart disease in Singapore, epilepsy in children in Singapore, congenital rubella in Singapore; phototherapy, Reyes-like syndrome, childhood obesity among primary school children in Singapore – epidemiological review and anthropometric evaluation, thyroid disorders in Singapore children and adolescents, genetic counselling, febrile seizures in Singapore children and molecular characterisation of the CYP2 gene for congenital adrenal hyperplasia in Singapore. In 2018, Prof Ho Lai Yun delivered the 16th Haridas Memorial Lecture entitled 'Building an Inclusive Early Childhood Intervention Ecosystem in Singapore 1988–2017'.

Box 1. Common diseases in children requiring admission to Singapore General Hospital wards 12/13 (1933–1941):

Infections	Malnutrition
• Respiratory infection	• Beri beri
• Gastroenteritis	• Scurvy
• Tuberculosis	• Keratomalacia
• Meningitis	• Rickets
• Septicaemia	• Nutritional anaemia
• Tetanus neonatorum	• Failure to thrive
• Diphtheria	
• Typhoid	
• Malaria	
• Congenital syphilis	
• Worm infestation	

Adapted from: Wong HB. History of paediatrics in Singapore.[7]

OUTPATIENT FOLLOW-UP AND DR WILLIAM HENG

The first referral and outpatient clinic for children was started by Dr William Heng. He returned from the UK in 1939 and worked in Wards 12 and 13 at SGH as House Physician. In September 1941, Dr Heng set up and ran the first follow-up liaison clinic for children from the ward, which soon developed into a children's clinic to which cases were referred from the Infant Welfare Clinics, the private practitioners and later diverted from the general outpatients. Children of government employees were also seen at the clinic. Two sessions a week were reserved for the treatment of congenital syphilis, and biweekly injections of bismuth and oral arsenic. An important part of the follow-up clinic was dietetic education of the mothers, as beri beri was a commonly observed condition in newborns. The clinic grew rapidly until 50 to 60 patients were seen daily. Dr Heng had just one nurse and two 'amahs' (female service staff) as assistants.[6-10]

ST ANDREW'S MEDICAL MISSION AND PAEDIATRICS IN THE EARLY YEARS

The wife of the Bishop of Singapore, Dr (Mrs) CE Ferguson-Davie, had a mission to 'minister to the physical and spiritual needs of those most neglected in society – women and children'. Thus, in 1913, the St Andrew's Medical Mission (Anglican) in Singapore was founded. From a humble dispensary, it grew into a full-fledged St. Andrew's Mission Hospital for Women & Children at Erskine Road in 1923. The hospital had 60 inpatient wards and an outpatient service.[6,7,15]

In 1939, the St Andrew's Orthopaedic Hospital at Siglap was set up to treat children with tuberculosis of the bones and joints. Thereafter, the St Andrews's Mission Hospital for Children was established in 1948 at Tanjong Pagar with 30 beds (Fig. 1). Dr G Keys Smith was its first Medical Officer-in-Charge.

With the consolidation of national paediatric services in public institutions, demand for paediatric charity hospitals

Fig. 1 St Andrew's Mission Hospital at Tanjong Pagar. [adapted from www.samh.org.sg[16]].

Fig. 2 Mistri Wing for Paediatrics at the Singapore General Hospital.

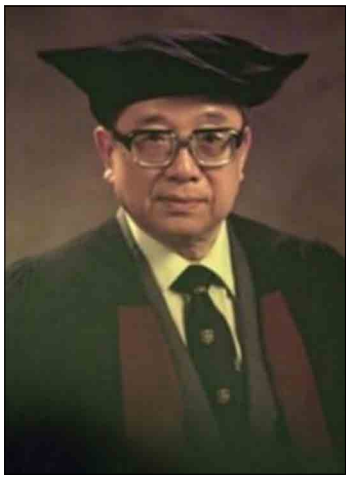

Fig. 3 Prof Wong Hock Boon, our first Professor of Paediatrics.

declined, and the inpatient services at St Andrew's Mission's Hospital ceased operations in 1982. The St Andrew's Orthopaedic Hospital ceased operations in 1987.[16] In 2007, St Andrew's Community Hospital became the first community hospital to provide paediatric inpatient rehabilitation services (Box 2).

THE 1950S, THE SGH MISTRI WING AND TO THE 1980S

Mr Navroji Rastomji Mistri was a prominent Parsi entrepreneur, known as the 'Bachelor Godfather' of Singapore's poor children and 'Godfather of the Poor'. He had made his fortune selling soda water. He was a patient of Professor Arthur Ransome and, in June 1952, donated S$950,000, a kingly sum in those colonial times, to SGH for the building of a third-class ward for non-paying paediatric patients. "*I cannot bear to think of sick children and their mothers lying on the floors of hospital wards…I donated my recent gift of S$950,000 because I thought it was my duty to do something for Singapore's children*".[17,18] With this significant donation from Mr Mistri, the government subsequently built a S$1,500,000 block for sick children at SGH. This was a four-storey building with 280 beds/cots. There were eight wards in the Mistri Wing, built in cubicle style with only partial enclosure, thus maintaining the cross ventilation that is important for preventing cross infection (Fig. 2).[6]

Box 2. Early years of paediatrics and child health in Singapore:

1. Institutional Paediatrics
- St Andrew's Mission Hospital
- Singapore General Hospital (SGH) Wards 12 and 13

2. Preventive Paediatrics
- Municipal Infant Welfare Clinics
- Rural Infant Welfare clinics
- School Health – annual checks by nurses (height, weight and visual acuity)

3. Ambulatory Paediatrics
- SGH outpatient follow-ups (inpatient discharges from Wards 12 & 13)
- Outpatient services run by St Andrew's Mission Hospital
- Private practitioners – graduates from Singapore, the United Kingdom, Hong Kong

Adapted from: Wong HB. History of paediatrics in Singapore.[7]

Dr Haridas retired in 1954, and Dr Quah Quee Guan ran the unit until Dr Elaine Field, who had previously trained at Great Ormond Street Hospital, assumed headship of SGH Paediatrics in April 1955.[6-10] Dr Field also served as the Second Master of Academy of Medicine, Singapore from 1959 to 1960. In 1962, she left for Hong Kong, where she became the Founder Professor of Paediatrics at the Hong Kong University.

In 1951, Dr Louis Sammy, in memory of his sister Jane, set up the annual 'Jane Prize' for 'the best essay by a final year student' on 'their own original observations on children'.[6] Prof Wong Hock Boon was awarded a scholarship to the UK for postgraduate studies in paediatrics in 1956 and returned to Singapore in 1957 after passing the requisite examinations. In 1960, Dr Field proposed to the University of Singapore to establish a Chair in Paediatrics to 'foster the teaching of paediatrics to both the undergraduates and the postgraduates, so that Singapore will be able to train more doctors to be specialists in Paediatric Medicine'. Prof Wong Hock Boon was appointed the Founder Professor of Paediatrics in Singapore in 1962 (Fig. 3) and led a very strong academic university department at SGH. Following the establishment of the University Unit of Paediatrics and after much negotiations, the Mistri Wing was divided into two units, the Government Unit (Paeds East) and the University Unit (Paeds West).[7]

Each wing had three 40-bedded wards from Levels 2 to 4 and an admitting ward of 20 beds on the ground floor.[9] When combined, there were 280 inpatient beds in total for paediatrics in Mistri Wing. Prof Wong led Paeds West while Dr Tan Kwang-Hoh led Paeds East from 1964 to 1969 and was succeeded by Dr Chan Sing Kit in 1969. Paeds West also ran the neonatal unit at KK Hospital (led by Prof KL Tan and Dr Thomas Wong), and Paeds

PHOTO GALLERY

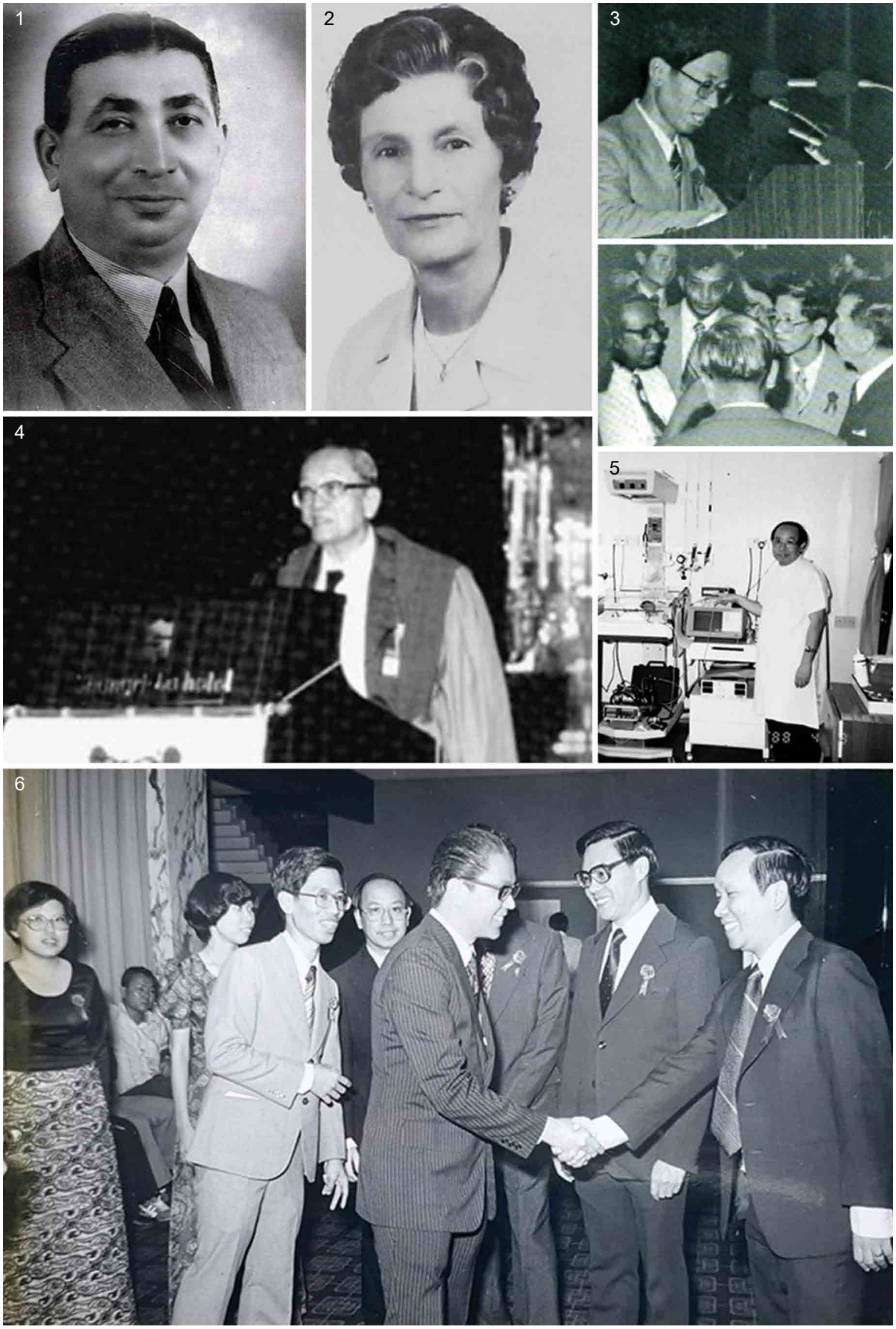

Figure legend:

1. Paediatric benefactor, Mr NR Mistri
2. Dr Constance Elaine Field
3. Prof Phua Kong Boo at the 'Today's Children, Tomorrow's Nation' Convention, organised by the Singapore Paediatric Society, Celebrating International Year of the Child 1979 – with President Benjamin Sheares
4. Emeritus Professor Wong Hock Boon delivering the inaugural Chapter of Paediatricians Lecture, 'The Future of Medicine from the Standpoint of the Practising Paediatrician' at the Opening Ceremony of the 9th ASEAN Paediatric Federation Conference in 1998
5. Prof Ho Nai Kiong at the Neonatal Department, Toa Payoh Hospital
6. Profs Phua Kong Boo, Ho Nai Kiong, Tan Cheng Lim and Ho Lai Yun with Dr Tony Tan at the Singapore Paediatric Society Convention in 1979
7. Prof Tan Cheng Lim (standing far left) with staff and patients at a ward at Mistri Wing (Paeds East)
8. Christmas 1978/9 at Mistri Wing (Paeds West): Prof Quak Seng Hock (far left), Dr Freda Paul (seated 2nd from left) and Prof Yap Hui Kim (seated 2nd from right)
9. Department of Paediatrics, Alexandra Hospital: Dr Frances Chia (seated far left), visiting expert from Australia, Dr Victor Yu (seated 2nd from left), Dr Tan Keng Wee (seated 3rd from left); standing: Dr Malathi (far left), Dr Choong Chew Thye (3rd from left), Dr Daisy Chan (4th from left) and Dr Loke Hing Leng (5th from left)
10. The 50th anniversary celebration of the Singapore Paediatric Society in 2002: Prof Ho Lai Yun (seated 2nd left) with Dr G Keys Smith (seated 3rd left) and Prof Tan Cheng Lim (seated far right)
11. Department of Paediatrics, Tan Tock Seng Hospital: (seated left to right) Drs Tan Ah Moy, Lim Khim Wee, Cheng Heng Kock, June Lou and Tan Chor Kiang, with Drs Sylvia Choo and Chay Oh Moh (standing behind Dr Tan Ah Moy)

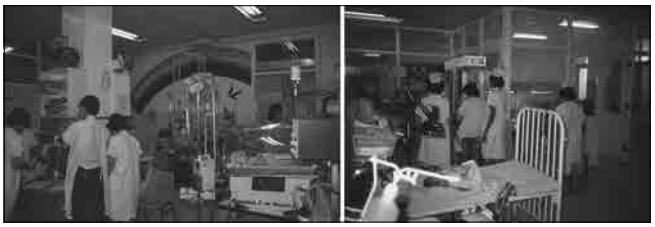

Fig. 4 Alexandra Hospital Paediatric and Neonatology Department in the 1980s. [Photographs courtesy of Dr Tan KW].

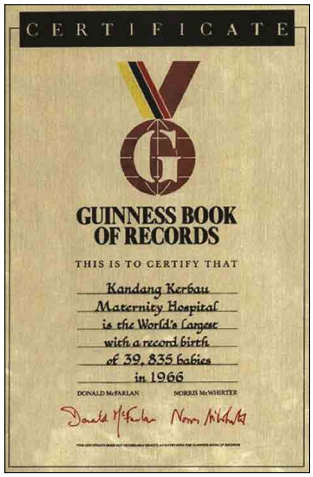

Fig. 5 Kandang Kerbau Maternity Hospital Guinness Book of Records with 39,835 deliveries in 1966.

East ran the neonatal unit at TPH, established as Thomson Hospital for the Chronic Sick in 1959 and renamed the Thomson General Hospital in 1968, later becoming TPH in 1975. A key milestone during this period that greatly reduced neonatal mortality related to neonatal jaundice was the introduction of phototherapy by Dr KL Tan at KK Hospital. Paeds East and Paeds West at Mistri Wing, SGH continued to care for children up to the mid-1980s. Both Paeds East and Paeds West shared a small two-to-four-bedded paediatric intensive care unit located at Ward 26.[6-10] Paediatric Surgery was formally introduced in 1972 at SGH, and the Department of Paediatric Surgery, SGH was established in 1981.[9]

PAEDIATRICS AT AH AND TTSH

In 1971, a paediatric department was set up at AH (Fig. 4). Dr Teo Hoon Cheow led the department till 1975, and Prof Tan Cheng Lim headed the department until he took over from Dr Chan Sing Kit as Head of Paediatrics at Paeds East, SGH in 1977. Prof Tan Keng Wee took over as the Head from 1977 and was succeeded by Dr Frances Chia in 1989 after he moved over to head one of the two neonatal departments at KKH (Neonatal 2/NNII). The paediatrics department at TTSH was set up in 1975 and was led by Dr Cheng Heng Kock until both TTSH Paeds and AH Paeds with SGH Paeds shifted to the new KK Women's and Children's Hospital (KKH) in May 1997.

PAEDIATRICS AT SGH AND NUH

With the transformation of University of Singapore to the National University of Singapore at Kent Ridge in 1984, the NUH was established. This marked the end of a significant era in Singapore

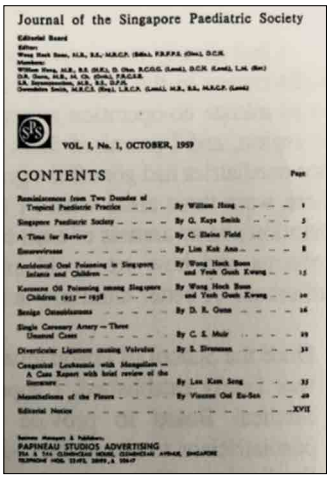
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Fig. 6 First issue of the Journal of the Singapore Paediatric Society, October 1959.

Paediatrics when Paeds West shifted over to NUH in 1985 with Prof Wong as the Head. Paeds East remained in SGH campus as the Department of Paediatrics SGH, with Prof Tan Cheng Lim as the Head.

NEONATOLOGY IN SINGAPORE

While it was only in 1960 that Dr Alexander Schaffer first coined the term 'neonatology' addressing the special needs and concerns of newborns, Singapore provided care for the newborns way before this, as did many other countries worldwide. KKH was set up in 1858 as a general hospital and became a maternity hospital in 1924. Dr Elaine Field, Head of SGH Paediatrics, was tasked to care for the newborns at KKH soon after her arrival. Dr Gwen Smith later joined Dr Field and took over the major part of the paediatric developments at the KK Maternity Hospital.[6] Dr Smith established exchange transfusions for the jaundiced babies and developed a separate unit for 36 premature babies. In 1966, KKH delivered 39,835 babies, recording the most number of babies born in a single hospital, and was featured in the Guinness Book of World Records (Fig. 5).

Thomson Road Hospital located at Toa Payoh Rise was set up in 1959 and took care of the chronic sick. It was renamed Thomson Road General Hospital (TRGH) in 1968 and subsequently renamed Toa Payoh Hospital (TPH) in 1975.[19] Paediatric East ran the neonatal services for the O and G unit in TRGH in 1969 when an obstetric unit opened, with around 5,000 deliveries a year.[20] Prof Ho Nai Kiong was sent to TRGH from Paediatric East in 1972 to take charge of newborn services after he passed his Master of Medicine (MMed) examinations in 1971. In 1977, the Neonatal Department was established at TPH and Prof Ho was appointed the first Head of the Department. Thus, this department became the first government department providing full-time neonatal services in Singapore.[21,22]

One of the outstanding and landmark achievements in neonatology in Singapore was by Prof Wong Hock Boon, who identified the relationship of hyperbilirubinaemia and kernicterus with G6PD deficiency in newborns. Prof Wong subsequently initiated screening for G6PD deficiency in cord blood, which has saved many lives and improved the overall health of children

Fig. 7 The first elected office bearers of the College of Paediatrics and Child Health, Singapore: back row (L to R) Dr Rajadurai Victor, Samuel (Honorary Treasurer), Dr Quak Seng Hock (President), Dr Low Cheng Hock (Master of Academy of Medicine Singapore); front (L to R) Dr Ho Lai Yun (Vice-President), Dr Chan Kwai Lin, Daisy (Council Member), Dr Goh Yam Thiam, Daniel (Honorary Secretary), Dr Lee Bee Wah (Council Member), Dr Goh Eng Kim, Anne (not in picture). [Reproduced from Quak et al. Recent Development in Paediatrics: from Chapter to College[28]].

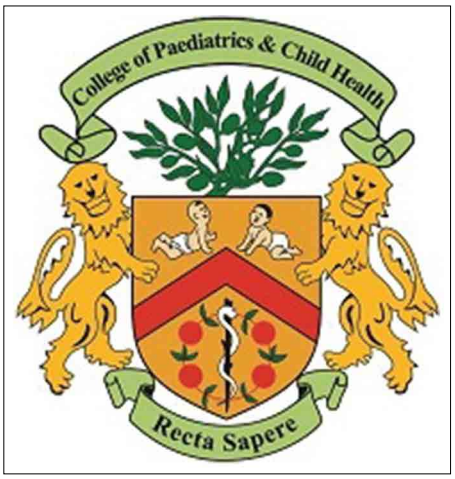


Fig. 8 Coat of Arms of the College of Paediatrics and Child Health, Singapore. [Reproduced from Quak et al. Recent Development in Paediatrics: from Chapter to College[28]].

Table I. Development of Postgraduate Paediatric Specialist Training after World War II.

Phase	*Period*	*Paediatricians trained in Singapore*
1	*1946–1960*	*6*
2	*1960–1970*	*5*
3	*1970–1997*	*176*

Adapted from: Wong HB. History of paediatrics in Singapore.[7]

Box 3. Paediatric morbidities over the centuries:

Classical paediatric morbidities (1900s to 1960s)
- Infectious diseases
- High infant mortality rates
- Poor nutrition
- Few cures for chronic diseases
- Epidemics (e.g. influenza, polio)
- Diseases of overcrowding

The new morbidity (1960s to 1980s)
- Family dysfunction
- Learning disabilities
- Emotional disorder
- Functional distress
- Educational needs

Beyond the new morbidity (1980s to 2000s)
- Social disarray
- Political ennui
- New epidemics (e.g. violence, HIV, crack/cocaine, homelessness)
- Increased survivorship
- High technology care

Millennial morbidity (2000 to present): disorders of the bioenvironmental interface
- Socioeconomic influences on health, including poverty
- Health disparities
- Technological influences on health
- Overweight and obesity
- Increasing mental health concerns

in Singapore. The first clinical trial of exogenous surfactant for respiratory distress syndrome in newborns was conducted in 1965 in KKH. In 1991, Prof Ho Nai Kiong was invited to conduct the international collaborative trial of synthetic exogenous surfactant Exosurf worldwide (the OSIRIS trial) with 36 countries. Singapore was the only Asian country to participate in this important international neonatal trial.[23,24]

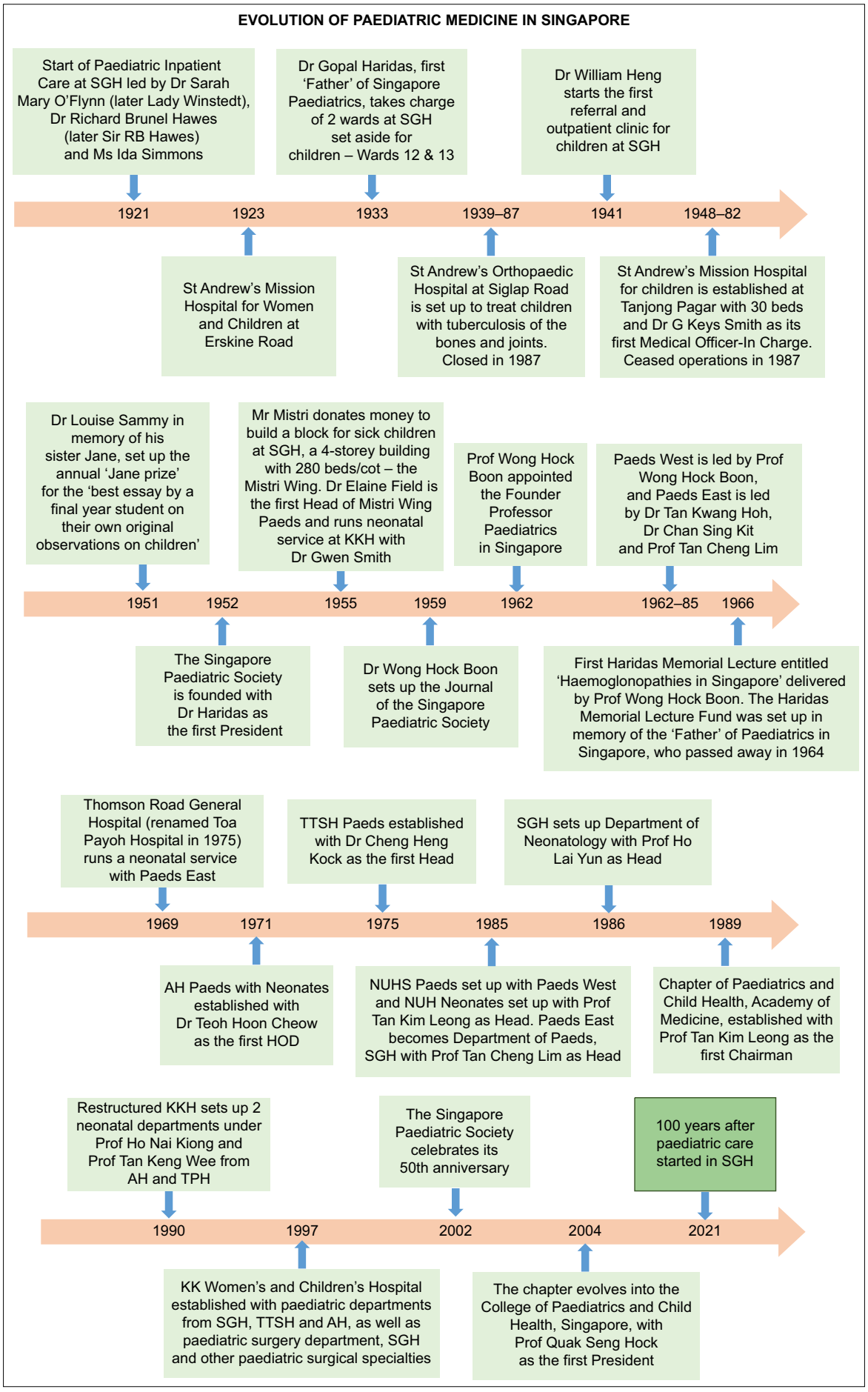
The Neonatal Unit at AH was set up in 1971 under the Paediatric Department to support AH's 'busiest department', Obstetrics and Gynaecology,[25] with 5,000 annual deliveries.[20] With the shift of Paeds West to the National University of Singapore in 1985, a neonatal service was established at NUH. SGH set up its neonatal department in December 1986. Soon after, in 1989, with the restructuring of KKH, the neonatal departments from TPH and AH moved to KKH as Neonatal Departments 1 and 2 or NN1 and NN2, respectively.

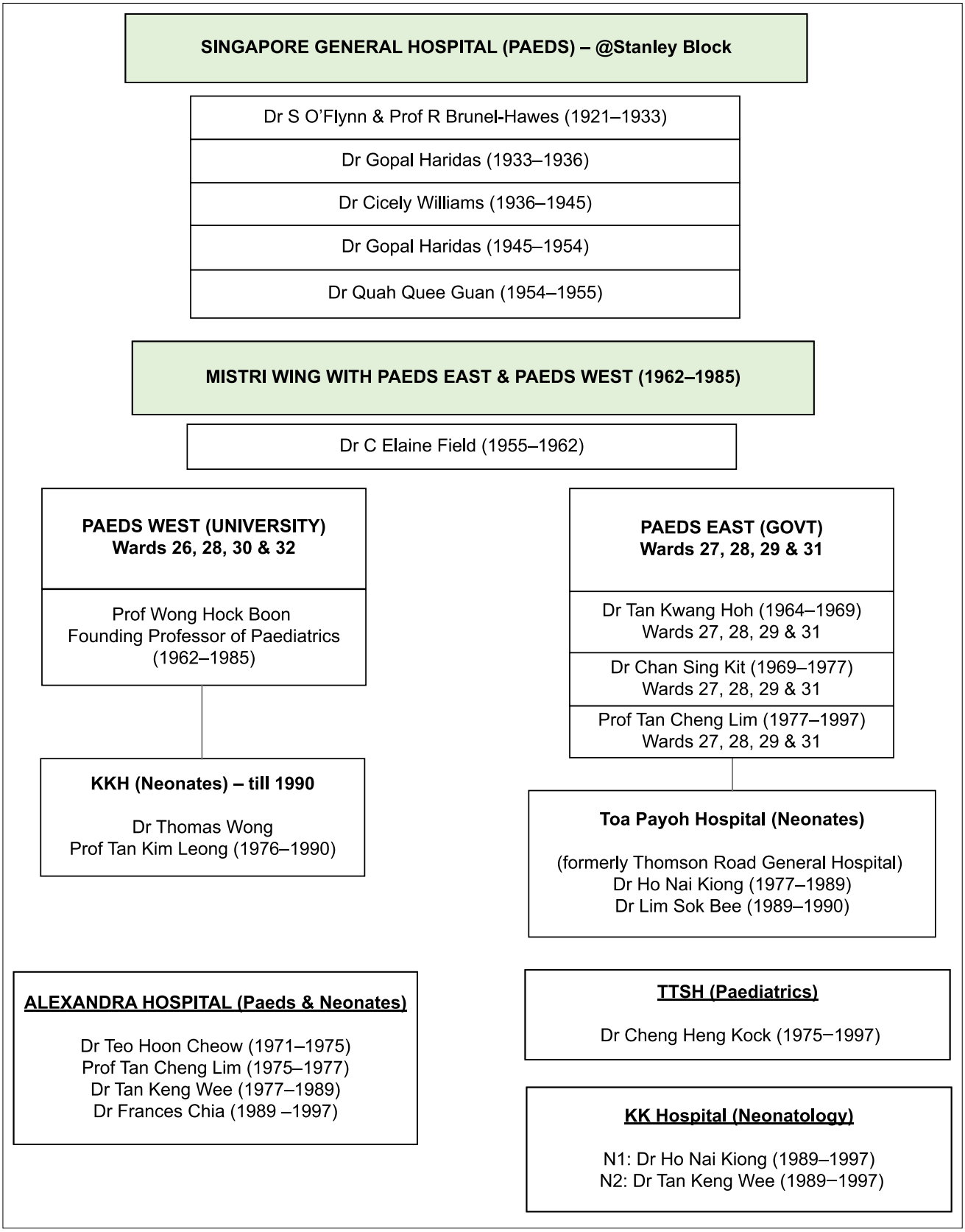
PAEDIATRICS AND NEONATOLOGY AT KKH

In the 1990s, the MOH decided to set up KK Women's and Children's Hospital and organised visits to the US and Australia to study the model of similar maternal and child hospitals. Dr Tan Keng Wee chaired the MOH neonatal workgroup. On 10 March 1997, the O&G and neonatal departments moved from the old facilities to the new hospital.[26] Dr Tan served as Head of Department of Neonatology of the new KKH from 1997 to 2001, and Prof Ho Nai Kiong served as the hospital's first Divisional Chair of Paediatrics. Two months later, on 10 May 1997, the three departments of paediatric medicine from SGH, TTSH and AH, together with the SGH Department of Paediatric Surgery, moved over to KKH.

POSTGRADUATE PAEDIATRIC SPECIALIST TRAINING IN SINGAPORE

After the war and before 1970, postgraduate paediatric training was obtained overseas through scholarship awards. This was what Prof Wong termed 'Phase 1' of Singapore's paediatric postgraduate training.[7] In 1960, the then University of Singapore set up a Postgraduate Board of the Faculty of Medicine, and Prof Wong was appointed Chairman of this committee to facilitate this collaboration between the Australasian Colleges of Medicine and Singapore. During this period, the Royal


EVOLUTION OF PAEDIATRIC MEDICINE IN SINGAPORE
Start of Paediatric Inpatient Care at SGH led by Dr Sarah Mary O'Flynn (later Lady Winstedt), Dr Richard Brunel Hawes (later Sir RB Hawes) and Ms Ida Simmons
1921
St Andrew's Mission Hospital for Women and Children at Erskine Road
1923
Dr Gopal Haridas, first 'Father' of Singapore Paediatrics, takes charge of 2 wards at SGH set aside for children – Wards 12 & 13
1933
St Andrew's Orthopaedic Hospital at Siglap Road is set up to treat children with tuberculosis of the bones and joints. Closed in 1987
1939–87
Dr William Heng starts the first referral and outpatient clinic for children at SGH
1941
St Andrew's Mission Hospital for children is established at Tanjong Pagar with 30 beds and Dr G Keys Smith as its first Medical Officer-In Charge. Ceased operations in 1987
1948–82
Dr Louise Sammy in memory of his sister Jane, set up the annual 'Jane prize' for the 'best essay by a final year student on their own original observations on children'
1951
The Singapore Paediatric Society is founded with Dr Haridas as the first President
1952
Mr Mistri donates money to build a block for sick children at SGH, a 4-storey building with 280 beds/cot – the Mistri Wing. Dr Elaine Field is the first Head of Mistri Wing Paeds and runs neonatal service at KKH with Dr Gwen Smith
1955
Dr Wong Hock Boon sets up the Journal of the Singapore Paediatric Society
1959
Prof Wong Hock Boon appointed the Founder Professor Paediatrics in Singapore
1962
Paeds West is led by Prof Wong Hock Boon, and Paeds East is led by Dr Tan Kwang Hoh, Dr Chan Sing Kit and Prof Tan Cheng Lim
1962–85
First Haridas Memorial Lecture entitled 'Haemoglonopathies in Singapore' delivered by Prof Wong Hock Boon. The Haridas Memorial Lecture Fund was set up in memory of the 'Father' of Paediatrics in Singapore, who passed away in 1964
1966
Thomson Road General Hospital (renamed Toa Payoh Hospital in 1975) runs a neonatal service with Paeds East
1969
AH Paeds with Neonates established with Dr Teoh Hoon Cheow as the first HOD
1971
TTSH Paeds established with Dr Cheng Heng Kock as the first Head
1975
NUHS Paeds set up with Paeds West and NUH Neonates set up with Prof Tan Kim Leong as Head. Paeds East becomes Department of Paeds, SGH with Prof Tan Cheng Lim as Head
1985
SGH sets up Department of Neonatology with Prof Ho Lai Yun as Head
1986
Chapter of Paediatrics and Child Health, Academy of Medicine, established with Prof Tan Kim Leong as the first Chairman
1989
Restructured KKH sets up 2 neonatal departments under Prof Ho Nai Kiong and Prof Tan Keng Wee from AH and TPH
1990
KK Women's and Children's Hospital established with paediatric departments from SGH, TTSH and AH, as well as paediatric surgery department, SGH and other paediatric surgical specialties
1997
The Singapore Paediatric Society celebrates its 50th anniversary
2002
The chapter evolves into the College of Paediatrics and Child Health, Singapore, with Prof Quak Seng Hock as the first President
2004
100 years after paediatric care started in SGH
2021


SINGAPORE GENERAL HOSPITAL (PAEDS) – @Stanley Block
Dr S O'Flynn & Prof R Brunel-Hawes (1921–1933)
Dr Gopal Haridas (1933–1936)
Dr Cicely Williams (1936–1945)
Dr Gopal Haridas (1945–1954)
Dr Quah Quee Guan (1954–1955)
MISTRI WING WITH PAEDS EAST & PAEDS WEST (1962–1985)
Dr C Elaine Field (1955–1962)
PAEDS WEST (UNIVERSITY)
Wards 26, 28, 30 & 32
Prof Wong Hock Boon
Founding Professor of Paediatrics
(1962–1985)
KKH (Neonates) – till 1990
Dr Thomas Wong
Prof Tan Kim Leong (1976–1990)
PAEDS EAST (GOVT)
Wards 27, 28, 29 & 31
Dr Tan Kwang Hoh (1964–1969)
Wards 27, 28, 29 & 31
Dr Chan Sing Kit (1969–1977)
Wards 27, 28, 29 & 31
Prof Tan Cheng Lim (1977–1997)
Wards 27, 28, 29 & 31
Toa Payoh Hospital (Neonates)
(formerly Thomson Road General Hospital)
Dr Ho Nai Kiong (1977–1989)
Dr Lim Sok Bee (1989–1990)
ALEXANDRA HOSPITAL (Paeds & Neonates)
Dr Teo Hoon Cheow (1971–1975)
Prof Tan Cheng Lim (1975–1977)
Dr Tan Keng Wee (1977–1989)
Dr Frances Chia (1989 –1997)
TTSH (Paediatrics)
Dr Cheng Heng Kock (1975–1997)
KK Hospital (Neonatology)
N1: Dr Ho Nai Kiong (1989–1997)
N2: Dr Tan Keng Wee (1989–1997)

Colleges of Australasia agreed to hold postgraduate lectures in Singapore. Our local doctors would then go to Australia for practical exposure, take their postgraduate examinations in Australia and obtain their MRACP and FRCAS from the Australasian colleges (Phase 2).

The Vice Chancellor of University of Singapore in 1970 set up the Postgraduate Medical School. This was an independent body from the Faculty of Medicine and was 'subordinate to the senate of the university'. The board members included representatives from the MOH, Faculty of Medicine and the Academy of Medicine Singapore. The higher clinical qualification was designated Master of Medicine (MMed). Prof Wong was appointed the first Foundation Director of the school.

Initially, only three disciplines were selected, namely Internal Medicine, Surgery and Obstetrics. Prof Wong pushed to include Paediatrics, which was eventually accepted by the board. There were 11 candidates for the first MMed (Paeds) examinations, of whom the following five successfully passed: Dr Cheng Heng Kock, Dr Tan Keng Wee, Dr Foong Yew Chun, Dr Lee Seow Lang and Dr Ong Eng San. Hence, Singapore moved into Phase 3 of postgraduate training of its paediatric specialists (Table I).

In 2006, neonatology was recognised as a subspecialty within Paediatrics by the Specialist Accreditation Board (SAB), Singapore Medical Council. In 2018, five additional paediatric subspecialties, namely paediatric cardiology, paediatric intensive care medicine, paediatric gastroenterology, paediatric haematology and oncology, and paediatric nephrology were recognised by the SAB.

SINGAPORE PAEDIATRIC SOCIETY AND THE COLLEGE OF PAEDIATRICS AND CHILD HEALTH, SINGAPORE

Singapore Paediatric Society

The Singapore Paediatric Society (SPS) was founded in 1952. 22 doctors were present at the first meeting held on 1 August 1952, and Dr Haridas was the first president of SPS. Meetings were held in SGH and at St Andrew's Hospital once or twice a year, with an annual weekend conference. SPS organised the First Asian Regional Paediatric Congress in May 1958. The congress had 192 participants from Singapore, Malaya and 17 other countries. Many of the papers were subsequently published in a 1958 issue of Indian Journal of Child Health.[6-8,27] In 1959, Prof Wong started the 'Journal of the Singapore Paediatric Society' (Fig. 6) with the help of Dr William Heng and Dr Foo Chee Quan. Prior to this, from 1952 to 1959, SPS had a 'Proceedings of the Society', edited by Dr G Keys Smith.

College of Paediatrics & Child Health, Singapore, Academy of Medicine

The College of Paediatrics and Child Health, Singapore (CPCHS), Academy of Medicine started as the Chapter of Paediatrics and Child Health in 1989 to look after the interests of paediatricians in the Academy of Medicine.[8,28,29] The inaugural meeting was held on 31 March, with the Master, Academy of Medicine, Dr NC Tan chairing the meeting. The inaugural chapter office holders were Dr Tan Kim Leong (chairman), Dr Ho Nai Kiong (Vice Chairman) and Dr Chay Oh Moh (Honorary Treasurer), with Dr Phua Kong Boo, Dr Yap Boh Ghee and Dr June Lou as committee members.

The chapter evolved into the CPCHS, Singapore 15 years later, and CPCHS was incorporated on 17 August 2004. The first elected office bearers of the College were Dr Quak Seng Hock (President); Dr Ho Lai Yun (Vice-President); Dr Goh Yam Thiam, Daniel (Honorary Secretary); Dr Rajadurai Victor, Samuel (Honorary Treasurer) and Drs Goh Eng Kim, Anne/Chan Kwai Lin, Daisy and Lee Bee Wah (council members) (Fig. 7).

In the CPCHS Coat of Arms of the College, designed by its members, the chevron at the centre of the shield symbolises the coming together of all medical specialties to provide the best medicine care for the nation. The two children represent paediatrics and healthy children. The snake coiling around the rod symbolises 'healing'. The four circular red dots joined together by olive leaves symbolise the four races living harmoniously in Singapore and in the pink of health. Supporting the shield are two lions, which represent Singapore. The olive branches symbolise anointing and medicinal values. The motto 'Recta Sapere' urges us to seek and savour the truth at all times[28] (Fig. 8).

The Chapter, and later, the College Lecture is open to distinguished members of the medical profession by invitation (local as well as overseas), with the subject offered for the lecture being scientific in content and in the field of paediatrics. Prof Wong Hock Boon delivered the first lecture for the Chapter in 1998 – 'The Future of Medicine from the Standpoint of the Practising Paediatrician' and Prof Tan Cheng Lim delivered the next in 2000, entitled 'The Future of Paediatrics in Singapore'.

The Stuart Gan Memorial Fund was set up in memory of an unfortunate boy who succumbed to an indeterminate immunodeficiency syndrome. The objectives of this fund are to organise and support activities and events related to the genetic, antenatal diagnosis, prevention and other related fields pertaining to immunodeficiency states. These activities include research projects, seminars or lectureships. Since its inauguration, the Stuart Gan Memorial Fund has enabled several prominent speakers to be invited to Singapore to deliver lectures on immunodeficiency and related topics.

In 2012, the CPCHS, SPS and Singapore Perinatal Society jointly organised an annual scientific meeting called the 'Singapore Paediatric and Perinatal Annual Congress' or SiPPAC. In March 2021, CPCHS and SiPPAC partnered with the UK Royal College of Paediatrics and Child Health (RPCPCH) and held the first ever international RCPCH-partnered academic conference entitled 'Learning Together to Improve Child Heath'. This webinar meeting drew more than 700 participants from around this region and also across the world.

CONCLUSION

Paediatrics and child health in Singapore have improved tremendously over the last 100 years. Our paediatric fraternity

has been blessed with great academic clinician leaders who have led our discipline in Singapore through the war and into independence, and into the 21st century. The health needs of our children have evolved, reflecting our first-world environment. Among some of these key health needs for children in this century are what Judith Palfrey terms the 'millennial morbidities' – the primarily metabolic and mental wellness of our children (Box 3).[30] Today, 100 years after SGH took in its first paediatric patients, we are truly standing on the shoulders of our giant paediatric pioneers as we continue to collectively improve medical care for all our children in Singapore.

ACKNOWLEDGEMENTS

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Transforming paediatric practice by leveraging on genomic medicine

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ABSTRACT Genomic medicine entails the use of an individual's genomic information in his or her clinical care to aid diagnosis and personalise management. As genetic conditions significantly contribute to neonatal and paediatric morbidity and mortality, paediatricians can incorporate genomic medicine in their clinical practice. Through this review, we aim to describe the basic concepts of genomic medicine, discuss the types of genetic and genomic testing available, present examples of how genomics is already being used in paediatrics and summarise the challenges of genomic medicine. The purpose of this review is to help paediatricians decide the suitable genetic or genomic test, understand the possible outcomes of testing and appreciate the requirements of appropriate counselling of patients.

Keywords: genetics, genome sequencing, genomics, variant

INTRODUCTION

The Human Genome Project, completed in 2003, resulted in the generation of the first draft of the human DNA sequence. This has prompted numerous initiatives aimed towards personalised medicine that is tailored to an individual's genetic make-up. Options for genetic testing have increased exponentially with technological advances that allow rapid, high-throughput DNA sequencing. While traditional cytogenetic tests, such as karyotyping and fluorescence *in situ* hybridisation, require cell cultures to visualise numerical or structural abnormalities of chromosomes, molecular genetic tests can be performed on DNA extracted from nucleated cells, such as fresh blood, saliva or even stored tissue sample. These molecular genetic tests include chromosomal microarray analysis (CMA), single-gene- or gene-panel-targeted variant testing, sequencing of whole genes or panels of genes, and sequencing of the entire coding and noncoding regions of the human genome. Knowledge and understanding of the wide array of genetic tests, especially their clinical applications, is essential for the paediatrician, given that most genetic disorders present during infancy and childhood. In fact, congenital anomalies are identified in approximately 3% to 6% of live births,[1] and they contribute significantly to neonatal and infant hospital admissions and mortality.[1-3] In this review, we present the new advances in genomic technology and discuss the application of genomic tests in paediatric practice. In addition, we discuss the potential challenges in the realisation of precision medicine for better personalised patient-centric care in the near future.

WHAT IS GENOMIC MEDICINE?

A genome is the complete DNA sequence of an organism and includes genes as well as the intergenic regions. In humans, this includes the approximately 20,000 genes present in our entire genome. The term 'genomics' refers to the study of an organism's genome, whereas genetics refers to the analysis of single genes and their inheritance. Genomic medicine is defined as the practice of using an individual's genomic information in his or her clinical care.[4] It is increasingly applied in the fields of rare and undiagnosed diseases, oncology, pharmacology and infectious diseases. The integration of genomics into clinical care is made possible with increased understanding of the role of genomic information in human health and diseases through a broad range of collaborative research and improved technologies and computation analysis in interpreting this information. In the realm of rare paediatric diseases, accurate genetic diagnosis allows access to relevant information in the literature, targeted management and surveillance for the patient, and better understanding of the prognosis and genetic implications to the patient's existing and future family members.[5-7]

TYPES OF GENETIC AND GENOMIC TESTS

Karyotyping (chromosome analysis)

Karyotyping is a cytogenetic method that involves the analysis of numerical and structural chromosomal abnormalities under a light microscope.[8] In this method, circulating lymphocytes from peripheral blood or other cell types from the skin, bone marrow, chorionic villi or cells from amniotic fluid are cultured under strict sterile conditions. Following the use of mitogens to stimulate these cells to mitotically divide, colchicine is used to arrest the cells during metaphase when chromosomes are maximally visible. Giemsa banding (or G-banding) is the most commonly applied staining method to identify individual chromosomes by producing a characteristic pattern of light and dark bands on each chromosome. Abnormalities such as loss or gain of entire chromosomes, translocations of all or part of an arm of one chromosome to another or subtle changes in the banding patterns associated with various genetic disorders can be identified.

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A limitation of karyotyping is that it is time-consuming, as it involves cell culture and the preparation requires several days. In addition, the resolution, which is a measure of the level of magnification of the genome, is lower than that achieved using other technologies. A standard G-banded karyotype usually has a resolution of approximately 3–5 Mb (i.e. it can detect changes of greater than three to five million base pairs). Despite these limitations, karyotyping remains the test of choice when suspecting common genetic conditions with obvious phenotypes, such as trisomy 13 (Patau syndrome), trisomy 18 (Edwards syndrome), trisomy 21 (Down syndrome) or monosomy X (Turner syndrome). Karyotyping is also the test of choice for detection of balanced structural rearrangements such as balanced translocations, and when mosaicism is suspected.

Fluorescence *in situ* hybridisation

Fluorescence *in situ* hybridisation (FISH) is a method that combines cytogenetics and molecular genetic technology.[8] Fluorescence-tagged single-stranded DNA probes are used to identify specific targeted DNA sequences during metaphase or interphase of cells. After hybridisation with the patient's sample, the targeted regions can be visualised using a fluorescence microscope. The resolution of FISH is in the range of 100–200 kb, depending on the probe size. This renders FISH useful in the diagnosis of submicroscopic chromosomal abnormalities, including deletions, duplications and translocations. Common microdeletion syndromes that can be diagnosed using targeted FISH probes include velocardiofacial syndrome (22q11.2 deletion), Williams syndrome (7q11.23 deletion), Wolf-Hirschhorn syndrome (4p16.3 deletion), etc. FISH can be applied to interphase cells, resulting in a rapid turnaround time of 24–48 hours, allowing rapid detection of chromosomal aberrations. FISH techniques also allow the study of chromosomal aberrations in nondividing cells, for example, in cytological preparations and tissue sections. However, FISH requires prior knowledge of the specific region that might be abnormal and, therefore, has limited utility as a first-tier test for clinical diagnosis of nonspecific clinical syndromes.

Chromosomal microarray analysis

Chromosomal microarray analysis (CMA), also known as array comparative genomic hybridization, has been shown to be useful in the detection of copy number variants (CNVs), which are genomic alterations that result in an abnormal number of copies of one or more genes.[9] Compared with karyotyping, CMA has an improved resolution of approximately 50–100 kb.[10] This technology uses oligonucleotide probes capable of capturing unique genomic sequences in recurrent disease-causing CNVs associated with microdeletion and/or microduplication syndromes.[8,9] In 2010, the American College of Medical Genetics, now renamed the American College of Medical Genetics and Genomics (ACMG), recommended CMA as the first-tier clinical diagnostic test for children with unexplained developmental delay/intellectual disability, autism spectrum disorders or multiple congenital anomalies.[10] Multiple publications have reported the diagnostic yield of CMA in various cohorts of patients, with a worldwide average rate of 15%–20%, compared with that of G-banded karyotyping, with a rate of approximately 3%.[10,11] CMA has certain limitations in that it cannot identify smaller insertion-deletion (indels) or single-nucleotide variants. In addition, CMA cannot detect balanced translocations, inversions or insertions, as there is no net loss or gain of chromosomal material in these chromosome rearrangements. CMA cannot reliably detect low-level mosaicism as well.

Sanger sequencing

Sanger sequencing, which was developed by Frederick Sanger and his colleagues in the 1970s, has been the gold standard in molecular diagnostics owing to its accurate determination of sequence of nucleotide bases.[12] This method combines a DNA polymerase with a mixture of standard and chain-terminating dideoxynucleotides, which results in early termination of sequencing reactions during polymerase chain reaction (PCR).[12] The DNA fragments of varying lengths are placed into four columns on a gel and separated using gel electrophoresis, thus allowing the DNA sequence to be read. Sanger sequencing is time-consuming, as it can analyse only a single DNA segment at a time. It does not detect mosaicism below 15%–20%[13] and can miss a significant proportion of low-level mosaic variants.[14] Although Sanger sequencing is slowly being replaced by other rapid DNA sequencing technologies such as next-generation sequencing (NGS), it retains its role as an orthogonal method to confirm sequence variants identified by NGS and provide coverage for genomic regions not well-covered by NGS.

Next-generation sequencing

NGS, also known as massively parallel sequencing, is a revolutionary high-throughput sequencing technology that can simultaneously sequence multiple genes or even entire exomes or genomes in a single reaction.[15] NGS has been used in research settings for establishing the genetic basis of Mendelian diseases, especially in paediatric rare genetic disorders that can be caused by single-nucleotide variants (SNVs) or small insertions and/or deletions (indels), as NGS has an extremely high sensitivity for the detection of SNVs and indels.[16] This powerful technology has successfully identified causative genetic variants in children with suspected genetic disorders presenting as developmental delay/intellectual disability, congenital anomalies and/or autism spectrum disorders, with a yield of 25%–40% using a targeted multiple gene approach.[17,18] NGS has also been proven to be effective in identifying the genetic aetiology of children with disorders that exhibit significant locus heterogeneity, such as Noonan syndrome and related RASopathy disorders.[19] NGS is now increasingly applied in clinical paediatric practice as a diagnostic test for various genetic Mendelian disorders at different ages of presentation.

As genetic testing has become more readily available, NGS-based whole exome sequencing (WES) or whole genome sequencing (WGS) has emerged as a possible first-line diagnostic tool for paediatric rare genetic disorders with highly heterogenous phenotypes, and both methods show higher diagnostic and clinical utility than those of CMA.[5] WES examines the exons

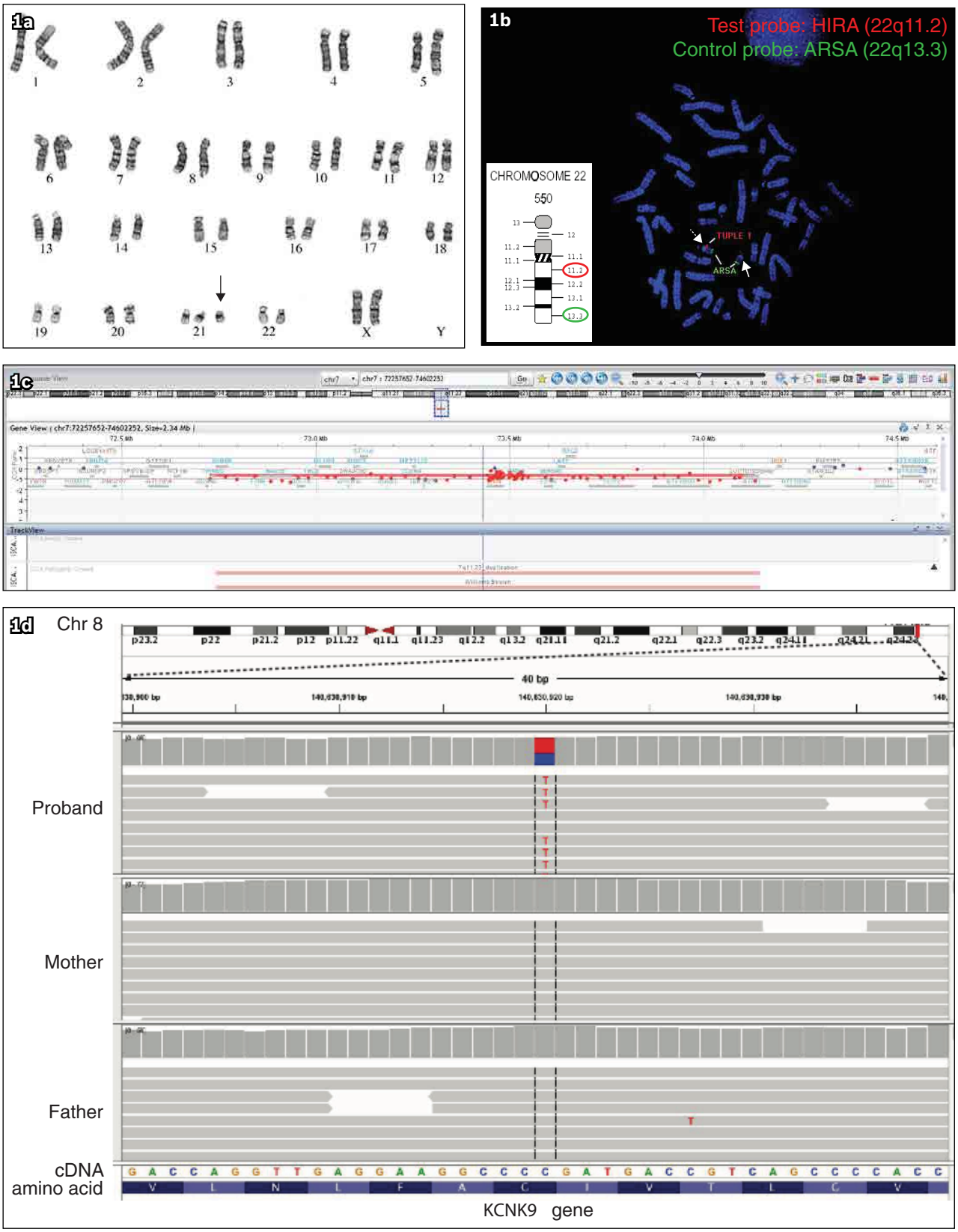

Fig. 1 (a) Karyogram shows 47,XX,+21: Female karyotype with trisomy chromosome 21 (arrow), consistent with the diagnosis of Down syndrome. (b) Fluorescence in situ hybridisation on a metaphase chromosome spread shows no signal for the test probe (HIRA) (red) and normal signal for the control probe (ARSA) (green) on one chromosome 22 homologue (solid arrow). Dotted arrow indicates the normal chromosome 22 homologue showing normal signal for both test and control probes. (c) Chromosomal microarray analysis (CMA) shows a copy number loss of 1.407 Mb at 7q11.23 at the Williams syndrome region (red bar). CMA allows delineation of the genes included in the deleted region; in this case, the deletion affects 25 genes including ELN and GTF2IRD1. (d) Integrative Genomics Viewer screenshot of next-generation sequencing reads shows a *de novo* variant in the KCNK9 gene (dotted box) in the proband, which is absent in the parents.

Table I. Summary of commonly used genetic and genomic tests.

	Karyotyping	Fluorescence *in situ* hybridisation	Chromosomal microarray analysis (CMA)	Single-gene analysis/ NGS gene panels	Whole exome sequencing (WES)	Whole genome sequencing (WGS)
Resolution	3–5 Mb	100–200 kb	50–100 kb	1 bp	1 bp	1 bp
Genetic variants detected	Aneuploidies; variants > 3–5 Mb	Submicroscopic copy number variants	Aneuploidies; copy number variants of ≥ 50–100 kb	Variants in single gene/genes included in panel	Single-nucleotide variants in coding regions	Single-nucleotide variants in the whole genome
Advantages	Genome-wide; can detect mosaic chromosome anomalies; can detect balanced chromosome rearrangements	Decreased probability of variant of uncertain significance; localisation of gain/loss on chromosomes possible; may be cheaper than CMA	Genome-wide; uses a DNA sample, and hence no need for dividing cells; diagnostic yield of 15%–20%	Decreased probability of incidental findings or variant of uncertain significance; usually cheaper that WES/WGS	Genome-wide; diagnostic yield of 25%–30%	Genome-wide
Limitations	Resolution of 3–5 Mb; requires dividing cells	Probe-specific	Cannot detect balanced chromosome rearrangement; may not detect lower levels of mosaicism; cannot detect certain polyploidies; cannot detect single-nucleotide variants	Less useful for nonspecific phenotypes or phenotypes with genetic heterogeneity; sequential testing may increase cost and time to diagnosis	Increased probability of incidental findings; expensive	Increased probability of incidental findings; expensive
Availability in Singapore	Available	Available	Available	Single gene analysis available for a number of conditions; clinical exome sequencing available as RapidSeq and PaedSeq tests at KKH; all other tests can be sent to accredited laboratories overseas	Available on a research basis locally; clinical WES can be sent to accredited laboratories overseas	Available on a research basis locally; clinical WGS can be sent to accredited laboratories overseas

KKH: KK Women's and Children's Hospital: NGS; next-generation sequencing

(protein-coding regions) of all 20,000 genes (approximately 1.5% of the entire genome) in which most disease-causing variants (~85%) are concentrated.[6] WGS involves the sequencing of the entire genome of three billion base pairs that include all the exons and introns (non-protein-coding regions).

WGS has the advantage of being able to detect disease-causing CNVs, structural variations, repeat expansions, and non-exonic regulatory and splicing variants.[5] The diagnostic yield of WES/WGS varies depending on the clinical features and on whether the testing approach is proband-based or trio-based (proband and both parents). For example, in a cohort of children with severe intellectual disability, the diagnostic rate for trio-based WGS was 42% and that for trio-based WES was 40%, compared with the diagnostic rate for proband-only WES, which was 28%.[15] Table I and Fig. 1 summarise the commonly used genetic and genomic tests at present.

GENOMIC MEDICINE: CURRENT APPLICATION IN CLINICAL PRACTICE

Genomic technologies are increasingly being used in different clinical settings in paediatrics, including the diagnosis of rare Mendelian diseases in children using next-generation DNA sequencing.[5,6,15] Recently, the clinical utility of rapid genomic sequencing in critically ill infants and children has been reported in multiple studies.[7] Next-generation DNA sequencing also improves the diagnostic and prognostic utility of newborn

screening programmes. This technological advancement has enabled sequencing of individual genes, such as those for cystic fibrosis (*CFTR*), to be used in newborn screening programs in many countries, including Singapore, as a confirmatory test for screen-positive infants. The emergence of novel therapeutics, including gene therapy for spinal muscular atrophy (SMA), have supported the use of PCR test for homozygous deletion of exon 7 of the *SMN1* gene from dried blood samples in newborn screening programmes in several countries.[20-22]

Other emerging clinical applications of genomic sequencing include preconception carrier screening and genetic predisposition screening for disease risk assessment of adult-onset genetic conditions. Genetic carrier screening can be offered to couples to facilitate informed reproductive decision-making by identifying couples who are carriers for pathogenic variants associated with Mendelian disorders and, hence, have an increased risk of having affected offspring. Genetic predisposition testing is helpful for individuals with a positive family history or those who are at a risk of certain genetic disorders. They may be asymptomatic at the time of testing, as disease manifestation may occur later in life. Predictive testing can also identify genetic variants that increase a person's risk of developing disorders with a genetic basis, such as genes *BRCA1* and *BRCA2* in breast cancer.

THE CHALLENGES

Interpretation of CNVs and sequence variants

One of the major challenges in genomic medicine is the large number of variants and their subsequent interpretation to determine the clinical significance of each variant identified in CMA and NGS-based genomic tests. Well-established guidelines from ACMG in the interpretation and reporting of constitutional CNVs and sequence variants help to standardise the interpretation of these variants across different laboratories.[23-25] Each of the variants identified is classified into various categories ranging from benign, likely benign (both are usually not reported), variant of uncertain significance (VUS), likely pathogenic and pathogenic, based on various non-overlapping criteria. The factors assessed during CNV interpretation include the genomic content, i.e. whether it contains known functionally important regions, number of genes, detailed evaluation of genomic content using published literature, public databases and/or internal lab data, and inheritance pattern.[24] In sequence variant interpretation, a variant is assessed based on the current literature describing the gene function using functional studies, computational and predictive data assessing the effect of the variant on gene function, the frequency of the variant in general population databases such as gnomAD, and the frequency of the variant in patients with clinical abnormalities using current literature and databases such as ClinVar (https://ncbi.nlm.nih.gov/clinvar/),[26] segregation and allelic data, and inheritance of the variant. The curation of each variant identified is a complex process that ensures accurate classification of the variant. However, some variants may still be classified as VUS owing to insufficient information regarding the association of these variants in genes with a genetic syndrome or phenotype. The high-throughput NGS-based genomic tests, especially WES or WGS, may potentially reveal more VUS, which may cause uncertainty among both parents of the paediatric patients and physicians regarding the appropriate clinical management to be adopted.

Multiple collaborative efforts of clinicians and scientists, including ClinGen[24,27] and ClinVar, have led to the development of various methods to improve the interpretations of these variants and consequently reduce the uncertainty.

Incidental and secondary findings

In genome-wide tests such as WES and WGS, with increasing accuracy and predictive power, there is a possibility of detecting clinically significant variants that are unrelated to the phenotype reported and clinical indication at the time of testing; these are known as incidental findings. The genetic condition incidentally identified may be an adult-onset genetic condition and may or may not have effective treatment available. The ACMG has recommended pathogenic variants in 59 genes[28] that are deemed 'medically actionable', known as secondary findings, to be specifically looked for and reported by the clinical laboratory if the parents of the paediatric patients wish to have the information provided. The estimated prevalence of likely pathogenic and pathogenic incidental findings in a cohort of 377 individuals in Singapore was 1.6%,[29] compared with a corresponding prevalence of 1.7% in individuals of European ancestry and 1.0%, in individuals of African ancestry.[30] These incidental or secondary findings may have implications for the patient's future and that of his or her immediate family members. This is especially so for adult-onset conditions, which may raise concerns about negative psychosocial impacts and about depriving the child of an 'open future'.[31] However, these incidental or secondary findings may allow at-risk parents to be identified, manage their health better and improve their ability to support their child. This information may be indirectly beneficial for the child's welfare.[31] For example, WES performed in a child with congenital anomalies may identify an incidental finding of pathogenic variant in *BRCA1*, and this variant could be inherited from either parent. This means that the affected parent and other family members who are identified to carry the same pathogenic variant in *BRCA1* may require surveillance and monitoring for associated cancers. Parents should be counselled carefully regarding the risk and benefits of receiving this information and should be provided the option of receiving or declining these findings.

ADOPTING GENOMIC MEDICINE IN CLINICAL PRACTICE

Personalised medicine, also known as precision medicine, is the practice of genomic medicine where an individual's genomic data are utilised for the prevention, diagnosis and individualised treatment of his or her disease. The Singapore Undiagnosed Diseases Research Endeavour for Kids (SUREKids) study began in 2014 and was conducted at KK Women's and Children's Hospital (KKH) and the National University Hospital (NUH). Collaborating with the Agency for Science, Technology and Research (A*STAR) Singapore, the study aimed to explore the utility of genomic sequencing in patients with Mendelian disease.[32] Out of 196

probands whose data was reported, molecular diagnosis was made in 73 probands, with an overall diagnostic yield of 37.2%; 65 cases were diagnosed via WES (yield 37.8%) and eight, via WGS (yield 33.3%).[32] Higher diagnostic yield was observed in the cohort with global developmental delay (yield 43%), neuromuscular disorders (yield 50%) and skeletal dysplasia (yield 50%).[32] The result of this large-scale local study supports the clinical implementation of genomic sequencing in clinical practice by demonstrating high clinical utility of WES and WGS in providing accurate genetic diagnosis and management of the underlying disorder.

Clinical vignette

A six-year-old boy underwent genomic sequencing after presenting with a multisystem phenotype including poor growth, developmental delay and hepatosplenomegaly with liver transaminitis since infancy.[33] He had a history of pancytopenia when he was one month old. Despite extensive immunological and gastrointestinal investigations, no unifying diagnosis was identified. Research trio exome sequencing identified a *de novo* heterozygous missense variant in *EIF6* (c.182G>T; p.Arg61Leu). This variant is absent in population databases, including the genomeAsia100k (https://browser.genomeasia100k.org/) and Singapore Exome Consortium, affects a highly conserved amino acid residue and is predicted to be deleterious by multiple *in silico* prediction software systems. However, prior to this, no disease-causative variants in *EIF6* had been reported in humans. EIF6 protein is known to interact with SBDS and EFL1 protein, both of which are associated with Shwachman-Diamond syndrome (SDS). The patient's clinical features fulfilled the diagnostic criteria of SDS according to the published international consensus guidelines,[34] and when the patient later developed frequent loose and bulky stools, pancreatic insufficiency that is associated with SDS was considered as a possible cause. This was supported by severely low stool elastase levels at <15 mcg E1/g. Subsequently, the patient was started on pancreatic enzyme replacement therapy (CREON) and since then, he has shown reduced stool frequency and improved growth. His pancytopenia improved with time, which is in contrast with the progressive bone marrow failure typically observed in patients with SDS1 due to biallelic variants in *SBDS* and in those with SDS2 due to biallelic variants in *EFL1*. Thus, our patient has a novel SDS-like phenotype with transient bone marrow failure but persistent pancreatic insufficiency.

The detailed clinical phenotyping and clinical acumen of Professor Phua Kong Boo led him to recognise the novel disease presentation in the patient. In addition, the multidisciplinary collaboration between Prof Phua, other clinical subspecialists and research collaborators allowed us to optimise the management of the patient.

ROLE OF GENOMICS EDUCATION

With the increasing use of newer genetic technologies in clinical practice, there is an urgent need to develop genomics literacy and competencies in all clinicians. Genomics education is essential for improving proficiency and skills in practical genomics, increasing confidence in identifying patients with suspected or at risk of genetic conditions for further genetic evaluation, and even ordering and interpreting genomic tests. Recognising the need for genomics education locally, an interactive workshop, Genetics Education for Healthcare Professionals, has been set up by the Genetics Service at KKH, involving faculty from KKH and NUH and supported by the SingHealth Academy and the College of Paediatrics and Child Health, Singapore. This workshop focuses on the application of a wide range of genetic and genomic tests, and practical pre- and post-test counselling skills. Its aim is to improve clinicians' genomics knowledge including basic interpretation of genetic and genomic test results, and boost their confidence in applying genomic medicine into their clinical practice.

With the rapid progress in the field of genomics, clinicians entering medical practice now and in future will require more than a basic understanding of human genetics, which is traditionally included in the undergraduate medical curriculum in most medical schools. Enhancing exposure to genomics for medical students during both pre-clinical and clinical years of training would be important to prepare future physicians for clinical practice in the era of genomic medicine. A combination of formal and active experiential learning would be ideal to equip them with the knowledge and skills required to apply genomic medicine across a range of specialties.

FUTURE OF GENOMIC MEDICINE IN PAEDIATRICS

The Human Genome Project and DNA sequence data gathered from individuals with disorders have provided opportunities for the study of genomics and the interaction between genetic components and human diseases.[35] The current advanced genomic tests, which are more affordable, and the significant improvement in bioinformatics including variant interpretation and analysis have revolutionised clinical practice in paediatrics by providing more accurate genetic diagnoses of paediatric genetic disorders. Extensive research efforts are being made for the development of novel cell and gene therapies that could be potentially life-changing for the affected individuals. For example, Zolgensma, used for the treatment of spinal muscular atrophy (SMA), could potentially reverse the natural history of this life-limiting condition if the gene therapy is given as early as possible. This is an *in vivo* recombinant adeno-associated virus 9 (AAV9)-based gene therapy designed to deliver a functional copy of *SMN1* gene to encode for human SMN protein, so that motor neurons can maintain their function.[36] Several clinical trials on gene therapies for different genetic conditions are ongoing, providing a new perspective in disease management, with potential curative treatment options. Genomic medicine is being more widely implemented in paediatric clinical practice; hence, it is important for clinicians to understand the basic principles of genomic medicine and familiarise themselves with the technical, ethical and legal developments in this rapidly evolving field of medicine.

CONCLUSION

Genomic testing will increasingly be integrated into mainstream paediatric practice. It is likely that genome sequencing will soon

be a frontline test in most specialties, including paediatrics. Clinicians should be aware of the basic principles of genomic medicine, including its benefits and challenges. In learning to apply these advanced genomic technologies in our clinical practice, we should not neglect the importance of keeping our clinical skills sharp to phenotype our patients well and recognise which patients will benefit from genomic testing. Finally, as the story of our patient with the SDS-like condition fittingly illustrates, a collaborative spirit to work within multidisciplinary teams is of prime importance that will enable us to truly harness the power of genomic medicine to improve patient care.

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Clinical spectrum of paediatric liver diseases in Singapore

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ABSTRACT A wide spectrum of disorders can affect the liver. This spectrum of acute and chronic liver diseases in children differs among populations from various parts of the world because of inherent differences in genetic and environmental factors. This review article provides a concise overview of important paediatric liver disorders prevalent in Singapore and discusses the epidemiology and outcomes of these conditions specific to our local context.

Keywords: cholestasis, hepatitis, liver disease, paediatrics

INTRODUCTION

The liver is the largest intra-abdominal organ that performs a myriad of key metabolic functions and processes in the body. It plays a vital role in carbohydrate, lipid and protein metabolism and synthesis; bilirubin and bile acid transport; and drug metabolism and detoxification. These functions, in turn, affect other physiologic processes in the other systems, including the haematologic, endocrine, skeletal, immunologic and central nervous system.[1] Hence, a wide spectrum of disorders can affect the liver, and the complications arising from fulminant or decompensated liver disease are often severe and multisystemic.

The aetiologies of acute and chronic liver disease in children differ in various parts of the world, most likely owing to inherent differences in genetic and environmental factors. For example, viral hepatitis is still considered more prevalent in Asian populations, whereas certain genetic conditions such as alpha-1 antitrypsin deficiency or cystic fibrosis-associated liver disease are more likely to be diagnosed in Western populations. By contrast, biliary atresia (BA), the aetiology of which is still unclear, affects patients worldwide, but has a seemingly higher incidence in Asian countries such as Japan and Taiwan.[2]

Through this review article, we aim to provide a concise overview of the paediatric liver diseases that are prevalent in Singapore, with specific emphasis on the local data on epidemiology, management and outcomes.

LIVER DISORDERS PRESENTING IN INFANCY

Anatomic/Structural disorders

Biliary atresia

BA is a fibro-obliterative disease of the extrahepatic and intrahepatic bile ducts, presenting typically with cholestasis and acholic stools in early infancy. The incidence of BA appears to be higher in Asia, and Taiwan and Japan have reported incidences of 1 in 5,000 and 10,000 live births, respectively.[2,3] In comparison, the incidence rates in the United Kingdom and Europe range from 1 in 15,000 to 1 in 20,000 live births.[4,5] In Singapore, around three to five new cases of BA are diagnosed annually, which equates to an estimated incidence of 1 in 10,000 live births. Although BA is considered a rare condition, it is the leading cause of chronic liver disease in childhood and is the most common indication for liver transplantation in children.[6] The cause of BA remains unknown, although there appear to be two distinct phenotypes: a syndromic form with prenatal onset and association with other congenital anomalies (most notably cardiac and splenic malformations) accounts for 10%–20% of cases, and an acquired form of isolated BA represents 80%–90% of cases. BA with splenic malformation is exceedingly rare in Singapore, with no such cases reported in our local series.[7] Although the cause of BA remains unknown, it is likely to be multifactorial, with an interplay of a combination of genetic, infective/viral, pro-inflammatory and toxic factors.[2]

Diagnosis is suspected based on typical findings of conjugated hyperbilirubinaemia associated with pale or acholic stool in a young infant. On ultrasonography, the gallbladder (GB) is absent, contracted and/or dysplastic even after a four-hour fast, and the triangular cord sign (hyperechogenic liver hilum) may be present. The GB ghost triad, consisting of GB <1.9 cm, lack of smooth/complete echogenic mucosal lining with an indistinct wall and irregular/lobular contour, was demonstrated in 30 out of 31 babies with BA in a study conducted in Singapore by Tan Kendrick et al, and was found to be an accurate sign for the diagnosis of BA.[8] A hepatobiliary iminodiacetic acid (HIDA) scan is a radioisotope excretion study that typically shows good hepatic uptake but absent excretion into the intestines within 24 hours. Unfortunately, the finding of absent radioisotope excretion on HIDA scan is not specific for BA. Liver histology shows evidence of extrahepatic biliary obstruction by varying degrees of portal tract fibrosis, ductular proliferation and cholestasis with bile plugs.[2] Operative cholangiogram performed at the time of surgery is considered the gold standard for the diagnosis of BA.

The Kasai portoenterostomy (KP) is a surgical procedure that aims to re-establish bile flow and alleviate biliary obstruction. Substantial observational evidence shows that earlier diagnosis

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and surgical intervention result in better outcomes in terms of preservation of native liver function.[3,9,10] However, various international studies have reported jaundice clearance rates of 40%–60% at six months after KP,[11,12] and progressive biliary fibrosis and cirrhosis still occur in the majority of cases. Retrospective local single-institution data comprising 72 patients over a 27-year period reported an overall six-month jaundice clearance rate of 55.6%.[13] Post-KP corticosteroids have been used in some centres as an adjuvant therapy,[14] which may reduce the ongoing inflammation that contributes to the progressive biliary fibrosis; however, the benefit of post-KP corticosteroids remains controversial, and hence, this practice has not been universally adopted.[12]

Cholangitis is a frequent complication in BA, with an incidence of 64.3%, which exerts a significant burden on healthcare and financial resources.[15] In a study published in 2014, Lee et al found that patients with BA in Singapore experienced an average of 3.6 episodes of cholangitis, and the average length of hospital stay per episode was 15 days, amounting to an estimated cost of S$8986.61.[15] Despite the use of extended courses of prophylactic perioperative antibiotics together with the addition of post-KP corticosteroids, Goh et al were unable to demonstrate a reduction in cholangitis rates in the first two years after KP in their cohort of patients with BA (1.44 vs. 1.85 episodes per patient-year, $p = 0.13$).[16]

Even after 'successful' KP, children with BA will have some degree of hepatic fibrosis or cirrhosis. Disease progression and eventual development of complications associated with portal hypertension and liver decompensation occur in two-thirds of patients. In Singapore, a 72% survival rate has been observed in patients with their native livers at two years after KP and a 46% survival rate has been observed at five years after KP.[7] BA remains the most common indication for liver transplantation among children in Singapore.[17]

Choledochal malformation

Choledochal malformation is characterised by inherent dilatation of a part of or the entire biliary tree, and can be categorised into distinct anatomic subtypes. Type I, which describes the classical cystic or fusiform dilatation of the common bile duct, is the most common type, accounting for 85% of the cases. Choledochal malformations are reported to be more common in Asians than in Western populations, and a marked female predominance has been observed.[18] The pathogenesis is postulated to be related to an abnormal pancreatobiliary junction that promotes the reflux of activated pancreatic enzymes into the proximal bile ducts, leading to damage and weakening of the biliary wall and resultant dilatation. By contrast, intrahepatic ductal dilatations in types IV and V are more probably the result of disruption to embryonic ductal plate remodelling.

Choledochal malformations may present in infants and children with obstructive jaundice, cholangitis, abdominal mass and/or pancreatitis, but can present late into adulthood. Choledochal cysts may sometimes be identified prenatally on routine antenatal scans. For extrahepatic choledochal malformations, surgical resection of the dilated extrahepatic bile duct and reconstruction with a Roux-en-Y hepaticojejunostomy is the standard approach. Complete cyst excision has shown favourable outcomes, based on a local study reported by Joseph et al.[19] Liver transplantation is a viable option for patients who develop complications from Caroli's disease.

Metabolic liver disorders

Depending on the specific individual disease, metabolic liver disorders could present at birth with hydrops fetalis, in infancy with cholestasis or acute liver failure, or later in childhood with acute liver failure, chronic liver disease, and/or isolated organomegaly. The diagnosis of such metabolic conditions has been expedited in recent times with the availability of rapid gene sequencing panels. Many of these conditions are inherited in an autosomal recessive pattern, and parental consanguinity is a recognised risk factor.

Fortunately, metabolic liver disorders are relatively rare in Singapore. For example, galactosaemia, tyrosinaemia and alpha-1-antitrypsin deficiency, which are important causes of acute or chronic liver failure in the West, are uncommon locally. Having said that, if a young child or infant presents with acute liver failure, the possibility of an underlying metabolic disease should be considered. According to data from Western countries, metabolic disease as a cause of acute liver failure was identified in 15% of children presenting below the age of three years and in 7% of children presenting at 3–18 years.[20] In our own local study, a metabolic cause was identified in 38.9% of children presenting with acute liver failure under 12 months of age.[21]

A detailed review of the full spectrum of metabolic disorders is beyond the scope of this article. However, two metabolic disorders of local importance are summarised here.

Citrin deficiency

Citrin deficiency, or citrullinaemia type 2, is an autosomal recessive disorder caused by mutations in SLC25A13 gene located on chromosome 7q21. This condition has a high prevalence in East Asian races, with carrier frequencies of 1:112 in Koreans, 1:69 in Japanese and 1:48 in Southern Chinese individuals.[22,23] A carrier frequency of 1 in 41 has been reported for citrin deficiency in Singapore.[24] Citrin is a mitochondrial aspartate-glutamate carrier associated with the urea cycle, which is expressed mostly in the liver. Mutation in the gene causes disruption in a diverse range of metabolic pathways, including the urea cycle, aerobic glycolysis, gluconeogenesis (with resultant hypoglycaemia) and, possibly, fatty acid synthesis. Accumulation of nicotinamide adenine dinucleotide in hepatocyte cytosol also inhibits galactose metabolism, resulting in galactosuria and secondary galactosaemia. Citrin deficiency can present in three distinct age-dependent phenotypes, namely neonatal intrahepatic cholestasis of citrin deficiency (NICCD), failure to thrive and dyslipidaemia caused by citrin deficiency in older children, and recurrent hyperammonaemia and neuropsychiatric symptoms in adults with citrullinaemia type II (CTLN2).[23]

In NICCD, in particular, infants present with early-onset neonatal hepatitis with cholestasis, hypoglycaemia and hypergalactosaemia. Typical biochemical features include hyperammonaemia; hypoalbuminaemia; and increased plasma levels of citrulline, tyrosine, threonine, arginine and methionine. In East Asian races, the presence of positive urinary reducing substance may be more indicative of NICCD rather than classic galactosaemia (secondary to reduced galactose-1-phosphate uridyl transferase activity), which is more prevalent in Western populations.[25] Initial management involves supplementation with lactose-free formula with medium-chain triglyceride and fat-soluble vitamins. The hepatitis appears to resolve spontaneously in most cases, usually within the first year of life, although in rare circumstances, it can progress to liver failure necessitating transplantation. In infants with resolved NICCD, features of CTLN2 may develop in later years; hence, ongoing health surveillance into adulthood is essential.

Glycogen storage disease

Glycogen storage diseases (GSD) are due to defects of glycogen synthesis or breakdown with resultant abnormal storage and mobilisation of glycogen. They have a number of subtypes, each with a specific enzyme defect. The liver and/or muscle may be affected. GSD type Ia/b and type III are most commonly encountered locally, but GSD type IV, VI and IX, which are less common, can also involve the liver, with varying severity of liver dysfunction, hepatomegaly, hypoglycaemia, hyperlipidaemia and lactic acidaemia. Dietary management to prevent hypoglycaemia is the mainstay of treatment. Surveillance for hepatic adenomas is important, as patients are at a risk of malignant transformation. Certain subtypes such as GSD type IV and IXb/c may be associated with more severe liver dysfunction that can progress to cirrhosis and portal hypertension.[26] Liver transplantation is indicated for progressive liver failure, symptomatic multiple hepatic adenomas, hepatocellular carcinoma or failure to achieve metabolic control. Successful long-term outcome with improvement in metabolic control in GSD type 1 has been documented following liver transplantation in Singapore.[27]

Genetic disorders

Alagille syndrome

Alagille syndrome is an autosomal dominant condition arising from mutations in either JAG1 (95% of cases) or NOTCH2 (5% of cases), with an estimated frequency of 1 in 30,000.[28] This syndrome is rare in Singapore, with a new case diagnosed every four to five years. Features include cholestasis with paucity of intralobular bile ducts on histology, cardiac disease (peripheral pulmonary stenosis), skeletal anomalies with butterfly thoracic vertebrae, posterior embryotoxon seen on slit-lamp examination of the eyes and characteristic facies (triangular face, prominent forehead, deep-set eyes, small-pointed chin). There is a lack of genotype-phenotype correlation in Alagille syndrome, and clinical manifestations may vary in affected members of the same family. Management of a child with Alagille syndrome involves alleviation of pruritus, monitoring and treatment of dyslipidaemia, optimisation of nutrition and provision of fat-soluble vitamin supplementation. Liver transplantation is reserved mainly for advanced or decompensated cirrhosis or for patients with poor quality of life from intense/refractory pruritus. Genetic counselling and family screening are important, particularly to accurately assess the risk in further children.

Progressive familial intrahepatic cholestasis

Progressive familial intrahepatic cholestasis (PFIC) is a group of rare genetic conditions that affect bile metabolism and transport. Four genes have been previously identified to be implicated in PFIC, namely FIC1 (PFIC1 or Byler's disease), ABCB11 (PFIC2), MDR3 (PFIC3) and TJP2 (PFIC4). More recently, mutations in NR1H4 and MYO5B that manifest as PFIC-phenotype have also been identified. All PFIC subtypes present with low gamma-glutamyl transferase cholestasis in infancy, with the exception of PFIC3. The diagnosis of PFIC is now aided by gene panels using next-generation sequencing technologies. Management involves the use of ursodeoxycholic acid, alleviation of pruritus with medications or surgical biliary diversion, and optimisation of nutrition. Liver transplantation is indicated for progressive liver disease, which will be curative for PFIC types 2, 3 and 4. In PFIC1, extrahepatic manifestations (diarrhoea, pancreatitis, sensorineural deafness), which are the hallmark of this subtype, may worsen after transplantation.[28]

Maralixibat is a novel, potent inhibitor of the apical sodium-dependent bile acid transporter/ileal bile acid transporter on the luminal surface of ileal enterocytes, which has shown early promise in alleviating pruritus as well as in improvement/normalisation of liver biochemistry in patients with PFIC.[29] Singapore is currently the only site from the Asia Pacific region that is participating in a worldwide, multicentre randomised-controlled phase 3 study to evaluate the efficacy and safety of Maralixibat in the treatment of patients with PFIC.[30]

Neonatal hepatitis in pre-term infants and multifactorial liver injury

Pre-term infants are at a risk of developing cholestasis owing to immaturity of the hepatobiliary system, exacerbated by other events such as hypoxia, prolonged fasting, parenteral nutrition, drug toxicity and sepsis.[31] In a local study examining the causes of early-onset neonatal cholestasis before 14 days of life, secondary multifactorial liver injury was the most common cause. This liver dysfunction was observed to resolve typically within three months in all surviving infants with supportive management.[32]

LIVER DISORDERS PRESENTING IN OLDER CHILDREN

Viral hepatitis

Hepatitis B virus (HBV) infection is the commonest viral hepatitis in Singapore. Although Singapore is in an endemic region for HBV infection, the HBV carriage rate is relatively low, at 5%–6%.[33] Chronic HBV infection is defined as having positive serum HBsAg for more than six months and is strongly associated with the risk of hepatocellular carcinoma (HCC), even in the paediatric age

group. Individuals infected perinatally are more likely to develop chronic HBV infection (90%) than those infected in adulthood (1%). A local study by Chan et al during the pre-vaccination era in the early 1980s showed a vertical transmission rate of 48% from HBsAg carrier mothers to their infants.[34] In a separate study by Quak et al, the prevalence of HBsAg carriers among infants in Singapore was 8.9%.[35] With the introduction of universal HBV vaccination for all newborns in Singapore since 1987 and the use of passive immunisation with HBV-immunoglobulin for infants born to HBeAg-positive mothers, vertical transmission rates have reduced tremendously, with protection rates of up to 90%–98% achieved.[36] Lee et al reported that the overall rate of failure of vaccine immunoprophylaxis in term infants delivered by HBV-carrier mothers in Singapore was low at 2.7%, with no difference in failure rates between monovalent and combination (monovalent plus combination '6-in-1') HBV vaccines.[37] Another similar local study reported adequate antibody response in preterm infants of HBV-carrier mothers using a three-to-four dose (depending on birth weight) HBV vaccination schedule.[38]

Chronic HBV infection in children is generally a mild disease, and is marked by four phases: (1) immune tolerant phase, characterised by normal liver enzymes, high HBV DNA levels, positive HBe and HBs antigens; (2) immune clearance phase, characterised by active liver inflammation with increased liver enzymes, decline in HBV DNA levels and seroconversion to anti-HBe antibodies; (3) inactive carrier phase, with low/undetectable HBV DNA levels, normal liver enzymes and positive anti-HBe antibody; and (4) reactivation phase, which occurs in 5% of anti-HBe-positive children, which leads to increase in HBV DNA levels and development of HBeAg-negative active hepatitis.

The main goals of therapy are to prevent disease progression and reduce the risk of cirrhosis and HCC. HBsAg clearance, however, is difficult to achieve with the current treatment options. Guidelines recommend that treatment should be considered in children with persistently elevated alanine transaminase (>1.5 times the upper limit of normal) for at least six months, and in those with high HBV DNA levels.[36] Drugs used for treatment of chronic HBV in children include interferon-alpha and nucleos(t)ide analogues such as lamivudine, entecavir, adefovir and tenofovir, each with specific minimum-age cut-offs. The challenges with HBV treatment option are the need for regular subcutaneous injections and the side effects associated with interferon-alpha, and an indefinite treatment duration and risk of antiviral resistance in relation to the use of nucleos(t)ide analogues. Locally, we have observed that spontaneous HBe seroconversion occurs in about 30% of children in the second decade of life, and we continue to maintain a relatively high threshold to initiate treatment for children with chronic HBV infection. Other viral hepatitis (hepatitis A, C and E) cases are relatively rarer among children in Singapore.

Autoimmune liver disease

Paediatric autoimmune liver disease (AILD) can be classified into two types: classical autoimmune hepatitis (AIH) and the AIH-sclerosing cholangitis overlap syndrome (or autoimmune sclerosing cholangitis, ASC).[39] These are progressive inflammatory liver disorders that are associated with positive auto-antibodies and raised immunoglobulin G. Two types of AIH are recognised: AIH type 1 with positive antinuclear antibody (ANA) and/or smooth muscle antibody, and AIH type 2 with positive anti-liver/kidney microsome (anti-LKM) and/or anti-liver cytosol type 1 antibodies. AIH-1 affects children and adults, whereas AIH-2 affects younger children and has a more fulminant presentation. ASC is significantly more common in children than in adults, and is usually characterised by concomitant features of AIH, sclerosing biliary disease on histology ('small-duct disease') and/or cholangiogram, and a strong association with inflammatory bowel disease. The prevalence of AIH in Singapore was reported to be 4 per 100,000 children.[40] Low et al described a series of 10 Singaporean children (six female) with AIH with a median age of five years, of whom seven had AIH-1 and three had ASC, and the majority were in biochemical remission.[41]

First-line management for both AIH and ASC is immunosuppressive treatment with prednisolone, and azathioprine is commonly added as a steroid-sparing agent. For patients who do not respond to first-line treatment, mycophenolate mofetil and calcineurin inhibitors may be used. Ursodeoxycholic acid is also added to the treatment for patients with ASC. Children with AIH who respond to immunosuppression have a good long-term prognosis. ASC is associated with worse outcome because of progression of bile duct disease that does not respond to immunosuppressive treatment.[39] Lee et al retrospectively reviewed children with primary sclerosing cholangitis and ASC in association with inflammatory bowel disease from Malaysia and Singapore, and reported that after a median follow-up period of 4.7 years, 75% of the children showed active persistent disease and 12.5% progressed to liver failure.[42] Progression to cirrhosis and end-stage liver failure is an indication of liver transplantation. Recurrence of AIH is a recognised complication after liver transplantation.

Wilson disease

Wilson disease is caused by mutations in the ATP7B gene encoding a copper-transporting ATPase that is involved in copper excretion in the bile. Progressive accumulation of copper in the liver and other organs such as the central nervous system, cornea and kidneys leads to a wide range of clinical manifestations. Children present with liver diseases ranging from asymptomatic, incidental finding of abnormal liver biochemistry to acute hepatitis, hepatomegaly or acute liver failure. Neuropsychiatric symptoms usually develop later, from the second decade of life. Pathognomonic Kayser-Fleischer rings may be detected on slit-lamp examination but are usually more common in children with central nervous system involvement. Coombs-negative haemolytic anaemia has also been found to be associated with this condition. Diagnosis is suspected when serum caeruloplasmin is low and 24-hour urinary copper excretion is elevated at baseline and/or exceeds 25 μmol/24 hours after penicillamine challenge. Liver copper content on a biopsy tissue is not routinely measured because of lack of facility to perform this test in Singapore. Liver

histology may show increased copper deposition on rhodamine staining; however, this is neither a sensitive nor specific feature. In recent times, diagnosis of Wilson disease is preferably confirmed by mutation analysis of the ATP7B gene, which can also be used to screen asymptomatic family members.

Treatment is based on reduction of excess copper. This can be achieved by zinc salt, which acts by blocking intestinal absorption of copper, or copper-chelating agents such as D-penicillamine and trientine. Copper-chelating therapy could carry a risk of worsening of neurological symptoms. Avoidance of copper-rich food (shellfish, nuts, chocolate, mushrooms, organ meats) is advised until remission of disease is achieved.[43]

Non-alcoholic fatty liver disease

In recent years, non-alcoholic fatty liver disease (NAFLD) has emerged as the most common chronic liver disease, affecting a quarter of the global population, and has become one of the leading indications for liver transplantation in adults.[44] The prevalence of obesity in Asian countries has been increasing over the past three decades, and the current prevalence rates of NAFLD in China, Japan, India and Korea range between 25% and 40%.[45] Childhood obesity is seeing a similar trend, with increasing global prevalence in recent decades. The prevalence of overweight/obese children in Singapore is estimated to be 12.0% among primary school students and 10.5% among secondary school students.[46] Given its close association with obesity, it is expected that the incidence of NAFLD in children has correspondingly increased. Based on our personal experience, the volume of referral of new paediatric cases of NAFLD to the gastroenterology/liver clinics has been steadily increasing in the past two decades. In addition to sedentary lifestyle and dietary habits, other risk factors found to be associated with NAFLD include diabetes and insulin resistance, male sex and genetics factors such as PNPLA3 polymorphisms.[47]

NAFLD is usually asymptomatic, and patients typically present as part of screening because of obesity or because of an incidental finding on liver biochemistry or abdominal imaging ordered for other indications. Even so, it has been shown that the NAFLD in children appears to be more severe than that in adults, with 15% of children having stage 3 fibrosis or higher at diagnosis.[48] Owing to an earlier onset, NAFLD in children may represent an aggressive phenotype of the disease compared with adult-onset NAFLD. Hence, screening for NAFLD in at-risk children (those with obesity, metabolic syndrome or a family history) is recommended, as detection before the onset of irreversible, end-stage liver disease is crucial. At the same time, before arriving at a diagnosis of NAFLD, clinicians should exclude other causes of hepatic fatty infiltration and/or elevated liver enzymes such as viral hepatitis, metabolic disorders, Wilson disease and use of hepatotoxic medications. Increasingly more paediatric centres are adopting the use of vibration-controlled transient elastography, a technique well-validated in adults with NAFLD, as a noninvasive tool to assess liver fibrosis.[49]

Management is centred on lifestyle modification to improve diet and increase physical activity, with weight loss as the main goal. Asian data support a 7%–10% weight loss target, although there is evidence to suggest that NAFLD can improve with 3%–5% weight reduction.[45] With regard to pharmacologic therapy, there has been research interest in the use of various medication and supplements such as Vitamin E, metformin, ursodeoxycholic acid, docosahexaenoic acid and probiotics in the management of paediatric NAFLD. However, no medication or supplement has been shown to be of significant therapeutic value.[48] Bariatric surgery has been shown to improve obesity and diabetes as well as reduce hepatic steatosis and fibrosis in adults.[50] However, owing to limited data in paediatrics, bariatric surgery is not recommended as a specific therapy for NAFLD, although it may be considered for selected adolescents with BMI >35 kg/m^2 who have noncirrhotic NAFLD and other serious comorbidities such as diabetes or sleep apnoea that may improve with weight loss surgery.[48]

Acute liver failure

Paediatric acute liver failure (PALF) is a rare but life-threatening condition characterised by hepatocellular necrosis and rapid deterioration in liver function in the absence of a pre-existing chronic liver disease.[51] The aetiology of PALF varies widely depending on the age of the child, and geographic and socioeconomic factors. Viral hepatitis A and B are reported to be the major causes of PALF in Asia, whereas indeterminate or seronegative hepatitis is the most common cause in Western populations.[52] Mortality rate without a liver transplant can be as high as 70%. Medical management of PALF is focused on supportive care, prevention and treatment of associated complications, investigation of the cause and provision of disease-specific treatment if a treatable cause is identified. Liver transplantation is a life-saving procedure in fulminant PALF in which spontaneous recovery does not occur despite medical therapy. In regions where shortage of size-matched deceased-donor organs remains a challenge, particularly in Asian countries such as Singapore, living-donor liver transplantation is an important and viable option, with comparatively favourable outcomes.[53,54]

A recent study in Singapore comprising 34 children with PALF found that the top three aetiologies were indeterminate (41.2%), metabolic disorders (26.5%) and infectious (26.5%).[21] In fact, no cases of hepatitis A of B infection causing PALF were observed. Spontaneous recovery was observed in 38.2% of the patients, and the overall mortality rate was 47.1%. Out of six patients who underwent living-donor liver transplantation, five (83.3%) survived at one year after transplantation.

CONCLUSION

The liver is involved in many critical metabolic processes in the body. A single defect, mutation or impairment affecting any of these pathways can lead to significant downstream effects on liver function as well as other organ systems, giving rise to an extremely wide and varied spectrum of paediatric liver disease. The current technological advances in diagnostics and constant improvements in therapeutic options in paediatric hepatology

will allow us to maximise the long-term outcomes and quality of life of children with liver disease in Singapore.

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Evolution and expansion of newborn screening programmes in Singapore

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ABSTRACT In Singapore, the newborn screening programme was started in 1965 in order to reduce the high neonatal mortality and neurological morbidity owing to severe hyperbilirubinaemia caused by erythrocyte glucose-6-phosphate dehydrogenase deficiency. About 25 years later, the national newborn screening for congenital hypothyroidism was established. Subsequently, universal newborn hearing screening and screening for multiple inborn errors of metabolism using tandem mass spectrometry were introduced as national programmes in 2003 and 2006, respectively. All these programmes are widely accepted as standards of care, and practically every newborn is screened despite the absence of any legislation. Two other evidence-based bedside screening tests, namely pulse oximetry screening for critical congenital heart disorders and physical examination of the hips for developmental dysplasia of the hips with selected ultrasonographic screening have been widely performed in hospitals, and they are soon expected to be in the national screening programmes.

Keywords: G6PD deficiency, hearing impairment, hypothyroidism, inborn errors of metabolism, neonatal screening

INTRODUCTION

In 1963, mass newborn screening to detect phenylketonuria was conducted in America by Dr Robert Guthrie, the father of newborn screening.[1] The method of collecting heel-stick blood samples on filter paper was simple and showed good sensitivity, establishing the feasibility of conducting mass newborn screening. Almost all the affected children were managed with dietary treatment to prevent developmental retardation. Newborn screening in Singapore was started in 1965, wherein the umbilical cord blood was screened to detect erythrocytic glucose-6-phosphate dehydrogenase (G6PD) deficiency to prevent mortality as well as neurodevelopmental morbidity due to severe hyperbilirubinaemia.[2]

The huge success of these programmes fuelled enthusiasm to extend screening for other disorders. In 1975, Dussault et al[3] reported a method of screening for congenital hypothyroidism (CH). Within 15 years, in 1990, screening for CH was established in Singapore. Nationwide screening for hearing impairment (HI) and screening for inborn errors of metabolism (IEM) using tandem mass spectrometry (TMS) were introduced in 2002 and 2006, respectively.[4] Current neonatal screening includes screening for disorders detectable by not only invasive blood collection for analysis of the samples but also bedside clinical testing. These include pulse oximetry screening for critical congenital heart disorders and screening for developmental dysplasia of the hips (DDH).

Neonatal screening for G6PD deficiency, CH, HI and IEM form one prong of a multipronged National Health Policy for the prevention of neurodevelopmental delay and mental retardation. All these programmes are widely accepted as standards of care, and practically every newborn is screened despite the absence of any legislation or national funding. The screenings are hospital based, and an advisory committee is periodically convened by the Ministry of Health (MOH) to consider developments in neonatal screening from a national perspective. In this article, the lessons learned from experience with the various neonatal screening programmes, the issues that have arisen and the future possibilities of further expansion of screening are described.

SCREENING FOR G6PD DEFICIENCY

In Singapore, severe hyperbilirubinaemia resulting in kernicterus used to be the leading cause of neonatal mortality and neurodevelopmental disability in the 1950s and 1960s. A clinical study revealed that the aetiology of severe hyperbilirubinaemia was secondary to haemolytic crisis due to red cell G6PD deficiency in 43% of the cases and liver immaturity in 25% of the cases.[2,5,6] In 1964, the Kernicterus Surveillance Programme was introduced, and in the subsequent year, a mass newborn screening programme for G6PD deficiency was started. This initiative was highly successful in Singapore, and thereafter, deaths from kernicterus decreased substantially from 150 in 1950s to just five in the late 1980s. The G6PD screening programme has been well established, with very high social acceptance. Since the 1990s, kernicterus has virtually been eradicated from Singapore.[5-7]

G6PD is an X-linked enzyme, and its deficiency is one of the most frequent hereditary abnormalities. Screening for G6PD is performed by quantitative measurement of red cell G6PD activity

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in umbilical cord blood. The tests are performed at the hospital at birth and the results are usually available within 12 hours. Initially, infants with G6PD deficiency are kept in the hospital for 21 days after birth for close observation and treated with phototherapy in the presence of significant jaundice. Parents are educated regarding the consequences of the abnormality and the triggers that precipitate haemolysis. The G6PD status is recorded in the health book of the infant, and written information in the form of a booklet containing the details about G6PD deficiency is provided to the parents. Screening has revealed an overall incidence of 1.6%–2.5%, with a 3.15% incidence in males and 0.11% in females. A distinct ethnic variation in the incidence has also been reported among male infants (Chinese 3.94%, Malays 2.95% and Indians 0.66%), and intermediate deficiency (1.83%) has been identified in Chinese female infants.[4,8] Three common molecular variants have been identified among the Chinese in Singapore, and six different variants have been identified among Malays.[9]

The practice of prolonged stay in the hospital, which emerged during the Kernicterus Surveillance Programme, continued for about three decades. Hospital stay was subsequently reduced to two weeks of inpatient stay, after the establishment of several primary care outpatient centres (polyclinics) in the country.[4,10,11] Experience and clinical studies conducted in the local population revealed that two clinical syndromes occur during the neonatal period in babies with G6PD deficiency: haemolytic jaundice with severe hyperbilirubinaemia occurring mainly during the first week of life and non-haemolytic hyperbilirubinaemia with lower levels of serum bilirubin but prolonged jaundice occurring in the absence of haematological evidence of haemolysis. The latter is probably due to co-existence of Gilbert's syndrome.[12] Studies have also shown that significant hyperbilirubinaemia usually occurs only during the first week of life, and infants who do not develop haemolytic jaundice during the first week are unlikely to develop it during the second week of life in the absence of trigger exposure.[4] Moreover, as high as 43%–55% of infants with G6PD deficiency never develop hyperbilirubinaemia. Parents are also less keen for their babies to stay in the hospital for more than a few days in the absence of significant jaundice requiring phototherapy. By early 2000, scientific evidence encouraged paediatricians and neonatologists to cautiously reduce the duration of hospitalisation to seven days. Since the last decade or so, babies without risk factors and those without significant jaundice in the first three days are discharged on Day 4 of life. [10,11,13] After discharge, these infants are closely monitored for jaundice and anaemia on an outpatient basis, either in the polyclinic or hospital, for two to three weeks.

This early discharge strategy for high-risk infants has been observed to be safe and has also reduced the social, emotional and financial burden of G6PD deficiency in Singapore. Moreover, in accordance with baby-friendly initiatives, breastfeeding and maternal-infant bonding have been facilitated, without any reported case of bilirubin-induced encephalopathy resulting in kernicterus. However, babies with G6PD deficiency should not be considered as low-risk infants; monitoring for jaundice, watchfulness and education of the parents must be continued by the younger generation of specialists and doctors.

SCREENING FOR CONGENITAL HYPOTHYROIDISM

Screening for CH in Singapore began in 1981 as an 18-month pilot research study in Kandang Kerbau Hospital, the then largest maternity hospital, where about 50% of the national births occurred.[14] The success of the programme and the experience gained led to its establishment in 1985 as a standard service at the National University Hospital (NUH). In 1990, it became a national programme.[15]

Cord blood was used for the screening, because this was already being collected for screening of G6PD deficiency. Another reason was that the majority of newborns were discharged from hospital within 48 hours of birth. Initially, the pilot programme used an isotope-based T4 supplemental thyroid-stimulating hormone (TSH) strategy. With the advent of enzyme immunoassays, the strategy changed to a primary TSH strategy, which has continued till today. The TSH cut-off for recall has been set at the 99th centile. This corresponded with a TSH value of 23 mIU/L. Babies who screen positive have a T4 measurement on the original cord serum specimen and are recalled for evaluation between Days 3 and 5. Those with extreme values are evaluated earlier. CH was diagnosed if serum TSH values remained > 20 mIU/L in the first week of life and the T4 values were below the age-specific mean. Prior to initiating treatment, radiography of the knee to assess bone age and radioisotope thyroid scan were performed whenever feasible. We found that in the majority of our patients, a starting dose of 25 mcg of thyroxine (8 mcg/kg/day) was sufficient to bring both the TSH and the fT4 values into the normal range within about two weeks of instituting therapy. With this strategy and threshold, permanent CH was being diagnosed at a rate of about one in 3,000 births.[16,17]

However, screening for CH has faced some challenges over the years. The first is attributable to the use of at least three different TSH analysers across the different hospitals in Singapore. Each analyser has a reference range that is slightly different from that of another. In a recent comparison, the range between the analysers was about 4 mIU/L at the 99th centile. This difference makes it necessary for cut-offs to be analyser specific and, by itself, is not technically difficult. However, it creates difficulties when parents compare the TSH values of their babies or when healthcare professionals have to evaluate a TSH value without knowing the analyser that was used. In order to unify the differences in the TSH analysers, the cut-off for the cord serum TSH value was revised to ≥ 25 mIU/L in the year 2000. In an audit conducted between August and December 1996 on a sample population of 145,843 newborn infants from the three restructured hospitals, 62 cases of CH were detected by the primary cord blood screening programme. This yielded an incidence of one in 2,350 births, with a female preponderance (sex ratio 2:1). Technetium isotope study of the thyroid revealed ectopia in 52% of the cases, eutopia in 33% of the cases and agenesis in 10% of the cases.

Osseous maturation was delayed in 75% of the cases, signifying fetal onset of hypothyroidism. Follow-up study showed that about 20% of the infants who were initially diagnosed as having CH and treated had only transient hypothyroidism, and thyroxine could be weaned off between 2.5 and 3 years of age.

The second challenge arose from the global observation that not every newborn with CH can be identified using any single strategy or cut-off value. The current understanding is that 10%–15% of CH cases may not be identified. In a recent local unpublished analysis, it was found that, in a screened population of about 12,000 newborns, nine babies with CH were identified using a TSH cut-off of 25 mIU/L. Two additional cases were identified when the physician in charge decided to investigate babies with a TSH value that was slightly lower than the 99th centile (24.6 mIU/L and 24.9 mIU/L). This meant an almost 20% difference in incidence, which was significant.

It should be noted that central CH and delayed-onset primary CH many not manifest as biochemical abnormalities during the first few days of life and may, therefore, be missed by our screening methodology. Moreover, none of the existing newborn screening strategies can identify all cases of CH, and hence, if any infant presents with clinical signs suggestive of hypothyroidism (such as prolonged jaundice, constipation, hypothermia, hypotonia, poor feeding, macroglossia, large anterior fontanelle or open posterior fontanelle), thyroid function tests (TSH and fT4) need to be performed urgently, even if cord blood screening yields normal results.

The third challenge arises from the recognition that the primary TSH measurement does not screen for central CH, a much rarer condition with highly variable fT4 and TSH values in the newborn period. This issue was previously explored when the national programme was being developed. It showed that the strategy of measurement of T4 and TSH markedly increased the number of babies that were recalled but did not yield a case of central CH.[15] Use of fourth-generation analysers along with thyroxine-binding globulin assays in the Netherlands has generated practical and feasible outcomes.[18]

The fourth challenge is the need to establish age-specific and local reference ranges in the first two weeks of life for the new generation of TSH and fT4 analysers. The Perinatal Society of Singapore, in collaboration with the College of Paediatrics and Child Health, has set up a professional group to study the above issues and propose national-level solutions. These are expected by the end of the year.

Early and adequate treatment of CH in infants have shown excellent prognosis for growth, puberty and neurodevelopmental outcomes, and disappearance of intellectual disabilities with intelligence quotient (IQ) < 70. Grosse et al[19] reported that the mean global IQ of patients identified early was 10–30 points higher than that of patients in the pre-screening stage. Cognitive outcome has been correlated with the age of onset of therapy, thyroxine dose, compliance with medication and the parents' socio-educational status.[20,21] However, despite early diagnosis by neonatal screening and treatment, subtle defects in sensorimotor function, memory deficits and reduced hippocampal volumes have been reported in children and adolescents, which have been correlated with the severity of CH at birth.[22] By contrast, the cognitive and behavioural defects in infants with delayed diagnosis and treatment depend on the severity of CH and the time taken to achieve biochemical euthyroidism.

SCREENING FOR HEARING IMPAIRMENT

Hearing is closely linked to speech and language development. Even mild to moderate levels of hearing loss (HL) can lead to changes in the brain.[23] Evidence-based research supports that early identification and subsequent intervention within the first six months of life are critical to realise the benefits of early experience with language and sound.

In the past, students with severe HI used to receive their primary education in the School for the Deaf or the Canossian School for the Deaf. These students required eight years to complete their primary education instead of the usual six, and they also scored lower than their normal-hearing peers did in the Primary School Leaving Examination.[24] The median age at diagnosis of HI was 20.8 (range 0–86) months. Hearing aids were fitted at a median age of 42.2 (range 1–120) months. A greater delay in intervention was associated with poorer academic outcomes. Late diagnosis of congenital HI can result in significant delays in speech, language, and intellectual, social and emotional development.

Congenital HI is one of the most common disorders worldwide. In Singapore, the incidence of HI of any severity is 3–4 per 1,000 infants. HI is not a visible condition at birth; most children with congenital HL are born to normal-hearing parents and have no health issues or risk factors for HL.

The pilot screening for HL in newborns began in a restructured hospital in 1995.[25] In 2000, a study on the early detection and intervention of HI among children in Singapore recommended that a national Universal Newborn Hearing Screening (UNHS) programme was highly feasible and required a software programme for tracking.[26] The UNHS programme was started in 2002 in KKH as a Health Service Development Programme (HSDP) funded by the MOH, and became a fully paid service in KKH and a national programme in 2003.

The UNHS programme aimed to screen 95% of all infants by one month of life and to diagnose and provide intervention for HI by six months of life, in keeping with the recommendations by the Joint Committee of Infant Hearing of the American Academy of Pediatrics.[27] Guidelines on the establishment of the UNHS programme were reported by Lim and Daniel in 2008.[28] The UNHS is now implemented in all Singapore hospitals with obstetric service; hence, most infants born locally would have been screened, unless an infant was very unwell or the parents declined the screening. Congenital HI is detected by two methods, namely the automated auditory brainstem response (AABR) and otoacoustic emission (OAE) tests; both these methods are noninvasive. AABR detects neurosensory defects and has a lower repeat rate than OAE does; however, the former is more expensive and may require a longer time to complete.

All hospitals in Singapore follow a two-step protocol, and any infant that does not pass the second screen would be referred to

the otolaryngology department for further evaluation. KKH and Singapore General Hospital (SGH) use the AABR screen for all newborns; at-risk infants also undergo OAE screening. NUH uses the OAE screen for all their newborns, and their at-risk infants also undergo AABR screening. Most private hospitals also follow the two-step protocol using AABR or OAE. A hearing screening can be done as early as six hours of age, which allows for re-screening of some infants later during their hospital stay. This inpatient re-screening of an infant with a 'refer' result has been shown to reduce the chance of false positive results.[29] The outpatient re-screen is done 3–6 weeks after discharge, and any child with poor emissions is referred to the otolaryngology department for further evaluation of any HI.

Although the UNHS programme recommends that all newborns should be screened for HI after birth, some infants are more susceptible to HI. These at-risk categories are listed in Box 1; these infants should undergo a high-risk hearing screen (HRHS) at 3–6 months of life to identify late-onset HI. Daniel and Lim[30] highlighted the importance of the HRHS in combination with the UNHS programme to show the true incidence of HI in infancy. They showed an increase in incidence of HI from 2.8 per 1,000 with just the UNHS to 3.7 per 1,000 with both the UNHS and HRHS. The incidence is even higher in the neonatal intensive care unit (NICU). Jayagobi et al[31] investigated HI among infants in the NICU and found that the incidence of congenital permanent HI was 15.4 per 1,000 infants, based on the UNHS programme. This incidence increased to 19.9 per 1,000 with the HRHS.

Data from KKH from January 2010 to December 2019 showed that 116,495 infants (99.9% of all eligible infants) underwent the UNHS. Of these, 1,162 (1%) were referred to the otolaryngology department for further evaluation and, to date, we have detected 376 (42.6%) infants with HL, yielding an incidence of HI of any severity of 3.2 per 1,000 infants. Severe profound HI was observed in 1.6 per 1,000 infants. 60.4% of the infants with HI had sensorineural HL and 3.5% of the infants had mixed HL. 55% of these infants had bilateral HI. Hearing aids were fitted for 150 infants. 25 infants with bilateral severe profound HI who did not adequately benefit from hearing aids and auditory-verbal therapy went on to have cochlear implants. 56 infants were medically treated for conductive HI, whereas 38 infants were surgically treated as well. A post-UNHS implementation study showed that the median age at diagnosis of HI was 4.8 (range 1–24) months. Hearing aids were fitted at a median age of 7.6 (range 2–45) months.[32] The hearing screening programme in Singapore has not only allowed for the diagnosis and early intervention of congenital HI in a considerable number of infants, thus providing them an opportunity for development of normal speech and language, but has also shown the value of repeat screening in high-risk infants.

The latest guidance on childhood developmental screening announced by the MOH on July 2020[33] has acknowledged the UNHS programme. It advises all clinicians to ensure that the UNHS result is checked in the health booklet upon the infant's first visit, in order to ensure that the child has passed the hearing screen or to decide whether the child should be referred for further evaluation.

Box 1. Risk factors during infancy for hearing impairment or progressive hearing loss in childhood;

1. Family history of permanent childhood hearing loss
2. Neonatal intensive care for more than five days, or any of the following regardless of the length of stay: ECMO, assisted ventilation, exposure to ototoxic mediations (gentamicin and tobramycin) or loop diuretics (furosemide/Lasix) and hyperbilirubinaemia that requires exchange transfusion
3. *In utero* infections such as CMV, herpes, rubella, syphilis and toxoplasmosis
4. Craniofacial anomalies and temporal bone anomalies
5. Syndromes associated with hearing loss or progressive or late-onset hearing loss, such as neurofibromatosis, osteopetrosis and Usher syndrome; Waardenburg, Alport, Pendred, and Jervell and Lange-Nielsen syndrome
6. Postnatal infections associated with sensorineural hearing loss, including confirmed bacterial and viral (especially herpes virus and varicella) meningitis

The best indication of the success of the UNHS programme in Singapore was the closure of the Singapore School for the Deaf in 2017 owing to its 'dwindling enrolment'. This is attributable to the medical advances in screening, early diagnosis and provision of assistive devices, which has enabled most children with HI to hear well enough to attend mainstream schools.

SCREENING FOR INBORN ERRORS OF METABOLISM

Expansion of newborn screening by tandem mass spectrometry

In Singapore, prior to 2005, newborn screening was available for G6PD deficiency, hypothyroidism and HL. The development of electrospray ionisation tandem mass spectrometry (MS/MS) in the 1990s was critical in the expansion of newborn screening. A single dried blood spot test is applied for the simultaneous screening of a number of disorders, including amino acidopathies, fatty acid oxidation disorders and organic acidaemias. The primary and secondary disorders that the screening programme aims to detect are shown in Table I.

After much deliberation, in 2004, the National Newborn Advisory Committee approved the proposal to expand newborn screening to include IEM using TMS. In 2005, a Health Service Development Programme (HSDP 04/X03) Award was given to evaluate and implement newborn screening for IEM by MS/MS. This was done through a collaborative partnership among KKH, NUH and SGH.

A successful screening programme requires careful planning and integration of a comprehensive infrastructure involving education, screening, follow-up of abnormal results, diagnosis, treatment/management and evaluation of the system. Prior to the commencement of the pilot programme at KKH, a team comprising a senior neonatologist, paediatric metabolic specialist, scientific officer and medical technologist was sent to Adelaide, South Australia to be trained at the South Australian Neonatal Screening Centre for about a month.

Table I. List of primary and secondary targets of the expanded newborn screening programme by tandem mass spectrometry.

Group of disorders	Medical condition
Primary targets*	
Amino acid disorders	Phenylketonuria including biopterin defects Maple syrup urine disease Citrullinaemia type 1 Argininosuccinic aciduria Tyrosinaemia type 1 Homocystinuria (pyridoxine unresponsive)
Organic acid disorders	Propionic acidaemia Methylmalonic acidaemia (MUT) Cobalamin A/B Isovaleric acidaemia β-ketothiolase deficiency Glutaric acidaemia type 1 Malonic aciduria 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency Multiple carboxylase deficiency
Fatty acid oxidation disorders	Primary carnitine deficiency/Carnitine uptake deficiency Medium-chain acyl-CoA dehydrogenase deficiency Very-long-chain acyl-CoA dehydrogenase deficiency Long-chain hydroxy acyl-CoA dehydrogenase Trifunctional protein deficiency
Secondary targets†	
Amino acid disorders	Hyperphenylalanine Argininase deficiency Citrin deficiency Hypermethioninaemia Tyrosinaemia Types 2 and 3
Organic acid disorders	3-Methylcrotonyl-CoA carboxylase deficiency 2-Methyl-3-hydroxy butyric aciduria 3-Methylglutaconyl-CoA dehydratase deficiency Isobutyryl-CoA dehydrogenase deficiency 2-Methylbutyryl-CoA dehydrogenase deficiency/ short branch chain acyl-CoA Ethylmalonic encephalopathy Cobalamin C/D
Fatty acid oxidation disorders	Carnitine palmitoyltransferase deficiency type 1 Carnitine palmitoyltransferase deficiency type 2 Carnitine-acylcarnitine translocase deficiency Multiple acyl-CoA dehydrogenase deficiency/glutaric aciduria type 2 Short-chain acyl-CoA dehydrogenase deficiency Medium-/Short-chain hydroxy acyl-CoA dehydrogenase deficiency Medium-chain ketoacyl-CoA thiolase deficiency

**Conditions that the programme aims to detect. †Conditions that may be identified while investigating abnormal results for the primary targets*

Education

The initial challenge for the pilot programme in attracting private hospitals was a lack of knowledge of IEM and scepticism regarding the prevalence of these disorders in the local population. Correspondingly, there was a lack of interest among the general public and health professionals. In response, the team developed and printed information brochures in three languages; released educational videos; and conducted seminars for the health professionals, public and media.

Moreover, we also introduced and taught proper collection of dried blood spots to healthcare professionals. Our guidelines called for all infants, regardless of gestational age and feeding status, to have their samples taken for screening at more than 24 hours of age. Further, we had a premature newborn (< 36 weeks) protocol, which was adapted from the Clinical and Laboratory Standards Institute's guidelines.[34] It required the collection of three specimens — the first sample at 24–72 hours, second sample at two weeks of life and third sample at four weeks of life.

The pilot programme: a preview of the population disease distribution and frequency

The expanded newborn screening programme based at KKH started in the public hospitals in July 2006 and progressed in phases to include the private sector. To encourage participation in the public hospitals, a subsidised cost scheme for participation in the pilot programme was instituted. During the pilot phase, between July 2006 and July 2010, 61,313 newborns were screened. A total of 20 newborns were diagnosed with a variety of IEM (three medium-chain acyl-CoA dehydrogenase deficiency, one carnitine uptake defect [CUD], one very long-chain acyl-CoA dehydrogenase deficiency, one short-chain acyl-CoA dehydrogenase deficiency, three 3-methylcrotnyl carboxylase deficiency [3-MCC], two glutaric acidaemia type I, one citrin deficiency, one methylmalonic acidaemia, one cobalamin C metabolism defect, one ornithine transcarbamylase deficiency, one 6-pyruvoyl-tetrahydropterin synthase deficiency, and four maternal conditions – one 3-MCC, one vitamin B_{12} deficiency, two CUD), yielding a detection rate of one in 3,000.[35]

Since its implementation until December 2020, the IEM screening programme has screened 404,227 newborns across Singapore. A total of 131 true positive cases were detected, of which 47 were organic acidaemias; 44 were fatty acid oxidation disorders; 23 were amino acidopathies; and 17 were assorted cases of maternal deficiencies of vitamin B_{12}, 3-MCC and primary carnitine. The detection rate of IEM in Singapore is one in 3,158 live births, which is similar to the detection rates reported in other countries. Of note, this test is not efficient in screening for citrin deficiency, an amino acid disorder prevalent in the local and Asian population. The overall sensitivity and specificity of this test are 85% and 99.9%, respectively. The cumulative positive predictive value and recall rate for retests are acceptable (26% and 0.1%, respectively). The current participation rate of all birthing hospitals (private and public) is 92% of the annual live births.

Laboratory support and clinical follow-up team

The NBS MS/MS programme is supported by a rapid-response centralised confirmatory/diagnostic testing laboratory and a rapid-response team of metabolic specialists. The close collaboration between the screening laboratory and the two metabolic services located at KKH and NUH ensured that patients are seen within 24–48 hours of referral and that the same methodologies are used in evaluating the patients. In our experience of over 100 cases, more than 97% of presumptive positive patients were evaluated by a metabolic specialist within seven days of birth. Of these, 92% were clinically asymptomatic and another 4% had mild symptoms. After the clinical evaluation, samples were collected for confirmatory testing. Treatment was initiated if appropriate and necessary, and genetic counselling was also offered.

Evaluation of the system in the centralised laboratory

From the outset, we formulated a protocol for patient referral and follow-up, and established a laboratory quality system for both the MS/MS screening and diagnostic testing platforms. This ensured a robust and quick turnaround time in patient care. Our participation in the Collaborative Laboratory Integrated Reports programme helps us to evaluate our performance metrics (positive predictive value, false positivity rate, sensitivity, specificity) against those of other international programmes in Asia, Asia Pacific, Europe and America. Critical indicators are monitored and evaluated via external laboratory proficiency testing and assessment schemes such as CDC (Center for Disease Control and Prevention) and ERNDIM (European Research Network for evaluation and improvement of screening, Diagnosis and treatment of Inherited disorders of Metabolism).

Expanding the scope of testing in the newborn screening panel

In October 2019, we expanded the scope of testing to include five more disorders in the newborn screening panel, namely congenital adrenal hyperplasia, biotinidase deficiency, severe combined immunodeficiency syndrome, galactosaemia and cystic fibrosis.

This was accomplished in a partnership with PerkinElmer to establish KKH as a Centre of Excellence for Newborn Screening. Through this partnership, new laboratory equipment and instrumentation (Genetic Screening Processor, Victor EnLite) were introduced and validated in a pilot programme to screen for the disorders. In preparation for the launch, we expanded and recruited additional specialists (in the departments of endocrinology, respiratory and immunology) in the follow-up teams at both metabolic services at KKH and NUH. Recent one-year data (n = 35,888) since the launch of the newly revised panel showed positive screens in detecting congenital adrenal hyperplasia (one case), biotinidase deficiency (one case) and several cases of T-cell lymphopenia (three syndromic, two unresolved, four resolved) that were not related to severe combined immunodeficiency syndrome. The recall rate for the five tests was 0.04%–0.34%, with cystic fibrosis having the highest recall rate. The laboratory is currently fine-tuning the parameters and algorithms to further reduce this recall rate.

PULSE OXIMETRY SCREENING

Critical congenital heart defects (CCHD) are the most serious form of congenital heart defects; these require invasive intervention or they could result in death within the first year of life. The incidence of CCHD is 2–3 per 1,000 live births.[36] Pre-symptomatic diagnosis of CCHD has been shown to improve mortality and morbidity. The initial feature of mild hypoxaemia that is present in most cases of CCHD may not be clinically discernible. Screening using pulse oximetry has been found to be beneficial, cost-effective, safe and simple to perform. Many centres worldwide have included pulse oximetry in their newborn screening programmes.

The primary targets for pulse oximetry screening are hypoplastic left heart syndrome, pulmonary atresia, tetralogy of Fallot, total anomalous pulmonary venous return, transposition of great arteries, tricuspid atresia and truncus arteriosus.[37] Other cardiac defects that less consistently cause hypoxia in newborns may also be detected.

A meta-analysis of 19 studies with almost 440,000 patients reported that pulse oximetry had a 76.3% sensitivity, 99.9% specificity and a false positivity rate of 0.14% for detection of CCHD.[38] In another meta-analysis, the sensitivity of postnatal physical examination alone for the detection of CCHD was 53%; however, the sensitivity improved to 92% when physical examination was combined with pulse oximetry screening.[39] It has been estimated that pulse oximetry screening, in combination with antenatal ultrasound and postnatal physical examination, can identify 92%–96% of infants with CCHD.[40] State-wide implementation of mandatory pulse oximetry screening in the US has been associated with 33.4% reduction in early infant cardiac deaths, compared with the rate in states without these policies.[41]

Between 27% and 77% of the false positives have significant non-CCHD pathologies that require immediate treatment or follow-up, such as respiratory conditions (e.g. persistent pulmonary hypertension, congenital pneumonia, transient tachypnea of newborn, pneumothorax, meconium aspiration syndrome), sepsis and non-critical cardiac defects.[36] The detection of these cases allows for early management, and therefore, they are sometimes regarded as secondary targets of pulse oximetry screening.

The false positivity rate is higher (0.42%) when screening is performed within 24 hours of birth compared with after 24 hours of birth (0.06%).[38] Although early screening with higher false positivity rates may increase the number of investigations, it helps in earlier detection of significant non-CCHD pathologies. The lower false positivity rates with later screening have to be balanced against the risk of deterioration before screening. These are important considerations in the settings of early discharge before 24 hours of life and in home births, in which pulse oximetry screening has been found to be feasible.[42]

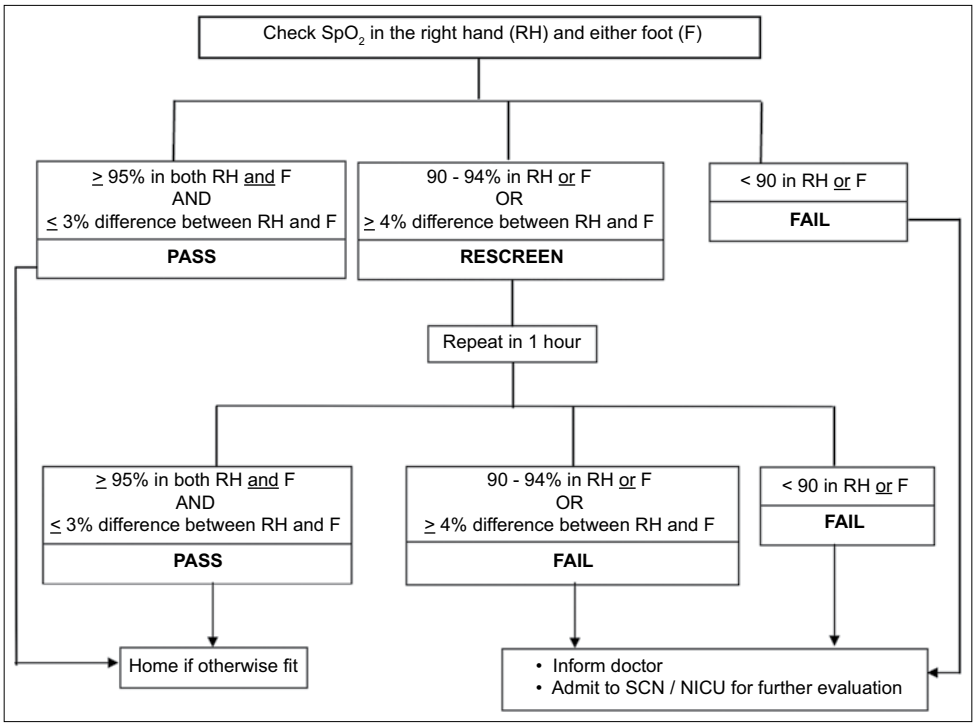

Fig. 1 Pulse oximetry screening algorithm at KK Women's and Children's Hospital.

Sensitivity and specificity did not differ significantly between screening with pre- and post-ductal measurements versus post-ductal measurements alone.[38] Although post-ductal screening alone is easier and quicker, it may miss conditions such as transposition of great arteries with reverse differential cyanosis. It is well established that left heart obstructive lesions are most commonly missed, with or without pulse oximetry screening. The addition of perfusion index measurement may improve the sensitivity of pulse oximetry screening for these lesions.[43]

Pulse oximetry screening was implemented at KKH in June 2014 (Fig. 1).[36,37] Nursing staff were trained to perform the screening during routine caregiving. All infants admitted to the well-baby nurseries are screened between 22 and 36 hours of life, and again prior to discharge if they remain inpatients beyond the first screening day. Neonates in the NICU and special care nursery are not included in the screening, as they are monitored by continuous pulse oximetry. In the first year, most of the 10,295 infants screened passed the first screening, and 0.07% of infants passed the repeat screening after a 'rescreen' result. One infant that passed the screening was diagnosed with coarctation of the aorta on physical examination on the same day. No infants failed screening in the first year.

To date, no CCHD has been detected through screening of asymptomatic infants in the well-baby nurseries at KKH, but infants with non-CCHD pathologies have been detected. We postulate that effective prenatal ultrasound screening combined with good postnatal monitoring contributed to the lack of detection of CCHD through pulse oximetry screening. Pulse oximetry is now considered a screening test for general well-being in apparently healthy-looking infants.

In Singapore, pulse oximetry screening has been implemented widely and has become a national programme. Considerations prior to implementation include prenatal detection rates, access to cardiology service and expertise in performing echocardiograms within individual settings. An individualised screening algorithm that strikes a good balance between detecting a serious condition and minimising false positive results is important.

SCREENING FOR ORTHOPAEDIC DISORDERS

The orthopaedic and neonatology departments should work very closely to ensure timely screening of orthopaedic conditions at birth. This will ensure the use of effective early interventions that are relatively noninvasive. The orthopaedic conditions that are screened at birth include DDH, clubfeet and primary muscular torticollis.

Developmental dysplasia of the hips

DDH is one of the common concerns encountered in paediatric orthopaedics. The definition of DDH includes dislocated, dislocatable or dysplastic hips diagnosed by imaging modalities. The cause of DDH remains largely unknown, although an interplay of genetic and ethnic factors has been found. Most developed countries report an incidence of 1.5 to 20 per 1,000 births. The variation is attributable, in part, to differences in diagnostic methods and the timing of evaluation.[44]

Infants with the following features have been considered to be at a higher risk for DDH: first born, female gender, breech presentation, positive family history and conditions associated with 'packaging disorders' of the uterus.[44] The observed natural history of DDH includes leg length discrepancy, gait abnormalities, chronic hip pain and early osteoarthritis.[44]

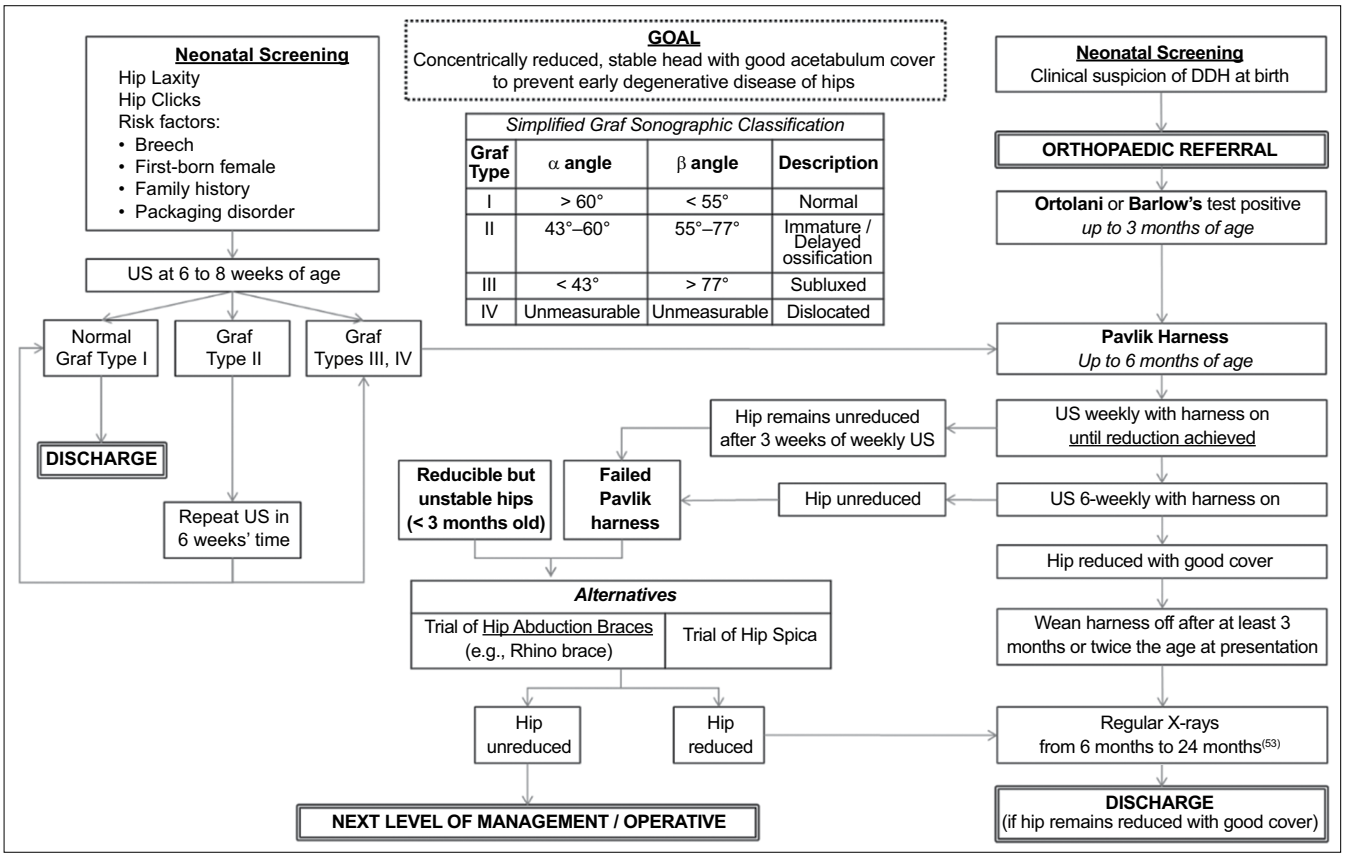

Fig. 2 Screening and management protocol for developmental dysplasia of the hips (DDH) at KK Women's and Children's Hospital.

In KKH, selective screening is practiced, in that only infants with a high risk for DDH with normal clinical findings at birth undergo the DDH ultrasound protocol, as described by Graf, at six to eight weeks.[45] All other neonates undergo the routine head-to-toe screening by the neonatologist shortly after birth, and if they are found to be Ortolani- or Barlow-positive, they are referred to the paediatric orthopaedic surgeon while still in the hospital. Once the findings are confirmed, treatment is immediately started with a Pavlik harness, as detailed in the protocol in Fig. 2. This protocol has evolved with the collaborative efforts of the orthopaedic, neonatal and diagnostic imaging departments. A local study conducted in 2015 showed that institutionalised newborn clinical screening appears to be the single most important factor for the prevention of late presentation of DDH, which leads to open surgery.[46]

Clubfeet

The incidence of congenital talipes equinovarus, commonly known as clubfoot, is estimated at 1–2 per 1,000 live births,[47,48] with variation in its global incidence, according to a 2014 estimate by the Global Clubfoot Initiative.[49] It has a male predominance, with a male-to-female ratio of 2:1.[50] Bilateral involvement is observed in 30%–50% of the cases.[51]

Clubfoot is another common condition that is screened at birth and treated early. This is especially important owing to the very short window of opportunity it presents to ensure good results. Once a structural clubfoot has been confirmed after referral by the screening neonatologist, serial manipulation casting by the Ponseti method[52] is started as early as possible, usually on Day 2 of life. Subsequent weekly casting and manipulation follows until clinical milestones are reached, as spelled out in the protocol. While the details of the protocol are beyond the scope of this article, screening and early intervention are crucial for achieving a success rate of over 95%, i.e. for the feet being fully corrected.

Primary muscular torticollis

While it may not be obvious at birth, early detection and screening of this condition by looking at risk factors such as the 'packaging disorders' is important. If this condition is missed at birth, it is mostly picked up at the well-baby clinic at around three months, when the child begins to develop head and neck control.

Early intervention would involve a series of physiotherapist-supervised stretches of the affected sternomastoid muscles. This helps to avoid long-term secondary effects of facial asymmetry, which can be difficult to reverse once the child is older. It has also been shown that physiotherapy is most effective below the age of one year, rendering the screening of this condition all the more important.

FUTURE DIRECTIONS

There is a need to establish a national Newborn Screening Centre in Singapore with full-time dedicated staff to take over the organisation, audit, bench-marking, quality assurance and

further development of screening. In future, screening could be made available for some of the other countries in the region, especially Indonesia, Brunei, Vietnam, Myanmar, Laos and Cambodia. Advances in molecular genetics have revealed that markers of degenerative diseases, namely obesity, diabetes mellitus, hypercholesterolaemia, systemic hypertension and ischaemic heart disease are present during the newborn period. The rapid advancement of technology has also made genomic screening on a single blood spot feasible. The potential benefits of such initiatives would be early identification and intervention, which may result in prevention or delay in the presentation of these diseases that have public health concerns in Singapore. However, more research is warranted to determine the sensitivity and specificity of these molecular and genetic markers and their predictive values. Moreover, the social, ethical, insurance and legal issues related to such screening strategies need to be addressed before embarking upon such initiatives.

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Evolution of postgraduate medical education in paediatrics: the Singapore story

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ABSTRACT Postgraduate paediatric education in Singapore has seen a seismic shift in the past 50–60 years, from a primarily time-based, passive, teacher-centric and apprenticeship model with hierarchical learning culture to a competency-based and learner-centric one. The postgraduate medical education system in paediatrics in Singapore will continue to evolve and adapt with best practices in evidence-based medical education, with the aim to train and develop the next generation of paediatricians who will strive to continually improve child and population health in Singapore.

Keywords: accreditation, competency-based medical education (CBME), paediatrics, postgraduate medical education, specialist training

INTRODUCTION

Postgraduate paediatric education in Singapore has seen substantial developments and changes since the establishment of 'formal' paediatric care in Singapore in 1921 at what we now know as Singapore General Hospital (SGH), when it first started to provide inpatient medical care for children. This evolution is especially evident in the past 50–60 years, with the setting up of the Mistri Wing in 1955 at SGH, which was the first ever dedicated children's hospital unit in Singapore.[1]

HISTORICAL CONTEXT

Singapore is a former British colony that gained full independence in 1965. Albeit the small size (728.3 sq. km) of our city-state, it has a population of 5.7 million people primarily concentrated in urban areas. Through the government's vision to make Singapore a global centre for international trade and commerce, Singapore has, in a relatively short time-frame, transformed from a developing to a developed country, with one of the most cost-effective and efficient healthcare systems in the world.[2]

Singapore's historical British roots and colonial past have played a significant role in the development of medical education here. Under British colonial rule, local graduates were not actively encouraged to undertake formal postgraduate training. This situation changed with the inauguration of the Singapore Academy of Medicine in 1957, which promoted specialisation and encouraged postgraduate study overseas to develop local expertise and training capacity.[3,4]

A STEP IN THE RIGHT DIRECTION

The School of Post Graduate Medical Studies was first established in 1970; this school was responsible for awarding the Master of Medicine degree for all the key specialties, as well as the accreditation of subspecialties.[5] In the same year, the first local Master of Medicine in Paediatrics was started.

In the 1960s and 1970s, specialist postgraduate paediatric training did not begin immediately after medical graduation. After graduation from medical school, all doctors were required to do a one-year internship/housemanship at one of the government hospitals. Thereafter, these young doctors were often tested in the real-world clinical environment as medical officers before they embarked on pursuing a career in specialist training of their choice and preference. Postgraduate medical training then was very much of the 'see one, do one, teach one' type, being an apprenticeship-style model of medical education. This was almost always time based, and there was no formal or structured training curriculum. Much of the teaching and learning happened 'on-the-job'. After completing the stipulated months of clinical attachments within the accredited departments at the public teaching hospitals in Singapore and passing the required clinical examinations, one could technically practice as a specialist.[6]

It was not until the 1990s that an initial advanced training programme was formalised. The Advanced Paediatrics training formally started in 1991, overseen by the Joint Committee of Specialist Training. The duration of this advanced training was three years. The primary focus on training then was on medical knowledge, patient care and communication skills. Over the subsequent years, a more formal curriculum was established and other training requirements were introduced to further enhance clinical training. Briefly, this training programme, known as Basic Specialist Training (BST), commenced a year after the compulsory housemanship year. BST normally lasted for a minimum of three years, during which all trainees were required to maintain a logbook record of their work and training. BST concluded with a high-stakes summative clinical examination, the Master of Medicine (MMed) in Paediatrics (the local Master of Medicine (MMed) in Paediatrics [Singapore] was awarded as a conjoined qualification with the MRCP [UK] [Paediatrics], the Membership of the Royal College of Physicians UK, Faculty of Paediatrics in 1997. Subsequently, in the year 2000, the local Master of Medicine [MMed] in Paediatrics was awarded as a conjoined qualification with the MRCPCH [UK], the Membership of the Royal College of Paediatrics and Child Health). This was

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followed by the three-year Advanced Specialist Training, which culminated in another high-stakes summative examination, the Exit Examination, which was a viva examination.[6] Paediatrics subsequently moved from Basic Specialist Training and Advanced Specialist Training to seamless training in 2008.

While this model of training had fulfilled its purpose during the late 2000s, it had become clear to the local health ministry and medical educators that the ground was shifting, and that there was an urgent and pressing need for postgraduate medical education reform owing to multiple factors, including but not limited to significant proportions of the workforce practicing without formal postgraduate training or qualifications.[3] There was also an urgent need to balance the requirement for service provision and training, and the need for greater supervision and a more formal training structure and curriculum. A shift from a time-based, teacher-centric model to a competency-based, learner-centric one was imperative.

ACGME-I AND COMPETENCY-BASED MEDICAL EDUCATION (CBME)

The United States (US)-based Accreditation Council for Graduate Medical Education (ACGME) was approached by the Ministry of Health (MOH) to oversee the external accreditation of postgraduate medical education at all public hospitals in Singapore in the latter half of the 2000s. A formal letter of agreement establishing the relationship between the ministry and ACGME-International (ACGME-I) was signed in 2009, and a vice president for accreditation services was appointed to lead ACGME-I later that year.[7]

In 2010, Singapore became the first country outside the US to adopt a training structure based on the ACGME Core Competencies framework and seek accreditation by the same council. Paediatrics was one of the first seven specialties that received a mandate from the MOH to redesign its postgraduate medical education structure to meet the standards of the newly constituted ACGME-International. This educational reform marked a dramatic departure from the traditional process-based curriculum in Singapore that, for many years, had emphasised content delivery (medical knowledge and patient care) and relied heavily on workplace-based global ratings and high-stakes summative assessments to ensure competence.[8,9]

The ACGME-International Competency-Based Medical Education (CBME) framework and curriculum focused on the assurance of a set of six core competencies,[10] namely patient care, medical knowledge, interpersonal and communication skills, professionalism, practice-based learning and improvement, and systems-based practice.

This new US-style system presents a more structured programme with clearly defined core competencies, greater documentation of supervision from the designated faculty, more rigorous formative assessments and feedback sessions, and a stipulated protected time for learning. Overall, this demanded greater accountability as well as documentation from both trainees and educators, while producing significant numbers of trainees who had completed the programme requirements.[11] With the adoption of the ACGME-I CBME framework, a protected time for training was introduced. Programme directors and core faculty members were also accorded protected time for their educational and administrative roles.

This era of CBME has brought forth numerous advantages, including but not limited to protected teaching time, maximum allowable duty hours worked, greater breadth of training and training in other aspects relevant for paediatric practice (such as evidence-based medicine, learning how to teach and team leadership skills).

Currently, the postgraduate residency training in paediatrics in Singapore is a seamless training programme spanning over a minimum of six years, and is targeted at developing a General Paediatric Specialist.[12] This consists of a basic training component, the Junior Residency (JR) years, which last for three years (R1 to R3). By the end of R3, an intermediate exam, the Master of Medicine (MMed) in Paediatrics (Singapore), must be successfully completed. The JR training is accredited by the ACGME-I. This is followed by the advanced training component, the Senior Residency (SR) years, which is also a three-year course (R4 to R6). The SR years culminate with the undertaking of the Paediatrics Exit Examination, a viva-style examination. In addition to the minimum years of training, as outlined above, in the true spirit and ethos of CBME, all Residents have an additional three years to complete their training and satisfy all the training deliverables and requirements.

Subspecialty training requires additional training time and requirements to be fulfilled, depending on the particular subspecialty. Currently, six paediatric subspecialties are recognised for Accreditation in a Paediatric Subspecialty, namely Neonatology, Cardiology, Haematology and Oncology, Nephrology, Gastroenterology and Hepatology, and Intensive Care. Other paediatric subspecialties are expected to follow suit in the near future.

In terms of postgraduate examinations, in addition to the previously mentioned Master of Medicine (MMed) in Paediatrics and the Paediatric Medicine Exit Exam, all JRs are required to appear for the annual In-Training Exam, a US-based Boards-style multiple-choice question (MCQ) exam, during their three JR years. Further, all SRs are required to pass the Postgraduate Examination (PGE) in Paediatric Medicine, either before or after the Exit Examinations, in order to successfully complete training as a Paediatric Specialist. The PGE is a hybrid MCQ exam, which includes the American Board of Paediatrics exam questions for Paediatrics as well as other questions more relevant to the local Singapore context.[13]

At the time of writing this manuscript, the Specialist Accreditation Board had recently approved the phasing out of the PGE, with the 2021 diet being the last exam sitting. The PGE will no longer be a pre-requisite for completion of training as a Paediatric Specialist. From January 2021, the PGE has been replaced by a robust Competency-Based Assessment (CBA) framework to continue to monitor and evaluate the performance of SRs to assess their readiness for independent practice as a paediatric specialist.

LOOKING AHEAD TO THE FUTURE

Singapore Health Services and National University Health System are the only two sponsoring institutions (SI) in Singapore that have a Paediatric Residency Training Programme.

To foster a spirit of national collaboration in paediatric training, cross-cluster rotations between the two SIs were introduced for SRs since January 2020. Unfortunately, with the Covid-19 pandemic and infection control measures, this had to be temporarily halted. We hope to restart this in the next academic year.

Much has happened in more than 10 years since the adoption of the ACGME-I and CBME model in postgraduate paediatric education in Singapore. There is a need to review and take stock of our journey so far. Our local Singapore national medical regulatory and training bodies have embraced CBME. At a national level, we need to not only continue to leverage on the strengths and advantages of CBME, but collectively, as a group, to also look ahead to the future to review and adapt this to best meet our unique local needs in Singapore.

Our local Singapore national medical regulatory and training bodies have taken the lead on this and are now playing a more direct and active role in the shaping of postgraduate paediatric education (as well as other medical specialties) in Singapore, hence setting the course for the future. The paediatric postgraduate community in Singapore is excited at this opportunity to review and further enhance the current CBME model with the introduction of Entrustable Professional Activities,[14] with an emphasis on CBAs.[15,16]

At the coalface, a mixed formative and summative approach to workplace-based assessment, and careful selection of assessment tasks and methods is currently practised to align the learning activities with our planned graduate outcomes, with effective consolidation and transformation of the 'old' and 'new' systems of postgraduate medical education. This has met with practical success in another local Singapore residency programme.[8]

CONCLUSION

The only constant in life is change. There has been a seismic shift in the postgraduate paediatric education system in Singapore from the time of our city-state's independence up to and including the present moment. We have gone from a system that was primarily a time-based, passive, teacher-centric, hierarchical learning culture and apprenticeship model to one that is primarily competency-based and learner-centric. While much good work has been done, the postgraduate paediatric education system in Singapore continues to evolve and adapt with best practices in evidence-based medical education, with the aim to train and develop the next generation of paediatric specialists in Singapore, who will be advocates for optimal child and population health in Singapore and empowered to continually improve the health and well-being of all children in Singapore.

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Adapting undergraduate paediatric medical education to the challenges of COVID-19 pandemic: perspective of NUS Medicine

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ABSTRACT COVID-19 significantly impacted the teaching-learning-assessment activities in many medical schools. In this article, we discuss the impact of COVID-19 on the Yong Loo Lin School of Medicine, National University of Singapore, focusing on paediatric training and the adaptations of the system and the people. The school developed strategies to promptly disseminate information and safety measures to protect all its staff and students. By leveraging on the school's infrastructure for technology-enabled learning, good-quality medical training and reliable assessments were able to be carried out swiftly. The paediatric curriculum was crafted based on these principles, and it provided distance-based learning with live and interactive sessions to teach core clinical skills. The faculty also tapped on standardised patients to provide consistent and life-like scenarios. Measures were implemented to minimise challenges with technology-enabled learning. Collectively, efforts from the staff, support from the leadership and students' adaptations tremendously helped to ease the transition.

Keywords: COVID-19, medical school, paediatric, undergraduate

INTRODUCTION

It has been more than a year since COVID-19 was first reported in Wuhan, Hubei Province, China.[1] This contagious viral illness has spread wildly within a short period of time, affecting many countries. As of 28 March 2021, there have been 126,359,540 confirmed cases of COVID-19 and 2,769,473 deaths reported to the World Health Organization (WHO).[2] Within a few weeks of identifying the first COVID-19 case in Singapore, the Disease Outbreak Response System Condition (DORSCON) level was raised from Yellow to Orange.[3] This had a major impact on the teaching-learning-assessment activities in the medical school. Student activities in clinical settings had to be limited, and clinical assessment formats had to adopt different platforms. In this article, we discuss the impact of the COVID-19 pandemic on the Yong Loo Lin School of Medicine, National University of Singapore (NUS Medicine), with a special focus on paediatric training. In addition, we share how the medical school adapted to this change, the challenges faced and the strategies used to mitigate the effects of the pandemic.

IMPACT OF COVID-19 PANDEMIC ON NUS MEDICINE

The COVID-19 pandemic had led to changes in the following six broad areas of the school.

1. A centralised system of management

The Education Team Contingency Workgroup was set up to develop strategies based on the new policies issued from the school or government bodies. The aim was to ensure business continuity while maintaining the safety of the staff. These strategies and their implementation had to be disseminated to all staff appropriately, accurately, transparently, consistently and in a timely manner.

Prioritising safety for all stakeholders

New measures were put in place to safeguard the school from COVID-19. These measures focused on early detection and reduction of the risk of widespread transmission. All staff and students were expected to take ownership of monitoring their health via documenting their temperatures, reporting to the central administration when ill, taking medical leave when necessary, etc. Split team work arrangements were implemented for the staff. There were restrictions on crossing to other healthcare institutions. NUS Medicine also had to exercise additional measures to achieve a high level of cleanliness so as to prevent the spread of the virus.

Transparency and consistency in information dissemination

Considerable effort was made by NUS Medicine to ensure that information dissemination was prompt, transparent, consistent and accurate. Apart from the strategies mentioned above, the information also included guidelines from government bodies, frequently asked questions and the number of infected cases on campus. One way of disseminating information was through an initiative by the school – the COVID-19 chronicles.[4] The

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chronicles were short educational cartoon strips, whereby key information on COVID-19 was disseminated to all NUS staff and students.

Leveraging on technology to deliver good-quality training

Prior to the outbreak, NUS Medicine had maintained the necessary infrastructure for technology-enabled teaching. This was particularly valuable when the size of gathering allowed decreased and during the circuit-breaker period, when no one was allowed on campus. We were able to swiftly move large-group non-clinical teaching online. As the COVID-19 restrictions eased, small-group teachings (involving fewer than 50 participants) were held face-to-face, while adhering to strict safety measures and regulations.

As the pandemic spread, clinical rotations were halted in February 2020. This mainly affected the Phase III students, who had completed only three out of their four clinical rotations (Phase IV students were on their elective period, and the final-year Phase V students had completed all their clinical rotations). The Phase III students were given a two-week break so that the faculty could replace the clinical teaching in their final clinical rotation with other forms of teaching. The availability of technology, standardised patients as well as a simulation centre enabled us to create this entirely new curriculum within two weeks. This new curriculum included elements such as pre-recorded online lectures, online live lectures, online live tutorials conducted via Zoom or Microsoft Teams, online live case-based learning, online self-directed learning using programmes such as Aquifer and simulation-based teachings. As COVID-19 improved over time, for the academic year beginning in June 2020, clinical postings were resumed, but only at 50% of their usual duration and with rigorous movement restriction and other safety measures. The other half of the time remained as campus-based learning, as described above.

Maintaining the rigour and quality of assessments and examinations

Conduction of continuous assessments was facilitated by the fact that we had gone online for all our clinical posting assessment forms. This meant that admin staff could work from home as they did not have to collect and process hard copy forms. Use of the online e-assessment forms also meant that we reduced the risk of the hard copy forms being fomites.

Conducting exams during the COVID-19 outbreak was a huge challenge, especially the graduating class' final MBBS exams in March 2020. The school was committed to conducting this exam, as it had the responsibility of providing 300 new graduates for the healthcare service, which was anticipated to come under duress in the event of a large COVID-19 outbreak. Fortunately for us, all our theory exams were already conducted on an e-exam system for several years. It was not too difficult for us to de-centralise and simultaneously conduct the theory exams at multiple sites, with each hosting up to only 50 persons while maintaining physical distancing, social distancing and many more safety measures.

The final-year clinical exams were held in NUS, as it was a non-clinical institution. Real patients were replaced with standardised patients (SPs), simulators and task trainers. We were able to do this as we had built these resources over the years. Student briefings, examiner briefings and exam team briefings were conducted online. Students, examiners, SPs and the exam team were assembled into small groups with minimal cross movement. Many other safety measures were put in place. The final-year exams were conducted without sacrificing the number of exam stations and without incurring a single COVID-19 infection. It probably did cause the exam team members to grow more white hairs. We did cancel the Phase II and Phase III clinical exams. However, the Phase III clinical exam would be replaced with a formative exam at the end of the Phase IV school term.

Adaptations of the school admission exercise

The 2020 admissions exercise was also affected. Under strict regulations, with no cross-campus movement of healthcare workers during this period of time, the number of assessors to invigilate the admission exercise was adversely affected. Therefore, the number of stations during admission exercise was reduced from five to two to accommodate this change. The admission process also moved online, leveraging on the technology that was available to us.

ADAPTATIONS OF UNDERGRADUATE PAEDIATRIC MEDICAL EDUCATION

The academic year 2020 (starting in June 2020) was meant to be the launch of the new Phase IV paediatric curriculum for NUS Medicine. The paediatric education team of NUS, NUH and KKH had spent many months planning and implementing this new curriculum. With the institution of the 50% reduction in clinical training and no cross-institution movement, all this preparation work was gone with the wind. Over a two-month period, we had to build yet another new curriculum for the paediatric posting in Phase III, Phase IV and Phase V. We had to figure out how to teach about 900 in-flight students while complying with the strict restrictions and lack of clinical patients.

With the clinical exposure halved, we needed to figure out how to use the home-based learning time to make up for the loss of clinical learning. We distilled the clinical skill sets that we thought we could still try to teach while the students were doing home-based learning. This has been summarised in Box 1.

We recognised that home-based learning meant that we could not help the students develop their tactile skills, e.g. experiencing how an enlarged liver feels like. Hence, we emphasised to the students that during their clinical weeks, they had to make all effort to touch and examine patients. We also ensured that they had clinical tutors during their clinical posting. The physical distancing and social distancing measures meant that we could not send the students to the usual places, as it would result in overcrowding. Thus, we used resources that we traditionally did not use for medical students, e.g. patients were seen in the clean areas of the paediatric emergencies.

Box 1. Clinical skill sets for home-based learning

History-taking: We developed online live history-taking sessions with simulated patients (SPs). Students would log into their sessions and take history from SPs, who were trained in certain scenarios. After the session, the students would receive learning materials about the expected points to be covered during that session. They would approach their core tutor in case of any concerns or questions.

Communication skills: After the above-mentioned history-taking session, the SPs would provide real-time feedback to each student.

Physical examination techniques: We taught the students the sequence of the examination techniques and also supplied video references.

Picking up signs visually: We incorporated pictures and videos into our teachings.

Picking up signs audibly: We provided videos and sound tracks of respiratory sounds. We also provided sound tracks of heart sounds and murmurs.

Problem-based approach and clinical reasoning: Almost all our teaching sessions involved live interactive teaching and were case-based. The tutors interacted with the students as they walked through a case while it unfolded. The teaching method was aimed to help the students develop a problem-based approach and clinical reasoning.

Clinical decision-making: Almost all our teaching sessions involved live interactive teaching and were case-based, with questions on what clinical decision the students would make in the specific scenarios.

Emergency management: We had online live teaching on red flags, how to recognise emergencies, how to manage them and how to provide first aid.

Covering cases that students would not be allowed to see: We were mindful that even when the students returned to the clinical space, with the COVID-19 restrictions, they would not be allowed to be near febrile children, coughing children, children with runny noses, etc. As such, we ensured that these bread-and-butter cases were covered in our case-based learning and were supplemented by videos that showed physical signs such as respiratory distress.

We also recognised that COVID-19 and the consequent changes to the medical education can add to the academic as well as psychological stress of the students. We were also cognisant that this situation could make the weaker students more vulnerable to failure. Hence, we instituted the role of the core tutor. This is elaborated in the next section.

ADOPTION AND CHALLENGES OF DIGITAL MEDICAL EDUCATION

Responding to the changes in the curriculum and social distancing measures, a new teaching role that utilised distance-based learning (DL) was created. Faculty members were invited to be core tutors and they were to journey alongside the students for the entirety of their paediatric posting (two weeks for Phase III, six weeks for Phase IV and three weeks for Phase V) by meeting with the students every week but via an online platform, usually Zoom or Microsoft Teams. For Phase IV and Phase V, each clinical group was assigned two core tutors. The core tutor was to be a mentor and counsellor for the students in case any of them were facing academic difficulty or psychological stress because of the modified curriculum. The online meetings were also used to assess and cover learning gaps. The meetings tended to be longer when the students were learning from home and shorter during their clinical weeks, and they were sometimes conducted during the students' lunch hour.

The core tutors found that the consistent contact with the students was useful in obtaining a more holistic view of the students' strengths and weaknesses. The general feedback from the students on the core tutor sessions was good, and they wished that some sessions could have been face-to-face. They liked the informal nature of the sessions and that they were given the chance to clarify their doubts and ask questions.

DL is a form of technology-enabled learning that has been progressively incorporated into undergraduate medical education over the years.[5,6] However, this pivot towards DL was sudden and huge; it posed some challenges to both tutors and students, as follows. The foundation of DL was dependent on the adoption of digital skills such as online content creation or video conferencing and the provision of technological equipment, including laptops and webcams.[7] Many tutors were required, at short notice, to learn these digital skills, be adept in them and to apply them during their online teaching sessions. Some of the impediments faced were the lack of resources to learn the digital skills or the lack of guidance on how to conduct DL.[8] This was probably more difficult for the senior tutors who conducted only traditional face-to-face teaching or those who were less familiar with digital learning.[9] Fortunately, most doctors were quick learners and could adapt, albeit with a steep learning curve.

A major limitation of DL vis-a-vis face-to-face teaching was the lack of bedside patient interactions.[10] The art of medicine revolves around doctor-patient interactions, and many core skills, such as history-taking and physical examination, require the student to physically interact with the patient. Therefore, DL could not totally replace all critical bedside skills.[11] The downstream impact would likely be the greatest for the Phase III students, as their opportunities to accrue these clinical skills in their first major clinical year were significantly curtailed. To minimise these limitations, many measures were introduced, such as online live history-taking sessions and incorporation of SPs in assessments and exams.

When conducting face-to-face teachings, the tutor often used various sensory modalities to engage with the students, such as body language and intonation. However, not all of these modalities can be created successfully, in partial or in full, during DL sessions, when one is facing a screen. A student might feel socially isolated if there is little or no interaction during DL.[12] With this in mind, the school strongly encouraged online teaching to be interactive. Almost every paediatric home-based learning session was interactive, with questions built into the cases. There were sufficient questions for the tutor to ask at least one question to every student during each session. Owing to the lack of physical presence, tutors also needed to be more aware

of the students' mood by attempting to hear between the lines and read the students' body language through the screens.[13] It was difficult for tutors to identify a struggling student in a large group teaching. Hence, the core tutor concept was implemented to mitigate this.

CONCLUSIONS

NUS Medicine is much more prepared today than it was during the SARS outbreak. The implementation of technology-based teaching and learning, standardised patients, simulators and task trainers had been in place for several years before COVID-19 struck. This allowed the school to adapt quickly and reduce the impact on student learning during the outbreak. While there were some constraints in the initial implementation of these adaptations, many measures were adopted to minimise the impact and many tutors quickly caught on to technology-enabled learning. We were also very fortunate to have a large database of SPs that the school managed to mobilise quickly to assist in teaching as well as in examinations. Most importantly, the collective effort from the staff, strong support from the leadership and students' adaptation to the situation tremendously helped to ease the transition.

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Current status of the early childhood developmental intervention ecosystem in Singapore

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ABSTRACT Childhood developmental-behavioural issues and disabilities have been identified as the major challenges in child health and to the national healthcare system in Singapore. Dealing with these morbidities requires new and innovative approaches that go far beyond hospital-based care into the community, with structured integration of medical services with education, and social and community support, including a strong collaborative partnership with parents and caregivers. A unique child development programme has evolved in Singapore over the last 30 years. Its main objectives are early identification and treatment of children with developmental and behavioural problems so as to correct developmental dysfunctions, minimise the impact of a child's disability or prevailing risk factors, strengthen families and establish the foundations for subsequent development. This paper aimed to provide an update of the current ecosystem, along with a review of the fast-changing landscape in recent years.

Keywords: childhood disabilities, developmental-behavioural paediatrics, early childhood developmental intervention

INTRODUCTION

The early years of a child are a period of considerable opportunity for growth as well as vulnerability of harm. Decades of scientific research have concluded that experiences in the first few years establish a foundation for human development that is carried throughout life.[1] Early childhood intervention can shift the odds towards more favourable outcomes in child health and development, educational attainment and economic well-being, especially for children at risk.

A child development programme has evolved in Singapore over the last 30 years.[2,3] It is a unique nationwide ecosystem, which is inclusive, multidisciplinary, community-based, family-focused and child-centric, with structured integration of medical services with education, and social and community support, including strong collaborative involvement of parents and caregivers. The landscape is fast-changing in recent years, as the government has committed to investing in our children at an early age. Significant progress has been made in the various components of the evolving ecosystem.[2,3]

DEVELOPMENTAL SURVEILLANCE AND SCREENING

Both developmental surveillance and screening are important for early identification and provision of timely intervention to children with special developmental needs. The Second Enabling Masterplan (2012–2016)[4] of the Ministry of Social and Family Development (MSF) recommended strengthening the national developmental surveillance and screening system by establishing a network of early detection touch points in the community, comprising primary healthcare professionals, child care centres, pre-schools and family service centres. The Masterplan also proposed that the Child Health Booklet be used as the main tool for routine developmental surveillance. Every child born in Singapore has a copy of the standardised Health Booklet. The Booklet contains developmental checklists at certain important and sensitive touch points of children, based on our validated Denver Developmental Screening Test, Singapore.[5,6] In the last revision of the Health Booklets, screening items that target early detection of autism have been incorporated in the checklists. In future revision, more touch points for children between the age of two and three years will also be included.

However, developmental screening should not be the sole responsibility of healthcare professionals. The aim is to encourage and empower the parents and caregivers at home to play a central role in monitoring the child's health and development. The information on developmental milestones of a child will also serve as anticipatory guidance for parents and caregivers. This method of developmental surveillance has been extended to involve pre-school educators who will be the caretakers of children once they are in playgroups, nurseries or kindergartens.

An important challenge for developmental surveillance is that children and families with the highest level of possibility of developmental problems are sometimes the least likely to avail the services. Many upstream projects have attempted to identify children and families at risk. The most recent nationwide initiative is the KidSTART programme launched by MSF in 2016 and currently led by the Early Childhood Development Agency (ECDA).

COMPREHENSIVE DEVELOPMENTAL ASSESSMENT

A seamless and hassle-free referral system has been established. The majority of children would come through the polyclinics to the two main assessment centres: Department of Child Development, KK Women's and Children's Hospital (KKH) and Child Development Unit, National University Hospital (NUH),

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Table I. Pattern of developmental problems in pre-schoolers (2010–2014).

Developmental problems	No. of children (%)				
	2010	2011	2012	2013	2014
Autism spectrum disorders	528 (21)	683 (21)	610 (21)	784 (20)	721 (17)
Speech and language delay and disorders	926 (37)	1,168 (36)	970 (33)	1,356 (34)	1,559 (38)
Global developmental delay	298 (12)	369 (12)	448 (15)	566 (14)	471 (11)
Learning problems/disabilities	204 (8)	315 (10)	231 (8)	299 (8)	425 (10)
Behavioural problems/disorders	255 (10)	372 (12)	316 (11)	482 (12)	600 (15)
Attention deficit hyperactivity disorder	66 (3)	48 (1.5)	58 (2)	167 (4)	75 (1.8)
Environment-related delay	141 (5.6)	131 (4)	187 (6)	163 (4)	151 (4)
Motor developmental delay	57 (2.3)	74 (2)	94 (3)	89 (3)	92 (2.2)
Cerebral palsy	13 (0.5)	12 (0.5)	8 (0.2)	8 (0.2)	5 (0.1)
Syndromic disorders	7 (0.3)	25 (0.8)	14 (0.5)	13 (0.3)	14 (0.4)
Impairment of special senses	7 (0.3)	7 (0.2)	11 (0.2)	17 (0.5)	19 (0.5)
Total	2,502	3,204	2,947	3,,944	4,132

Table II. Pattern of developmental problems in pre-schoolers (2015–2019).

Developmental problems	No. of children (%)				
	2015	2016	2017	2018	2019
Autism spectrum disorders	822 (21)	840 (20)	1,031 (21)	1,259 (23)	1,279 (24)
Speech and language delay and disorders	1,445 (36)	1,435 (34)	1,670 (34)	1,965 (35)	1,749 (33)
Global developmental delay	424 (11)	548 (13)	652 (13)	648 (12)	605 (11.5)
Learning problems/disabilities	381 (10)	357 (8.5)	413 (8.5)	409 (7.6)	399 (7.5)
Behavioural problems/disorders	629 (15)	767 (18)	827 (17)	922 (16)	934 (18)
Attention deficit hyperactivity disorder	50 (1.5)	50 (1.2)	71 (1.5)	74 (1.5)	71 (1.3)
Environment-related delay	103 (2.5)	110 (2.6)	98 (2)	121 (2)	103 (2.0)
Motor developmental delay	89 (2.0)	74 (1.8)	99 (2)	119 (2)	91 (1.7)
Cerebral palsy	7 (0.3)	3 (0.1)	7 (0.2)	2 (0.1)	8 (0.25)
Syndromic disorders	11 (0.5)	23 (0.5)	16 (0.4)	19 (0.4)	18 (0.40)
Impairment of special senses	6 (0.2)	13 (0.3)	15 (0.4)	19 (0.4)	13 (0.35)
Total	3,967	4,220	4,899	5,557	5,270

both under the Child Development Programme of the Ministry of Health, Singapore.

The purpose of a comprehensive developmental assessment is to accurately determine a child's developmental status in a number of domains: physical (including vision/hearing and gross and fine motor development), cognition, communication, social-emotional and adaptive. The assessment would attempt to determine the cause(s) of the delay in development. A multidisciplinary team coordinated by a trained paediatrician as the case manager is required to obtain a thorough understanding of the child's unique abilities, namely his weaknesses, strengths, attainment levels and needs. Every assessment should also identify the family's concerns, priorities and resources. Concerns are what family members identify as needs, issues or problems that they want addressed. Priorities allow family members to set their own agenda and makes choices about the involvement of subsequent early intervention in their life. Resources include finances, strengths, abilities and supports that can be mobilised to meet the family's concerns, needs and desired outcomes. Identifying these issues aids the development of early intervention outcomes, strategies and activities that will help families achieve their goals.

PATTERN OF DEVELOPMENTAL PROBLEMS IN PRE-SCHOOLERS

Table I shows the pattern of developmental problems in pre-schoolers seen under the Child Development Programme (both KKH and NUH) from 2010 to 2014. Table II shows the pattern of developmental problems in pre-schoolers from 2015 to 2019.

'Pre-schoolers' include children aged between 0 and 7 years who have not yet been enrolled into either mainstream schools or special schools in Singapore. The numbers only represent the developmental 'problems' seen in these children. A proportion of children with varying needs may require early intervention in the pre-school years and must not be considered as having disabilities.

A fairly consistent pattern of developmental problems can be observed in pre-schoolers. Autism spectrum disorders (ASD), and speech and language delay and disorders together accounted for

53%–58% of the developmental problems. Learning problems/disabilities and attention deficit hyperactivity disorders (ADHD) had not surfaced as major issues in this age range (< 10%). We anticipate that these two problems will emerge to dominate the developmental problems once the children enter primary schools and start to face different academic challenges and demands. Developmental delay, environment-related delay and other behavioural issues accounted for about 30% of the concerns.

Improved perinatal care and expanded nationwide neonatal screening programmes over the past five decades have considerably reduced the number of infants and children born with congenital malformations and those who may sustain significant brain damage during pregnancy or during the peripartum and postnatal periods. This is reflected in the fewer number of cases of cerebral palsy, syndromic disorders (such as Down syndrome) and impairment of special senses (visual and hearing impairment). About 30% of the children with developmental problems were seen before the age of three years and 50%, before they completed four years.

INDIVIDUALISED INTERVENTION PLAN

Development of the individualised management and education plan is based on the information gathered through the assessment of the child and family, directed by the family's concerns, priorities and resources in collaboration with the early intervention team. Any eventual intervention plan would involve the parents as the focal point; hence, their participation in the entire process is of paramount importance. Health services alone will be insufficient in this regard, and strong working relationships and partnerships with social services in the community as well as with schools are warranted. A follow-up evaluation system is in place to monitor the progress of the child and the family so that the management plan can be regularly reviewed and updated through documentation of the adjustments and achievements.

In the child's journey beyond early childhood, the case manager, who is usually the primary care paediatrician, will continue to monitor the progress of the child, support the family and play the important role of advocacy until the child reaches adulthood.

EARLY CHILDHOOD DEVELOPMENTAL INTERVENTION

There is growing evidence that early intervention (EI) can have a substantial impact on children with developmental needs and their families.[1] The goals and outcomes of EI would be to promote development in all important domains; promote child engagement, independence and mastery; build and support social competence; facilitate the generalised use of skills; support families in achieving their own goals; prepare and assist children with normalised life experiences in their families, schools and communities; help children and families make smooth transitions; and prevent or minimise the development of future problems or disabilities.

The five key principles in the design of our current approach to EI are: shifting the decision-making power on caring for the child from the professional to the family (family-centred); shifting diagnosis-based intervention to one that is based on the developmental needs of the individual child; shifting emphasis of intervention from disability to functional and developmental performance, participation and quality of life; shifting the settings of service and care delivery to a less restrictive, more natural and inclusive environment (e.g. childcare centres, pre-schools and schools, homes and the community); and shifting from a multidisciplinary to a transdisciplinary team practice.

The development of children varies considerably owing to a combination of biological and environmental factors. During pre-school years, some children display a level of developmental functioning that is below the functioning of their typically developing peers of the same age. The developmental conditions can range from physical issues, sensory issues, cognitive and learning issues, to behavioural and emotional problems. These children require varying levels of EI support entailing different and/or additional resources beyond what is conventionally available for their typically developing peers.

As the developmental trajectory of these children is still fluid, it may not be possible or desirable to make a confirmatory diagnosis of a specific disability condition. These children are more appropriately classified as children with developmental needs (DN). Among children with DN, some children, even during pre-school years, display functional impairments and disability conditions that can be clearly identified and would likely require specialised targeted provisions and support beyond pre-schools, either in mainstream schools or special education (SPED) schools. This subset of children with DN can be categorised as having special educational needs (SEN). The categorisation of children as having DN or SEN is not static and can change over time in children with DN during the pre-school years. Therefore, professionals should be mindful when discussing with parents about the longer-term educational needs and placement of their children, so that the parents can make informed decisions. Currently, over 80% of children with SEN are supported in mainstream schools, and the remaining 20% in SPED schools,[7] owing to the children's response to EI and/or maturational factors.

EARLY INTERVENTION AT KKH AND NUH

Each of the five community-based intervention centres of KKH and NUH consists of a multidisciplinary team of allied health professionals (AHPs) (occupational therapists, speech and language therapists, educational therapy professionals, educational psychologists), social workers and nurse practitioners. They serve the important role of providing EI at the tertiary level after the comprehensive assessment. Parents would go through the 'Signposts for Building Better Behaviour Programme' to assist them in understanding their children and to acquire skills and techniques in managing some of the difficult behavioural issues of their children. Children with mild developmental problems can be discharged after a short period of intervention. For children with more complex issues and those who are likely to require a longer period of intervention, the centres will continue

appropriate interim intervention in partnership with the parents until they are enrolled in the Early Intervention Programme for Infants and Children (EIPIC) centres. 'SG Enable' is the central coordinating body for arranging the children's placement at the EIPIC centres nearest to their respective homes.

EARLY INTERVENTION PROGRAMME FOR INFANTS AND CHILDREN

The government-funded EIPIC@Centres provide EI support to children aged two to six years with moderate to severe DN and SEN. In each EIPIC centre, the AHPs, social workers and related EI professionals adopt a transdisciplinary approach, in partnership with the families, to design and deliver individualised educational plans and goals. As of 2021, there are 21 EIPIC centres located across Singapore. They are run by the following Social Service Agencies (SSAs), which are non-profit voluntary welfare organisations *(in alphabetical order):* Autism Association (Singapore) Eden Children Centre; Autism Resource Centre, Singapore; Asian Women's Welfare Association; Canossian School; Cerebral Palsy Alliance, Singapore; Fei Yue Community Service; Metta Welfare Association; Rainbow Centre; SPD (former Society for the Physically Disabled); and Thye Hua Kwan Moral Charities.

Since July 2019, the EIPIC Under-2s programme has been rolled out progressively to serve children aged below two years who require medium to severe levels of EI support. The programme emphasises on imparting skills to the parents/caregivers and would require them to accompany the children. Home-based EI can be provided for a selected group of children who have medical or high-risk family factors that make their participation at EI centres difficult.

FROM 'MISSION: I'MPOSSIBLE' TO DEVELOPMENT SUPPORT PROGRAMMES

In 2006, the then KKH SengKang EI centre initiated a 'Therapy Outreach Programme' to the neighbouring pre-schools, which was a success. In 2009, with funding support from Lien Foundation, the programme was further expanded to more pre-schools in the region, and the project was renamed 'Mission I'mPossible' (MIP).[8,9] The MIP was completed in 2012. The MSF then decided to develop the MIP as the 'Development Support Programme' (DSP).

The DSP was officially launched by the MSF in May 2013 to provide learning support and therapy intervention to children with mild DN. Under this programme, a group of professionally qualified early childhood educators known as Learning Support Educators are deployed to work closely with teachers and parents. They play the key role of conducting screening to assist in understanding the child's developmental needs; providing in-class support to embed and generalise therapy goals back into the classroom after individual intervention with the therapists; providing targeted support in social skills, literacy, language and handwriting; and providing advice and support to classroom teachers and parents. AHPs and EI professionals from various EIPIC centres play a complementary role by providing appropriate therapy intervention to children who require greater support.

DSP was renamed the 'Development Support and Learning Support (DS-LS) programme' in 2017 to better reflect the therapy-based (i.e. DS) and psycho-educational (i.e. LS) aspects of the programme. The DS-LS programme should operate in a continuum with EIPIC, with varying intensities of interventions, to maximise the available resources. The Development Support-Plus (DS-Plus) programme is introduced for children who have made sufficient progress under the EIPIC@Centre programme, to help their transition to a pre-school setting. These children have generally progressed to require low levels of EI support.

All the EI programmes must work towards seamless integration with the regional pre-schools and be complementary to one another in the care and education of children. To ensure that EI services are affordable, the MSF has enhanced EI subsidies and broadened the income criteria for means-tested subsidies so that more families can qualify, and the out-of-pocket expenses are lowered for most income groups.

RIDING ON THE WAVES OF EARLY CHILDHOOD EDUCATION

Pre-school education has now been placed right at the start of a child's education journey in Singapore. Pre-schools are the seeding fields of an inclusive, fair and just society. Early pre-school exposure allows children of different races, languages, religions and creed to play, relate and learn in the same setting so that they will know from a young age the diversity in all cultural and ethnic groups.

Individuals schooled in the Singapore education system embody the Desired Outcomes of Education.[10] These individuals are expected to have a good sense of self-awareness, a sound moral compass, and the necessary skills and knowledge to take on the challenges of the future. They are responsible to their family, community and nation. They appreciate the beauty of the world around them, possess a healthy mind and body, and have a zest for life. In summary, they are confident individuals, self-directed learners, active contributors and concerned citizens.

In line with the Desired Outcomes of Education of the Singapore system, the key stage outcomes of pre-school education emphasise the need for children to build up confidence and social skills and be equipped with the necessary knowledge, skills and dispositions for life-long learning. At the end of their pre-school education, children should know what is right and what is wrong; be willing to share and take turns with others; be able to relate to others; be curious and able to explore; be able to listen and speak with understanding; be comfortable and happy with themselves; have developed physical coordination and healthy habits; participate in and enjoy a variety of arts experience; and love their families, friends, teachers and school.

The Ministry of Education (MOE) developed the Nurturing Early Learners[11] Curriculum Framework in 2012 to support and guide early childhood educators in Singapore. As per this curriculum, children are nurtured holistically through six learning areas, and their positive learning dispositions are also

cultivated through teacher-facilitated learning experiences. The six learning areas are: aesthetic and creative expression; discovery of the world; language and literacy; motor skills development; numeracy; and social and emotional development. The learning dispositions are positive behaviours and attitudes towards learning, which are important for children in their journey as life-long learners. The six learning dispositions (PRAISE) that pre-schools seek to develop in every child are perseverance; reflectiveness; appreciation; inventiveness; sense of wonder and curiosity; and engagement.

EARLY CHILDHOOD DEVELOPMENT AGENCY

The ECDA was set up in 2013 as an autonomous agency to serve as the regulatory and developmental authority for the early childhood sector in Singapore and to oversee key aspects of the development of children aged below seven years across both kindergartens and child/infant care programmes. To ensure that every child has access to affordable and quality early childhood development services and programmes, it promotes accessibility by master planning the infrastructure and manpower resources to support the early childhood sector. In addition, the ECDA provides subsidies and grants to keep quality pre-school programmes affordable. It also facilitates the training and development of early childhood educators and conducts public education and outreach activities that help parents learn about their child's early development.

The MOE embarked on a pilot programme of MOE Kindergartens (MKs) in 2014. Under this programme, MOE aims to increase the number of MOE Kindergartens to 60 by 2025 to provide more high-quality and affordable pre-school places. All new MKs will be co-located with primary schools to enable closer collaborations between MKs and primary schools on programmes and joint activities, which enrich the learning experience of pre-school children and support their smoother transition to Primary One.

Currently, there are two major anchor operators of Early Years Centres, namely the NTUC My First Skool and PCF Sparkletots. They will continue to focus on children's early years of learning and development, and collaborate strategically with the MKs to ensure a smooth transition and continuum of quality and affordable pre-school service for children aged two months to six years.

The ECDA is in the best position to advance and integrate support for children with developmental needs in the EI programmes within the pre-schools. An Inclusive Preschool Workgroup consisting of professionals from health, education and social sectors has been formed. The ECDA will work towards having every pre-school appoint an 'Inclusion Coordinator' within the existing staff, starting in the second half of 2023. The government will expand outreach for the DS-LS and DS-Plus programmes to more pre-schools to support children requiring low levels of EI support. The target of the DS-LS programme is to cover 60% of pre-schoolers by 2025 and 80% in the steady state. The ECDA will also pilot an Inclusive Support programme, starting at a few pre-schools, to integrate the provision of EI services at pre-schools for children aged three to six years who require medium levels of EI support. In addition, the ECDA will study integration opportunities for children who require high levels of EI support and who are best served in a separate specialised EI setting. These could include partnerships between EI centres and pre-schools to facilitate activities for social interaction.

NATIONAL INSTITUTE OF EARLY CHILDHOOD DEVELOPMENT

The National Institute of Early Childhood Development (NIEC) was incorporated in March 2018 and became fully operational from January 2019 through the consolidation of the early childhood training capabilities and expertise of the Institute of Technical Education (ITE), Ngee Ann Polytechnic, Temasek Polytechnic and NTUC's SEED Institute to become a major player in early childhood training landscape. The NIEC will centralise and drive all strategic and professional aspects of early childhood training, such as curriculum design and development, academic governance and faculty development. It will offer certificate- and diploma-level pre-employment training courses for post-secondary students interested in joining the pre-school sector. In addition, it will offer Continuous Education and Training (courses for mid-careerists, and in-service upgrading and Continuing Professional Development courses) to further develop the competencies of in-service teachers and leaders. The strategic partners of NIEC include National Institute of Education, ECDA, Workforce Singapore, Employment and Employability Institute, and other industry operators. NIEC will cover about 60% of the training of pre-school teachers in the sector. Other major training providers in the private sector include Kinderland Consortium International Institute and Asian International College, to allow more diversity in the training approach.

SUPPORT FOR CHILDREN WITH DEVELOPMENTAL NEEDS IN MAINSTREAM SCHOOLS

Mainstream school is the usual learning environment for children who have adequate cognitive skills to cope with the demands of the national curriculum, as well as the adaptive skills to communicate and learn in a large group setting. In Singapore, a multi-pronged approach is adopted to cater to the diverse educational needs of students with developmental needs. Around 80% of students with SEN are in mainstream schools. Many of them, as well as the majority of students with sensory and physical impairment, have specific learning difficulties such as dyslexia, ADHD and ASD. The other 20% of children who have moderate-to-severe SEN are in SPED schools,[7] where they receive a highly customised curriculum and pedagogy delivered by trained SPED teachers and supported by a range of allied professionals.

Teachers Trained in Special Needs (TSNs) are classroom teachers who have completed certificate-level training in special needs and are equipped with the skills required to support pupils with mild special needs by planning classroom instruction to cater to the pupils, adapting and differentiating the curriculum to suit the pupils' needs, monitoring their progress and sharing relevant

strategies with parents and fellow teachers, and facilitating the transition of pupils from one level to the next. In 2010, 10% of all primary school teachers have been trained as TSNs.

Mainstream schools have dedicated non-teaching staff known as Special Needs Officers (SNOs) with training in special education to support pupils with mild special needs by providing in-class support, providing individual/small group intervention or skills training, developing learning resources that are appropriate for pupils, monitoring the pupils' progress, communicating and working closely with the teachers in the schools as well as specialists from the MOE, communicating with parents regarding the learning needs and progress of the pupils, and working with external agencies. The SNOs are now known as Allied Educators (Learning and Behavioural Support) (AED[LBS]).

The Learning Support Programme caters to Primary 1 and 2 students who need additional help with English. It is held for 30 minutes a day and in small groups of eight to ten students. In some primary schools, the programme is broadened to provide remedial support to pupils who lag behind in their academic capabilities. School counsellors provide support to students with personal or academic challenges, while Student Welfare Officers help disadvantaged students continue their schooling and establish links between the families and the relevant community resources, such as the family service centres.

TRANsition Support for InTegration (TRANSIT) takes place during Primary 1 to help students with social and behavioural needs develop independence through learning of fundamental self-management skills based on their specific needs. Schools will proactively identify these students for support based on information gathered from parents, teachers and EI educators in pre-schools, and through systematic observations conducted by trained school personnel, including teachers and AED(LBS). TRANSIT will be introduced progressively to all primary schools by 2026.

Certain primary schools have a School-based Dyslexia Remediation Programme for students with dyslexia in Primary 3 and 4. Students with dyslexia in other levels will have access to the Main Literacy Programme conducted by The Dyslexia Association of Singapore (DAS). The DAS has also been given funds to provide early testing of pre-school children suspected of having learning disabilities, so that early intervention can be started to make these children better prepared as they enter mainstream primary schools.

To help children with emotional, social and/or behavioural difficulties and disorders, such as ASD and ADHD, schools work closely with REACH (Response Early Intervention and Assessment in Community Mental Health) services and parents on suitable school-based interventions and support.

Children with visual impairment, hearing loss and/or physical impairment may tap on itinerant educational support services, where personnel from SSAs such as AWWA and Singapore Association for the Deaf provide additional support in school to enhance the child's accessibility to learning and the environment. The MOE also provides assistive technology such as Frequency Modulation systems, magnifiers and text-to-speech software for children's use. In addition, there are barrier-free facilities to help children with physical impairments. All primary and secondary schools in Singapore will have lifts by 2025. The schools will also provide accessibility accommodations for children to complete tests and national examination papers, such as larger fonts, extra time, presence of prompters, and conductance of the examination in a separate room with fewer distractions. The advocacy role of the paediatricians would be even more important then.

Children with DN are vulnerable groups in schools and they need to be accepted and protected. Two intervention programmes have been introduced that leverage peer support: Circle of Friends for primary and secondary students, and Facing Your Fears for secondary students. Singapore Children's Society has been advocating for bully-free schools since 2008 and 'Bully-free Schools' campaigns have been organised on a regular basis. Some schools have taken up the bully-free programme as part of their co-curricular activities.

Pathlight School has been successful in offering the Singapore primary and secondary national curriculum to children with mild to moderate autism who lack adequate social and communication skills to allow them to cope in the usual mainstream schools. The school also has a suitable post-primary programme for students with ASD who are unable to access the national secondary curriculum. Several education tracks are designed according to the academic capabilities and behavioural competencies of these children. The MOE will set up two more similar schools for these students in the next few years.

In 2007, Northlight School was set up with the mandate to engage and to continue to provide learning opportunities to teenage premature primary school leavers or those who have not done well in the Primary School Leaving Examination. Assumption Pathway, another school of similar nature, opened in 2009. The goal is to assist these children to set aside their past academic failures, allow them to discover their individual strengths, maintain their self-esteem, and encourage character development and vocational training.

Crest Secondary School, a Specialised School for Normal (Technical) students, took in its first batch of Secondary One students in January 2013. This was followed by Spectra Secondary School in 2014. Both schools offer a customised curriculum that integrates both academic learning and vocational training. Apart from subjects such as English Language, Mathematics, Basic Mother Tongue (Chinese, Malay, Tamil) and Science, the schools also offer four ITE Skills Certificate courses, namely Hospitality Services, Retail Services, Facility Services and Mechanical Servicing. Learning will be practice oriented, with an emphasis on skills development to prepare students for progression to post-secondary skills training at the ITE and for employment. Industrial attachment will be an important component of the ITE Skills Certificate learning experience for the students. In addition, the schools will adopt innovative pedagogies to strengthen students' literacy and numeracy skills. A key cornerstone of the school's holistic education is in building students' character, with a strong focus on value education, and strengthening social and emotional competencies.

Students in Singapore are encouraged to discover and develop their own strengths, follow and pursue their diverse passions in academic fields, sports and the arts, and emerge from schools being confident of their abilities. Our educational system has become more flexible and diverse, with wider range of curricula and schools, providing students more choices in pursuing their interests along pathways that better fit their learning styles. The vision is to 'build a mountain range with many peaks of excellence'.

From 2008, streaming of primary school pupils into EM1, EM2 and EM3 (E: English, M: Mother Tongue) was phased out. Instead, depending on their strengths, the pupils will study subjects at different levels of difficulty – the Standard level or the easier Foundation level. Therefore, there is a shift from a 'fixed' menu to a subject-based 'a la carte' menu of study (subject-based banding). With more flexibility in the curriculum, catering to the different abilities of students instead of a one-size-fits-all approach, students will not be easily discouraged and leave the school system prematurely. These changes in our educational approach would allow many children with different developmental problems to be included in the mainstream schools, supported by trained teachers and integrated with their peers in their learning experiences. The emphasis is on allowing opportunities for them to continue to learn and develop their innate strengths so that their talents will be valued, thus widening the definition of success.

CARING FOR CHILDREN WITH SPECIAL EDUCATIONAL NEEDS

SPED schools provide education to about 20% of students of school-going age with SEN who have higher support needs.[7] From 2019, all children with moderate-to-severe SEN have been included within the Compulsory Education framework. Currently, there are 19 SPED schools run by 12 SSAs. SPED schools charge different fees, as they have to customise their programmes and services to meet the diverse and specialised learning needs of their students.

The MOE's vision for these students is to be 'Active in the Community and Valued in Society'. For this purpose, students need to be equipped with the knowledge, skills and attributes to participate meaningfully in their communities and become contributing citizens who are valued by the society. SPED schools are guided by the SPED Curriculum Framework, 'Living, Learning and Working in the 21st Century', released in 2012,[12] in designing and delivering quality and holistic education for their students. SPED schools offer customised educational programmes aimed at developing the potential of students and helping them to be independent, self-supporting and contributing members of the society. Besides being taught by specialised teachers, students in all SPED schools are provided with supporting facilities and also receive support from allied professionals such as psychologists, speech and language therapists, occupational therapists, physiotherapists and social workers.

The SPED schools have established long-term sustained Satellite Partnerships with mainstream schools, where there are opportunities for purposeful social interactions between the students through platforms such as joint co-curricular activities, recess, workshops and camps. For example, Townsville Primary School and Pathlight School for Children with Autism are located adjacent to each other in Ang Mo Kio. During the 30-minute break each day, students share their meals and play games such as badminton and table tennis. At Canossian School for the Hearing Impaired, students attend daily lessons and participate in co-curricular activities alongside other children from MacPherson Primary and Canossa Primary Schools. Students from Dunman High School and MINDS Towner Gardens School do joint community service projects, arts and craft, and science activities. The Play Inclusive Campaign organised by SportCares and Special Olympics Singapore also brings together student athletes from several SPED and mainstream schools to share sporting experiences as members of the same team. They also rehearse, practise and perform together during National School Games, Youth Festival and National Day Parade.

SOCIAL AND COMMUNITY SUPPORT

The social safety net in Singapore is a unique 'Many Helping Hands' approach, which involves the partnership of all sectors of the society and the government. The many helping hands consist of the MSF, NCSS and Community Chest (its fund-raising arm), community development councils, SSAs, philanthropic organisations and foundations, grass-roots organisations, financial corporations and consumer groups, as well as parent support groups and associations. The principle is to foster self-reliance. Family remains the primary line of support, including financial and emotional support. The emphasis is on social assistance and not welfare.

Supplementary services are available to provide tangible financial or other material help to families. Supplementary helps targeted specifically at children's needs are also available. The Community Care (ComCare) Fund was established in 2005 to provide sustainable funding for social assistance programmes for low-income Singaporeans, with the majority of the fund catering to programmes for children from disadvantaged families. The President's Challenge is a movement supported by the kindness and generosity of people from all walks of life. It calls for the nation to do its part to build a more caring and inclusive society and to help the less fortunate. Singapore Press Holdings sponsored the School Pocket Money Fund, which raised large sums for distribution to ensure, among other things, that poor children can afford food at school recess times. Many SSAs also organise activities such as walks to raise funds that can be tapped to supplement needs for needy children. Ethnic community organisations, such as the Chinese Development Assistance Council; Mendaki and the Association of Malay Professionals; Sinda; and the Eurasian Association – serving Chinese, Malays, Indians and Eurasians, respectively – have an educational focus. Besides financial assistance, they also provide low-cost tuition to school children and parental education.

In 2013, the MSF started setting up social service offices (SSOs) in Housing and Development Board (HDB) towns to

provide more accessible and coordinated social assistance to Singaporeans in need. The rollout of the full network of 24 SSOs was completed in 2015, and 95% of ComCare beneficiaries now live or work within 2 km of an SSO. Physical accessibility to and awareness of ComCare have increased because of the SSOs, making it easier for needy families to seek help. Besides providing ComCare assistance directly, SSOs also do ground-sensing and collaborate with SSAs and community partners to identify needs within each HDB town, to provide more holistic support to those in need.

In 2016, the ECDA initiated a new system of support for low-income and vulnerable children to enable them to have a good start in life. The new initiative, called KidSTART, coordinates and strengthens support across agencies, extends new forms of support and monitors the progress of these children from birth to six years of age. Through KidSTART, families requiring additional support are proactively identified. Their children are provided with early access to appropriate health, learning and developmental support. Parents are supported and equipped with parenting knowledge and resources to nurture the child at home, through home visits, parental education and/or family support programmes. Selected pre-schools will also provide additional support and work with parents to better support their child through the pre-school years and transition to primary school. The families will also be linked up with existing community resources for additional assistance, according to their needs.

The KidSTART programme will gradually expand to more regions in Singapore. A dedicated KidSTART Singapore office has been set up to partner an anchor SSA in each region, to support coordinated outreach to families and the programme implementation. Through the Growing Together with KidSTART initiative launched in 2019, the Government will continue to deepen and forge partnerships with the community and grow the pool of volunteers to reach more families.

In April 2019, the MSF launched Community Link (ComLinK), which has since been scaled up nationwide to provide comprehensive, convenient and coordinated support to families with children living in rental housing so that they can achieve stability, self-reliance and social mobility. ComLink is a key initiative under the SG Cares Community Network, a Singapore Together Alliance for Action announced in 2020. This is done through proactive outreach and closer case support, galvanising the community to offer customised programme and services to the families. At each ComLink town, the SSO leads a ComLink Alliance, comprising government agencies, corporate partners and community partners, to pool together resources and steer the effort.

Supportive services are social service provisions that strengthen the capacity of parents to fulfil their roles more effectively. Many families, including normal functioning families, require support to enable the social functioning of adults in their parental roles. These include affordable housing and healthcare services; job availability, training and re-training; family-friendly workplaces; and affordable quality childcare facilities for working parents and recreational facilities.

When both parents work, and when care by other family members is not available, alternative affordable and quality care arrangements by non-family members become necessary. While there are alternative care options by foreign domestic workers and family day-care providers who take care of a small group of children in their own home, infant and childcare and student care centres are some of the services that families have come to rely upon as more mothers join the work force.

Childcare centres cater to children from infancy up to the age of seven years as a service for working parents, with subsidised fees. Childcare centres are licensed by the MSF to ensure not only the children's safety and well-being, but also their learning and development. A number of these centres have also expanded their services to include parenting education and counselling, parent support services, as well as public education programmes for families with children under their care. The emphasis is on encouraging parental participation in the care of their children.

Student care centres cater to primary school children who have no adult at home when they return from school or before they go to school. These children may be lonely and bored, and may seek distraction outside the home such as frequenting shopping centres and getting involved in undesirable activities with questionable company without their parents' knowledge. Student care centres provide a place where these children can have a proper meal, do their homework and engage in recreational activities under the supervision of adults. The after-school services will be further extended to pre-schoolers, secondary school students and children with special needs.

An extensive network of family service centres (FSCs) is available in Singapore to offer general family-oriented programmes, ranging from parent education to family counselling and student care. The MSF will be rolling out the Strengthening Families Programme@FSCs at various locations across Singapore over the next few years. It will consolidate the existing FSC programmes and put in place a continuum of services, from upstream preventive initiatives targeted at couples who may face greater challenges and families showing early signs of stress to supporting families with complex and multiple issues. It will adopt a regional, integrated and multidisciplinary approach to support families in a holistic way. In each region, it will work closely with other service providers such as the respective SSOs and FSC partners, as well as bring together professionals trained in family counselling, financial counselling and psychology to address the families' needs.

STRENGTHENING PARTNERSHIPS WITH FAMILIES

Parents and caregivers play the most critical role in a comprehensive, inclusive early childhood intervention system. The family is the most powerful and pervasive influence, and the constant in a young child's life. The family is likely to be the only group of adults involved with the child's educational programmes throughout his or her entire learning journey. There are many success stories where parents heroically enter into the world of their children, discover their hidden talents and start a fruitful

learning journey together. Caring for the caregivers is one of the key areas to address in the Enabling Masterplan III (2017–2021).[13]

Professionals must always recognise the expert contribution of parents. They must always be aware that their attitudes and assumptions about parents would become roadblocks to a productive partnership: treating parents as vulnerable and helpless clients; keeping professional distance (aloofness and coldness); treating parents as if they need therapy and counselling; blaming parents for their child's condition; disrespecting parents as less intelligent; treating parents as adversaries; and labelling parents (as denying, resistant, anxious, uncaring, troublesome, hostile,…), so that the parents feel intimidated, confused and angry. Professionals must work in collaboration with families to address the child's needs in a way that is consistent with the priorities of the entire family. There should be a complete and unbiased exchange of information between families and professionals. Policies and programmes should address these diverse needs, and recognise and honour cultural diversity, and the strengths and individualities of all families. The principles of family-centred approach are empowering families, providing social support, building relationships with families as the basis for intervention, building communication skills and maintaining effective communication.

Since March 2011, a community-level programme called 'Signposts for Building Better Behaviour' ('Signposts') was introduced to help enhance the knowledge, skills and mental well-being of parents and caregivers of children with developmental needs, and to equip them to understand their child's difficult behaviour, develop better ways to manage them more effectively and prevent the development of behavioural consequences. 'Signposts' is delivered through a network of qualified and trained facilitators from KKH, NUH, EIPIC centres and other centres across Singapore. Parents who have participated in 'Signposts' continue to meet regularly to share and support each other through the parent-initiated CASPER (Caring And Sharing Parents, Ever Resilient) programme.

The Caregivers' Space has been set up at the Enabling Village by SG Enable in 2018 to serve as a meeting place for peer support groups, training of caregivers of persons with disabilities and engagement sessions by SSAs as well as community partners for caregivers. Caregivers will also be able to get information and advisory service at Enabling Village. Besides SG Enable, the Special Needs Trust Company and SSAs providing disability services are also part of the caregivers' network of support.

COMPLETING THE JIGSAW PUZZLE

Our vision of an inclusive early childhood intervention in Singapore is to start upstream in identifying families at risk even before the birth of the child. These families would receive early social and health support to ensure that the young child could receive optimal care and protection after birth in terms of appropriate nutrition, immunisations and early developmental stimulations. The regional social and community support system, with both the government and SSAs working closely in partnership, would ensure that these children receive early learning experience in childcare centres and pre-schools. Children with developmental needs are identified early and put under the continuum of care of EIPIC, DS-LS and DS-Plus programmes. The pre-schools would serve as an integrated and inclusive learning environment with trained pre-school teachers, learning support educators, inclusion coordinators and allied health professionals. Families are active participants in the entire process, which will facilitate seamless transition of the children from pre-schools to the next stage of education.

The transition from adolescence to adulthood after childhood interventions is a process, not an event, and should begin as early as possible, taking into account the young person's developmental stage and the functional impact of the disability. Some of the future expectations and challenges would include moving towards independence; developing social competence; moving towards post-secondary education; entering the work force; community living; participation in sports, leisure and community activities; issues of sexuality; and developing a life plan. Outcome evaluation is a continuous process and should be interpreted from the perspectives of the summative effectiveness and efficiency of the network of medical care, social and community support, education, and parental and family participation in the ecosystem. On the one hand, professionals in the childhood programmes must prepare to 'let go' of the developing young adults. On the other hand, they should go beyond their comfort zone of medical care and continue to be ready to take on the leadership role in advocacy to ensure that the young adults continue to receive the best possible care with the best possible outcomes, as their life-course commitment.

CONCLUSION

Singapore has a new vision towards building an inclusive society with a broader definition of meritocracy that entails recognising different strengths and different individuals. The narrow meritocratic system that focuses too much on academic qualifications will make way for a more flexible and diverse broad-based education system that provides many paths for students to grow and develop. We look forward to building a mountain range with many peaks of excellence. Tackling inequality and building a fair and just society have to start in pre-schools. However, pre-school education is only a component of a comprehensive early childhood programme. It must be complemented with an effective early childhood development and intervention programme, a nationwide supportive network of social and community services for the families, and an efficient legal framework in child protection. This way, every child's talent would be valued and no child would be left behind.

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Liver transplantation in children: the Singapore experience

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ABSTRACT Paediatric liver transplantation has come a long way since its acceptance as a treatment option for children with end-stage liver disease. From 1990 to 2020, a total of 434 liver transplants were performed in National University Hospital, Singapore, out of which 143 were performed in children. The majority of the liver grafts were from living donors, mainly the parents. Our long-term survival rates are comparable to those of major transplant centres worldwide. These patients usually have a productive and good quality of life.

Keywords: biliary atresia, living-related, paediatric liver transplant

INTRODUCTION

Liver transplantation (LT) has come a long way since its acceptance as a treatment option for patients with end-stage liver disease. The outcome of LT for paediatric recipients is no longer aimed at just survival but other measures such as good catch-up growth and quality of life. In fact, many studies have shown that the health quality of LT recipients significantly improves within six months after a successful transplant. Paediatric liver transplantation accounts for about 10% of the total number of LTs performed annually. Improvement in patient selection, pre- and postoperative care, surgical techniques, organ preservation as well as immunosuppression have resulted in excellent post-transplant survival and quality of life.

The first LT in Singapore was performed in 1990 in a patient with autoimmune hepatitis.[1] Since then, over 434 LTs have been performed in the National University Hospital (NUH), 143 of which have been in children. The paediatric transplant programme is based at the NUH. It comprises a multidisciplinary team, including transplant co-ordinators, transplant surgeons (adult and paediatric), paediatric gastroenterologists, paediatricians from various subspecialties, dieticians, nurses, pathologists, social workers, physiotherapists, radiologists and adult physicians (who assess the adult living donors). The programme also receives invaluable support from doctors in both public and private sectors. Prof Phua Kong Boo and Dr Ooi Boo Chye from KK Women's and Children's Hospital were the first visiting paediatric consultants to the programme.

INDICATIONS FOR LIVER TRANSPLANT

LT is indicated when the risk of mortality from one's native liver disease outweighs the risk of transplant. In general, a child should live with his/her own liver for as long as possible. Although LT is lifesaving, it carries the risks of surgery as well as the need for life-long immunosuppression. Children with chronic liver disease should be considered for LT in cases of faltering of growth, deteriorating synthetic function, progressive jaundice and intractable ascites. Severe intractable pruritus in the absence of decompensated liver disease is a relative indication. Although rare, fulminant liver failure would be an urgent reason for LT. While many of the cases of acute fulminant liver failure are idiopathic, some of the identifiable causes include viruses, drugs (medications) and metabolic disease. Contraindications to transplantation include uncontrolled systemic infection, unresectable malignancy outside the liver, genetic or metabolic conditions not treatable by liver transplant alone and irreversible severe neurologic injury.

LT is a labour-intensive and expensive procedure, both in term of finances and resources. A strong family support is required in order to ensure that the child adheres to the medications and treatment plans. It is vital that the child's parents and caregivers are able to provide the care and close supervision after transplant. At the same time, the members of the LT team (nurse specialist, medical social worker) should also be able to provide the family with the necessary education, counselling and psychosocial support.

PATIENT CHARACTERISTICS

Between 1991 and 2020, 143 LTs were performed in 135 children. Eight of these patients underwent a second LT because the first graft had failed. The aetiologies for LT in these 135 children are shown in Table I. The most common indication was biliary atresia, accounting for about 68% of the total patients. This is similar to the experience of other major paediatric centres.[2] Other indications included patients with Alagille syndrome and other hypoplastic bile duct syndromes, glycogen storage disease, acute liver failure, and a number of cryptogenic and metabolic liver diseases.

Fig. 1 shows the number and type of LTs performed in each decade. While the number is relatively small, a consistent trend has been observed, with the majority being living-donor transplants. Overall, 79% of paediatric LTs were from living donors. In fact, the past decade has witnessed only two deceased-donor grafts, likely owing to the shortage of paediatric deceased-donor grafts. While

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the bulk of our living-donor transplants are from parents, we are seeing an increasing number of non-related living donors. This is, in part, attributable to the good track record of living-donor safety, as well as a reflection of the altruism that exists in our society.

SURVIVAL

Paediatric LT recipients have shown excellent post-transplant survival outcomes. Table II shows the long-term survival rates in NUH and those in other major centres worldwide. The one-year, five-year and ten-year survival rates in NUH are 81%, 77% and 77%, respectively. These results are comparable to those of other major centres. The one-year survival rates range from 77.1% in Pittsburgh[3] to 95.7% in Brussels,[5] and the ten-year survival rates range from 69.4% in Pittsburgh to 90.4% in Brussels.

COMPLICATIONS

Several complications can occur following LT. Surgical-related issues[6] include those associated with biliary and vascular problems. These range in severity from requirement of minimal intervention to the need for re-transplant. Perihepatic fluid collections suggestive of biliary leak are not uncommon. Some of them resolve spontaneously, whereas others may require percutaneous drainage or open laparotomy. Isolated biliary strictures are treated by biliary stenting, while those with multiple strictures following secondary ischaemia may require re-transplant.

Vascular complications include hepatic vein thrombosis or stricture, hepatic artery thrombosis and portal vein thrombosis. Early hepatic and portal vein thrombosis are managed by surgical thrombectomy and re-do anastomosis. Hepatic vein thrombosis can be overcome by balloon dilation under radiology guidance by our interventional radiologists. We had encountered a patient with an anastomotic stricture of the hepatic vein, which underwent multiple balloon dilations.

Infections remain an important issue in LT, particularly opportunistic infections in the long term. Bacterial infections, with the sites of infection being intra-abdominal or line-related, would be the main concern in the immediate postoperative period. Paediatric recipients are routinely administered broad-spectrum antibiotics in the immediate postoperative period, and these are discontinued once all invasive lines and tubes are removed, or adjusted according to bacterial cultures if there is evidence of systemic infection. Patients exposed to broad-spectrum antibiotics prior to transplant or those in whom acute liver failure was the reason for transplant would have a relatively low threshold for antifungal therapy.

Of all the opportunistic infections, Epstein-Barr virus-related post-transplant lymphoproliferative disease (PTLD) is of particular concern in children. The overall incidence of PTLD in our paediatric transplant recipients is about 16%.[7] The risk of PTLD is higher in children aged < 2 years at transplant, those who develop primary cytomegalovirus (CMV) infection after transplant and those who experience acute cellular rejection. There appears to be synergism between CMV naivety and acute cellular rejection on the risk of developing PTLD.

Acute cellular rejection (ACR) is not uncommon and, in some instances, is believed to be harmless if it occurs within the first four to six weeks after transplant. Most of the time, ACR can be reversed by intensifying immunosuppression therapy. Although some patients show more resistant forms of rejection, the general requirement for immunosuppression in LT recipients is less than that required for recipients of other solid organ transplants such as the kidney or the heart. Theoretically, ACR can occur any time after LT. Later occurrence is associated with a greater risk of non-adherence. Graft loss from non-adherence has been reported, mostly among adolescent patients.

Table I. Indications for paediatric liver transplant in National University Hospital (n = 135).

Cause	No. (%)
Biliary atresia	92 (68.1)
Alagille syndrome and other hypoplastic bile duct syndromes	10 (7.4)
Glycogen storage disease	9 (6.7)
Acute liver failure	8 (5.9)
Cryptogenic cirrhosis	5 (3.7)
Autoimmune hepatitis	4 (3.0)
Wilson disease	4 (3.0)
Maple syrup urine disease and hyperoxaluria	2 (1.5)
Hepatoblastoma	1 (0.7)

Table II. Comparison of survival rates after liver transplantation.

Survival (yr)	%			
	NUH	Pittsburgh[3]	Kyoto[4]	Brussels[5]
1	81	77.1	81.5 (male); 86.7 (female)	95.7
5	77	72.6	78.8 (male); 84.6 (female)	91.4
10	77	69.4	73.1 (male); 79.8 (female)	90.4

NUH: National University Hospital

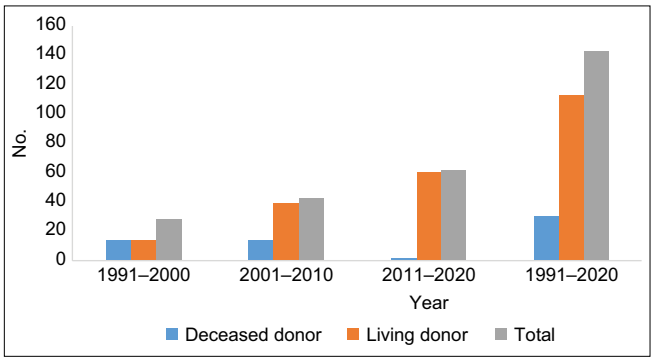

Fig. 1 Graph shows the number and type of liver transplants performed in each decade.

QUALITY OF LIFE

In terms of quality of life, our LT recipients have acceptable pedQoL score compared with the normal population. They also show good physical and social functioning scores.[8] As shown in Table II, many of our LT recipients have survived for

ten years or more after transplant. The majority of them have completed secondary education, and many have completed tertiary education. Most of the recipients who have completed their education are gainfully employed, and a small number of them are married with children.

CONCLUSION

Paediatric LT in Singapore has come a long way. Biliary atresia accounted for about two-thirds of our cohort of 135 patients. The one-, five- and ten-year survival rates are good and comparable to those of other major centres worldwide. Several concerns related to LT have been highlighted. Shortage of deceased donor organs resulted in the emergence of living donors as the main mode of LT among children in Singapore. Although LT is a labour- and resource-intensive procedure, careful selection of patients along with good patient and family support before and after transplant would ensure successful LT and the best patient outcomes.

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Paediatric gastroenterology in Singapore: historical aspects and recent advances

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ABSTRACT Paediatric gastroenterology in Singapore began in the 1970s. Led by Professor Phua Kong Boo and Professor Quak Seng Hock, paediatric gastroenterology has enjoyed significant strides in the areas of diagnostics, interventions, patient care and research. Several advances such as endoscopy, parenteral nutrition and liver transplantation are well established. The first paediatric small bowel transplant is anticipated in the next decade. Robust research activities have ensured the generation of local data on gastrointestinal disorders. One such research led to the discovery of the changing trends in the incidence of inflammatory bowel disease among the paediatric population in Singapore. The impact of the nation's paediatric gastroenterology extends internationally, with the notable involvement of Professor Phua in developing the rotavirus vaccine trials and other ongoing collaborative work with international centres. This review explores the history of paediatric gastroenterology from its origins to its remarkable transformation over the decades as centres of excellence in the region.

Keywords: hepatology, history, paediatric gastroenterology, Singapore

THE BEGINNING OF PAEDIATRIC GASTROENTEROLOGY

The last few decades have witnessed a remarkable development of paediatric medicine in Singapore, particularly with the rapid establishment and evolution of paediatric subspecialties including paediatric gastroenterology. Paediatric care in Singapore first began in the 1950s at the Singapore General Hospital, following the building of a children's wing with 280 beds. This was made possible by the generous donation of a philanthropist, Mr NR Mistri.[1] The building, known as the Mistri Wing, consisted of the West Wing housing the University department and the East wing housing the government department of paediatrics. In the early years, children admitted there were cared for by general paediatricians, who managed all their medical conditions. However, the beginning of the 1970s saw a keen interest in developing subspecialist care, as more clinicians and patients appreciated its value. Two eminent paediatricians, namely Professor Phua Kong Boo from the East Wing and Professor Quak Seng Hock from the West Wing, are undoubtedly the pioneers of paediatric gastroenterology.

Professor Phua Kong Boo started providing focussed gastroenterology care following his fellowship at renowned teaching hospitals in Sydney and Melbourne in 1976. Paediatric gastroenterology service under Professor Phua, together with the rest of the department, relocated to KK Women's and Children's Hospital (KKH) in 1997. Professor Quak Seng Hock received his fellowship training at Birmingham Children's Hospital in 1983 and 1989. He subsequently headed the paediatric gastroenterology and hepatology department at the National University Hospital (NUH). With the inception of these two departments, the specialty has seen remarkable growth in both services and technological advances over the last 50 years.

Paediatric gastroenterology remains one of the broadest subspecialties, as it encompasses gastrointestinal (GI), nutrition and hepatology conditions. Various techniques have been developed to aid in disease diagnoses. This article aims to highlight the key areas of development in this field over the last few decades.

DEVELOPMENT OF PAEDIATRIC ENDOSCOPY

Several diseases of the GI tract require mucosal biopsies for diagnostic and therapeutic purposes. Conditions such as celiac disease, inflammatory bowel disease (IBD), eosinophilic GI disease and peptic diseases are typically diagnosed based on specific macroscopic appearance of the gut mucosa and histological features.

The Crosby capsule, invented by William Crosby in 1957,[2] gained wide acceptance as a reliable method for obtaining gastric and intestinal biopsies in adults in the late 1960s in Singapore. The capsule is first attached to a long tube and swallowed by the patient. Once it reaches the desired area of the stomach or bowel, suction is applied, which triggers a spring-loaded knife to obtain the biopsy tissues. Over time, the Crosby capsule was deemed too big for safe biopsies in children and was replaced by the smaller Watson capsule in the 1960s.[3]

The Watson capsule was first used in Singapore by Professor Phua in the 1970s (Fig. 1). This procedure was performed without general anaesthesia. The Watson capsule has a high safety profile and was the diagnostic tool of choice for several GI conditions such as malabsorption conditions, giardiasis (Fig. 2) and celiac disease. Other indications included obtaining duodenal aspirate to check for tryptase activity in suspected pancreatic insufficiency. For neonates with suspected biliary atresia (BA), duodenal aspirate was obtained to test for the presence of bile. A positive result indicated that the infant was unlikely to have BA.[3] This technique has obviated

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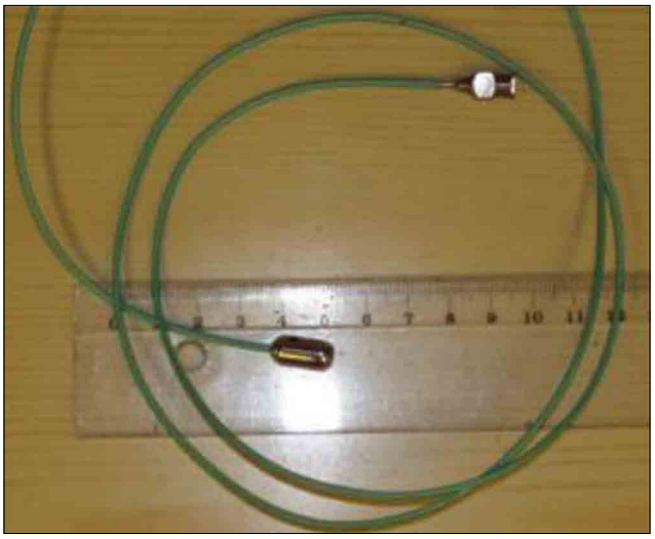

Fig. 1. Photograph shows the Watson capsule that was used for small intestinal biopsy in the 1970s (courtesy of Prof Phua Kong Boo).

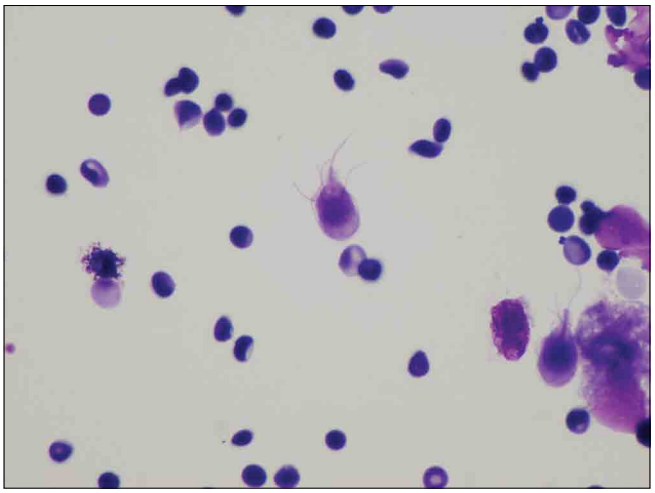

Fig. 2. Photomicrograph shows giardiasis diagnosed using the Watson capsule.

the requirement for further surgical intervention, including intraoperative cholangiogram.

The early 1990s saw the advent of gastroscopy and colonoscopy, which enable gastroenterologists to have a direct vision of the GI tract and perform biopsies for histology. Luminal endoscopy has replaced capsule biopsy and transformed paediatric gastroenterology practice by allowing rapid and accurate diagnosis of various GI conditions such as peptic diseases, celiac disease, inflammatory bowel disease, GI infections, intestinal polyps, etc.[4,5] Initially, gastroscopy and colonoscopy in children were performed by adult gastroenterologists owing to a lack of trained paediatric endoscopists. Professor Quak Seng Hock was the first paediatric gastroenterologist in Singapore to perform these procedures in children from as early as 1982. The first endoscopy was performed in the treatment room in Ward 32 at Mistri Wing. In 1990, Dr Ooi Boo Chye started performing GI endoscopies in Paediatric East after his return from The Royal Children's Hospital Melbourne. Initially, only a few cases were observed per month; however, the caseloads have increased steadily over the years, with hundreds of endoscopies performed annually.

Wireless video capsule endoscopy is a new technology developed in 2001 to explore the small intestine.[6] This technique is used in case of occult GI bleed, unexplained iron deficiency anaemia, small bowel Crohn's disease and small bowel polyps, and it has been performed in children for evaluation of small bowel pathology from the early 2010s in Singapore.[7]

MOTILITY DISORDERS, IMPEDANCE pH MONITORING AND GI MOTILITY INVESTIGATIONS

Although gastroesophageal reflux is common in infants, gastroesophageal reflux disease (GERD) is much less common in healthy children. By contrast, preterm infants and children with neurological impairment experience significant complications from GERD, including pulmonary aspiration, apnoea and poor nutrition.[8] The last decade has witnessed rapid development in diagnostic modalities for GI motility disorders including GERD.

Impedance-pH study remains the gold standard diagnostic tool for paediatric GERD. This tool correlates reflux occurrences with clinical events such as desaturation, cough and apnoea. Appropriate management plans are subsequently formulated based on the study results. Impedance-pH study has been conducted in children and infants since the early 2010s and is now the mainstay diagnostic tool for GERD. Other motility investigations such as manometry studies are performed in conjunction with adult gastroenterologists for indications such as achalasia and gut dysmotility.

DEVELOPMENT OF PARENTERAL NUTRITION SERVICES IN CHILDREN

Parenteral nutrition (PN), also widely known as total parenteral nutrition (TPN), involves provision of nutrition to a patient via the parenteral route. TPN is indicated when a patient is unable to meet his or her nutritional requirements by the enteral route alone owing to his or her clinical conditions. Dudrick et al[9] first introduced the concept of TPN in the 1960s by successfully administering intravenous nutrition to an infant.

TPN in children was first started in the 1970s by Professor Wong Hock Boon and Professor Phua Kong Boo at the Mistri Wing. They published a report of 12 infants with malignant diarrhoea who were successfully treated with PN.[10] In this study, intravenous access was obtained using a scalp vein needle. Instead of the commercial intralipid, post-prandial plasma was harvested and used as a source of lipids. Protein was provided by an essential amino acid infusion known as Sohamin (Tanabe Seiyaku, Japan). The final component of the PN, which was prepared and administered to the infants by nursing staff, was 10% glucose.

To date, TPN provision for children with various medical or surgical conditions has been well established. The last few decades have also seen improved survival of patients with short-gut syndrome and intestinal failures owing to advances in surgical techniques and administration of TPN. Hence, the

nutrition support team at KKH was formally established to provide multidisciplinary care to these patients in the early 2010s. The team consisted of paediatric gastroenterologists, dieticians, TPN pharmacists, nutritional support nurses and paediatric surgeons. Most patients received only short-term TPN support; however, certain patients with intestinal failure would require long-term TPN. For this purpose, the KKH Intestinal Rehabilitation Programme was established in 2014. Under this programme, wherever possible, patients were transitioned to home PN following intensive training by the nutrition support team.

Small bowel transplantation is a recognised treatment for patients with intestinal failure who develop complications due to long-term TPN.[11] Paediatric small bowel transplantation programme is currently at the planning stage in Singapore. The transplant team, comprising paediatric gastroenterologists, surgeons, intensivists, pharmacists and nurses recently went on training attachments to overseas transplant centres supported by the Human Manpower Development Plan grant. It is envisioned that the first paediatric small bowel transplant in Singapore will be performed in the next five to ten years.

RAPID RISE OF PAEDIATRIC INFLAMMATORY BOWEL DISEASE IN SINGAPORE

IBD, Crohn's disease, ulcerative colitis and IBD unclassified are chronic inflammatory conditions of the GI tract. Their aetiology is multifactorial, involving genetic predisposition, environmental factors, intestinal microbiome and immune dysregulation.[12] Historically, IBD was considered a disease of affluent Western countries. However, in recent years, the incidence rate of IBD has plateaued in Western countries, and a rising incidence has been observed in Asia.[13,14] Singapore has also witnessed a rapid rise in the incidence of paediatric IBD over the last three decades. A recent publication on the epidemiology of paediatric IBD in Singapore over a 22-year period showed an overall incidence of 1.26 per 100,000 individuals. During the first decade (1994–2004), the incidence of IBD was 0.23 per 100,000 individuals, which increased almost 10-fold to 2.28 per 100,000 individuals during the second decade (2005–2015). Additionally, paediatric IBD in the Singapore cohort had a more aggressive phenotype than that observed in Western data.[15]

Specialised multidisciplinary paediatric IBD clinics (comprising gastroenterologists, IBD nurses, dieticians and social workers) were established to provide care to paediatric patients with IBD since the early 2010s. Patients who reached adolescence were transitioned to the care of adult IBD physicians in a systematic manner via specialised transition clinics established in 2016. A national database for paediatric patients with IBD and collaborative work with other countries has been developed to better characterise disease phenotype and encourage future research in this area.

ADVANCES IN HEPATOLOGY

The last five decades have seen significant advances in the care of paediatric liver diseases in Singapore. This section will highlight the development of hepatology services and technological advances. Neonatal jaundice is a common condition affecting 50% of term and 80% of preterm infants.[16] Phototherapy is the recognised mainstay treatment for neonatal jaundice. Before phototherapy was discovered, babies with jaundice were exposed to early morning sunlight at the hospital attics in KKH. The first phototherapy for neonatal jaundice was performed in 1975 and it has since been well established in hospitals nationwide.

Singapore was an endemic region for hepatitis B infection, with a hepatitis B carriage rate of around 5%–6%.[17] Hepatitis B vaccination has drastically altered the epidemiology of hepatitis B infection in the population.[17] The vaccination was offered to neonates whose mothers were hepatitis B carriers from October 1985 and to all neonates from September 1987. Hepatitis B immunoglobulin was first introduced around 2005 to infants whose mothers were hepatitis B carriers.

BA is preponderant among the Asian population, and Kasai portoenterostomy is a well-established first-line treatment option. Chiang et al[18] reported the outcome data of 58 infants with BA who were treated from 1997 to 2013 at KKH. The majority of these infants had undergone Kasai portoenterostomy. Outcomes, as measured by survival of native liver at two and five years of age, were comparable to those reported by major centres internationally.

The first paediatric liver transplantation was performed in 1991 at NUH. To date, the well-established National Liver Transplant Programme in NUH has covered over 140 paediatric liver transplantations.

TECHNOLOGICAL ADVANCES IN THE DIAGNOSIS OF LIVER DISEASES

As percutaneous liver biopsy allows for histological diagnosis, it remains the gold standard for evaluation of hepatic diseases.[19-21] This procedure was traditionally performed using a 'blind' percussion technique. In recent years, imaging assistance has been shown to reduce complication rates and increase the likelihood of obtaining adequate sampling.[22] Ultrasound-guided liver biopsies are currently the investigative modality of choice, as opposed to the percussion technique.

Transient elastography (also known as FibroScan) is a recognised and well-established bedside method to measure liver fat deposition and stiffness in the liver without the need for liver biopsy.[23] In recent years, this technique has been increasingly performed to monitor liver fibrosis and steatosis in children with chronic liver diseases such as non-alcoholic fatty liver disease, BA and hepatitis B infection.

MULTIDISCIPLINARY TEAMS FOR MANAGEMENT OF COMPLEX GASTROINTESTINAL CONDITIONS

A multidisciplinary approach to patient care has long been established as one of the best models of care. Over the last 50 years, the paediatric gastroenterology departments at both KKH and NUH have witnessed a steady increase in the number of multidisciplinary teams and clinics. These services

Table I. Journey of paediatric gastroenterology in Singapore over the last five decades.

Year	Development of services and techniques in paediatric gastroenterology
1970s–1980s	1. Setting up of Paediatric Gastroenterology and Hepatology subspecialties at Mistri Wing at Singapore General Hospital by Professor Phua Kong Boo (East Wing) and Professor Quak Seng Hock (West Wing) 2. Watson capsule first performed in 1977 3. Phototherapy for neonatal jaundice 4. Total parenteral nutrition services 5. First Kasai portoenterostomy for biliary atresia performed in 1978
1980–1990	1. Paediatric Gastroscopy and Colonoscopy 2. Establishment of Paediatric Gastroenterology and Hepatology at KKH (Eastern Wing) and NUH (Western Wing) 3. Routine Hepatitis B vaccination for neonates
1990–2000	1. First liver transplant at NUH in 1991 2. Liver disease clinic for complex liver conditions
2000–2010	1. Motility studies including impedance-pH study for GERD 2. Wireless capsule endoscopy 3. Rotavirus vaccine trials and successful implementation of vaccination
2010–2020	1. Intestinal rehabilitation programme and nutrition support team 2. Inflammatory bowel disease clinics and national IBD database 3. Multidisciplinary feeding clinics and other specialised gastroenterology disease clinics 4. Establishment of paediatric gastroenterology training programme
Future plans	Paediatric small bowel transplant planning stage

GERD: gastroesophageal reflux disease; IBD: inflammatory bowel disease; KKH: KK Women's and Children's Hospital, NUH: National University Hospital

include: (a) the multidisciplinary feeding clinic (comprising gastroenterologists, speech therapist, dieticians and psychologists) set up for the management of children with feeding difficulties; (b) liver disease clinic (comprising paediatric surgeons and hepatologists) for the management of complex hepatology conditions; (c) multidisciplinary inflammatory bowel disease clinic; (d) metabolic liver disease clinic (comprising hepatologists and geneticists); (e) eosinophilic gastrointestinal disease clinic (comprising gastroenterologists, allergists and dieticians); and (f) nutrition support team for the management of children on long-term TPN.

RESEARCH ADVANCES IN PAEDIATRIC GASTROENTEROLOGY

With the rapid development of services at the two centres, research in paediatric gastroenterology has begun to take centre stage in recent years. Prestigious research grants, including National Medical Research Council grants and SingHealth Foundation grants, have been awarded to researchers within the specialty. The number of publications in peer-reviewed journals has also increased steadily over the years, with more than 200 publications to date. While it is beyond the scope of this article to delve into the many distinguished publications, the authors wish to highlight notable research by the pioneers of the specialty.

Professor Phua Kong Boo has made significant contribution to the prevention of rotavirus in children. He was the lead researcher in the development of the rotavirus vaccine RIX4414 (Rotarix) during Phase 2 and Phase 3 trials. The team recruited more than 10,000 infants in the vaccine trials, which demonstrated a high efficacy rate of 96.1% (95%CI: 85.1%, 99.5%) against severe rotavirus gastroenteritis up to two years of age.[24,25] The vaccine also has a good safety profile and is currently a part of routine vaccination for infants in Singapore and internationally.

Professor Quak Seng Hock is an avid researcher who has published widely in peer-reviewed journals. One of his notable research areas was GERD. His team at NUH demonstrated the efficacy of low-dose erythromycin in reducing GERD among preterm infants in a double-blind, randomised control trial.[26] Hence, low-dose erythromycin is a well-recognised therapeutic option for GERD and other gut dysmotility conditions.

TRAINING OF PAEDIATRIC GASTROENTEROLOGISTS

Both Professor Phua and Professor Quak started their careers as general paediatricians having a personal interest in gastroenterology, and would manage patients with more complex gastroenterological conditions. Following their return from fellowship training in the United Kingdom and Australia in the 1970s and 80s, they introduced specialised gastroenterology services, as detailed in earlier sections of this article. They trained rotating residents and developed the workforce by admitting interested trainee registrars into the service. There were no formal training programmes during those days, and trainees obtained the required knowledge through hands-on experience and in-service training.

In the 1980s, the Ministry of Health set up a Health Manpower Development Programme. This sponsored programme provided an opportunity for trainee registrars to further hone their skills and expertise through attachments at reputable overseas centres. In 2015, a structured paediatric gastroenterology subspecialty training programme was introduced in Singapore. This allows trainees who have completed the Paediatric Medicine Residency Training programme to receive sub-specialty training in the fields of paediatric gastroenterology, hepatology and nutrition. Upon fulfilling all the requirements of the two-year programme, the trainee would have to pass the exit examination to become

an accredited paediatric gastroenterologist. Since 2015, three trainees have entered the subspecialty training programme.

CONCLUSION

Since its inception at the Mistri wing of Singapore General Hospital, paediatric gastroenterology has evolved tremendously along with the growth of medical services, technological advances, research and international collaboration under the leadership of its pioneers. The establishment of paediatric gastroenterology as a subspecialty has led to better patient care, especially with the adoption of the multidisciplinary care model. With constantly emerging therapies, interventions and insight into disease states, further exciting progress in this specialty is anticipated. Continued efforts in implementing the best models of care, keeping abreast of therapeutic advances and robust research will ensure that Singapore's paediatric gastroenterologists continue to improve the lives of children with GI disorders.

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A history of paediatric surgery in Singapore

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INTRODUCTION

Singapore's children and their doctors have much to celebrate. With the 100th anniversary of the introduction of paediatrics in Singapore, we will also commemorate the 40th year of the establishment of paediatric surgery as a subspecialty in Singapore in September 2021.

Paediatric surgery first emerged as a recognised surgical subspecialty after the Second World War, with the formation of its first professional societies in the United States in 1948, the United Kingdom in 1953, Japan in 1964 and Asia in 1972 by groups of early visionary surgeons.[1,2] They realised that in order to improve the outcomes of surgery in children, paediatric surgery must be considered a dedicated discipline and be performed by separately trained specialist surgeons, and that children must be treated differently, and not merely as small adults. The development of paediatric surgery in parallel with paediatric anaesthesia, intensive care and neonatal care has drastically reduced the mortality associated with newborn surgery as well as surgery for congenital malformations. Over the last four decades, the survival rates for surgically correctable congenital malformations in Singapore have improved to levels on par with those of first-world dedicated units.[3,4]

THE BEGINNINGS OF PAEDIATRIC SURGERY IN SINGAPORE

In Singapore, the first medical specialties were introduced in the 1950s amidst a period of rapid socioeconomic development. At the Singapore General Hospital (SGH), Dr Yeoh Ghim Seng and Dr Yahya Cohen were appointed to head the surgical units 'A' and 'B', respectively. Despite a lack of distinction between adult and paediatric surgical practice at that time, the first conjoined twins, Karen and Kate, were separated by Dr Yeoh and Dr Choo Jim Eng at SGH on 12 December 1961.[5]

On return from an overseas attachment to a cardiothoracic unit in New Zealand, with no job openings available in cardiothoracic surgery, the then Dr V T Joseph joined the Surgery 'B' unit in SGH, under the headship of Dr Choo. Dr Joseph had a particular interest in paediatric surgery and worked tirelessly for the children, along with two other adult general surgeons, Dr Chua Wan Hoi and Dr J J Murugasu, who maintained a part-time paediatric surgical practice. Dr Chua and Dr Murugasu subsequently left for private practice, and following the restructuring of SGH, Dr Joseph established the first paediatric surgery unit in Singapore in October 1981.[5-7]

The first paediatric surgical inpatient unit was housed in Ward 9, Bowyer Block, where a section of the ward was separated off from the adult area and made into a nursery. Patients who required critical care after major surgery were kept in Ward 10, where they were nursed alongside adult patients. The ward was later relocated to Block 5 Level 5. Sister Seah Siew Hua oversaw inpatient nursing care. Sister Nyan Lee Kian was in charge of the operating theatre, and the paediatric cases were performed in OTL4 and then in OTL1. The emergency theatres were shared with adult surgeons at night, with an elective surgical list dedicated to paediatric cases during the day. In 1991, the department commemorated its first decade with an academic meeting at the College of Medicine Building (Fig. 1).

The first trained paediatric surgeons were Dr Ong Nai Theow, Dr Cheah Siew Leng, Dr Sim Chiang Khi and Dr K Prabhakaran. All these surgeons went to Melbourne for overseas training at the Royal Children's Hospital (RCH). Among them, Dr Sim and Dr Cheah were the first to be formally accredited after passing the Australian College of Surgeons fellowship examination.[8]

The later paediatric surgeons included Dr Grace Tan and Dr Carolyn Tan. Following the establishment of the National University Hospital (NUH) on the campus of the National University of Singapore in 1985, the 'A' unit of the Department of Surgery at SGH shifted to the Kent Ridge campus.[7] Dr Grace Tan left to practise in NUH, and Dr Carolyn Tan left NUH for SGH, subsequently taking over as the head of the department and, later, as the Division Chair in KK Women's and Children's Hospital (KKH). Subsequently, Dr Carolyn Tan left medical practice and moved to Perth.

In NUH, Dr K Prabhakaran began his practice following his training in RCH in 1983. He led the service at NUH and subsequently established a dedicated Department of Paediatric Surgery in 2001. In 1990, the NUH team established the Singapore Paediatric Transplantation Programme and performed the first paediatric kidney transplant in Singapore in 1989 and the first paediatric cadaveric liver transplant in 1991.

The foundation of a local postgraduate training programme in paediatric surgery followed closely after the establishment of the unit in SGH.[9] At its inception, the programme required paediatric surgical trainee applicants to first complete a full training tenure in general surgery and pass the FRCS exit examinations before entering paediatric training. One of the early surgical trainees to be admitted to the programme was Dr Anette S Jacobsen, who exited her training in 1993 and was awarded the first FAMS (Paediatric Surgery) in May 1996.

In 1997, the children's services of SGH were moved to the newly constructed KKH. The move also allowed several other dedicated paediatric surgical subspecialties to flourish, such as

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Fig. 1 Scenes from the commemoration of the 10th anniversary of the establishment of the Department of Paediatric Surgery, Singapore General Hospital. (a) Event banner; (b) Dr Phua Kong Boo; (c) Dr Anette Jacobsen (left) and Dr VT Joseph (right); (d) Dr Wong Keng Yean (left) and the late Dr Tan Cheng Lim.

otolaryngology, ophthalmology, neurosurgery, orthopaedics and cardiothoracic surgery. Being supported by dedicated paediatric anaesthetists, neonatologists and radiologists, the multidisciplinary setup in the new children's hospital served to further improve the outcomes for childhood surgical diseases. The advancements in these other aspects of paediatric care implied gentle pressure on the paediatric surgeons to develop in their field.

DEVELOPMENT OF PAEDIATRIC SURGICAL SUBSPECIALTIES

With miniaturisation of instruments in the late 1990s, paediatric surgeons began utilising more minimally invasive approaches. This led to faster postoperative recovery, less requirement of analgesia, and quicker return to normal activities and play. Dr Tan Hock Lim first introduced minimally invasive surgery for children at SGH in 1991 during the years he worked in Singapore.

Together with Dr Phua Kong Boo in the area of paediatric gastroenterology and hepatology, surgeons and paediatricians worked closely on the management of patients with biliary atresia, introducing stepwise improvements to surgical methods and medical care.[10] Dr Phua also worked closely with the newly formed department at KKH on one of the earliest international collaborative studies on intussusception in Singapore.[11,12]

Other early pioneering paediatricians such as the late Dr Tan Cheng Lim and Dr June Low took an interest in the management of paediatric oncology cases. On her return from an overseas attachment at RCH, Dr Grace Tan introduced and developed the implantation of long-term indwelling central venous access devices and gastrostomy buttons, and developed a local device for air enema reduction of intussusception. She was the earliest surgeon to focus on paediatric surgical oncology, a rapidly progressing subspecialty. In 1999, Dr Chui Chan Hon was sent as the first paediatric surgeon from Singapore to be formally trained in paediatric surgical oncology at the renowned St Jude Children's Research Hospital.

Paediatric urology has always been an integral part of paediatric surgical practice. In 1989, Dr Joseph, along with the late Dr Julian Wee, first described the Singapore flap – a pudendal thigh flap used in vaginal reconstruction.[13,14] In the same year, laser circumcisions were introduced. Now commonly used, the approach substantially reduced bleeding complication rates and operative time.[15,16] Dr Joseph was also known for the various novel flap techniques he described for hypospadias repair.[17,18] Later, Dr Cheah introduced urodynamic evaluations for children, and Dr Yap Te-Lu and Dr Chao Sin Ming established the first voiding dysfunction clinic.

Since then, the national fraternity of paediatric surgeons in Singapore has continued to grow, establishing the chapter of paediatric surgeons of the Academy of Medicine, Singapore in 2005. Among other national efforts, the Southeast Asia Paediatric Endosurgery Group was established in Singapore in 2008, building on shared interests in endosurgery among the local paediatric surgical community. The current paediatric surgery department at KKH comprises four teams of surgeons with various areas of subspecialisation, and the department at NUH has

developed dedicated expertise in paediatric transplantation.[19] Paediatric surgery specialty training is now a six-year programme with a regular stream of applicants, which ensures a bright future for the specialty in Singapore in the decades to come.

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SINGHEALTH DUKE-NUS PAEDIATRICS ACADEMIC CLINICAL PROGRAMME

The SingHealth Duke-NUS Paediatrics Academic Clinical Programme (Paeds ACP) is one of the ACPs under the umbrella of the SingHealth Duke-NUS academic medical centre. The academic medical centre builds on a partnership combining the collective clinical strengths of Singapore's largest healthcare cluster, SingHealth, with Duke-NUS' research and medical education capabilities. Pioneered by KK Women's and Children's Hospital (KKH) and Singapore General Hospital (SGH), the Paeds ACP was established in 2011.

With a mission to improve the health of children everywhere, the Paeds ACP plays a crucial role in shaping the future of child health in Singapore and beyond. Over the years, the Paeds ACP has earned a reputation for the high quality of clinical teaching and the commitment to translational research. As the largest paediatric healthcare network in Singapore, the Paeds ACP has three focus areas – medical research, medical education and clinical care.

In honour of some of our outstanding paediatricians through the years, we have established the following philanthropic funds to ensure their lifelong dedication to transforming the healthcare landscape of children lives on. We invite you to partner with us by making a gift towards their legacy.

Clinician Educator Faculty Development Fund in honour of Prof Phua Kong Boo

It is critical that our medical professionals receive the training to upgrade their educational capabilities and enhance their teaching skills to develop a culture of continuous teaching and learning, and in doing so, achieve a steady, sustainable pool of future-ready paediatricians to provide the best possible care for paediatric patients. Emeritus Consultant Professor Phua Kong Boo's passion and tireless dedication to public service in teaching and healing will inspire future generations of clinician educators and leave a lasting legacy of hope, healing, and health.

Community Child Health Faculty Development Fund

Delivering child health services to the community as close to the doorstep of children and their families as possible is crucial in moving beyond healthcare to health. Integrating healthcare services for children into the very heart of their community makes all the difference in the world for their holistic well-being. This can only be made possible when our faculty successfully builds strong collaborations with education, social and community supports inclusive of parents and caregivers. Emeritus Consultant Professor Ho Lai Yun's strong advocacy for world-class training for our paediatric healthcare professionals is one that we share and his distinguished public service through the years has truly changed the landscape of paediatric healthcare. His unwavering commitment to a better life for our children has inspired us to establish this fund in his honour for a lasting legacy.

J.M. Gomez Faculty Development Fund in Patient Safety and Clinical Quality

Excellence in healthcare requires that we continually strive to discover novel approaches to create effective, sustainable change and nurture a culture of patient safety and clinical quality. Understanding the importance of patient safety and clinical quality, this fund was created in memory of Dr Joseph Manuel Gomez, a beloved "healer, teacher and mentor", whose life and leadership elevated the quality of healthcare delivery in Singapore and impacted countless lives.

Tan Cheng Lim Research and Education Fund

In honour of our well-loved and distinguished Emeritus Consultant the late Professor Tan Cheng Lim, this fund was created to pioneer advances in paediatric medicine by creating patient-centered programmes; equip tomorrow's paediatric healthcare leaders through support of scholarly activities and initiatives, and promote innovative research among clinician-researchers leading to new multi-disciplinary cures. We are pleased to share the Fund has inspired budding clinician scientists and doctors to begin pilot research studies that would not have been possible otherwise.

For more information, please contact the KKH Development Department by email: development@kkh.com.sg or by phone: 6394 8180 / 6394 8439.

EVOLUTION OF PAEDIATRIC MEDICINE IN SINGAPORE