MEDICINE THEN AND NOW #8

KIDS' STUFF

Advances in general paediatrics

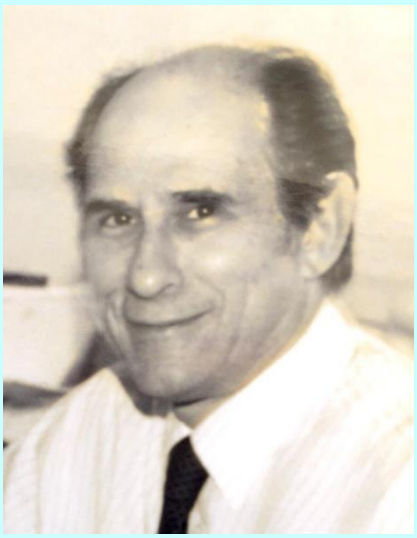
1960-2020

Gary Katz London

Jack Kussel Johannesburg

Changes in general paediatrics and child health since1960

Gary Katz of London writes:



Gary Katz writes: When we graduated my knowledge of Paediatrics was limited. We had excellent teaching at Baragwanath and the Transvaal Memorial Hospital (TMH). We were exposed to a vast array of clinical cases, unmatched by what I have seen in the UK or USA. Although the medical care in South Africa was excellent, the psycho-social needs of hospitalised children was not adequately met.

Medical care had advanced considerably in the first half of the 20th century. I never anticipated that this would be followed by exponential advances in most branches of medicine, including Paediatrics in the second half.

As this is personal rather than academic review of the changes, this account of changes in Paediatrics will not by any means be comprehensive. Several of our classmates (Avroy Fanaroff, Jeff Maisels, Martin Bobrow and Aubrey Milunsky) have been at the forefront of the astonishing advances in Neonatal Paediatrics and Genetics. We have had a taste of this in their biographies and notes of medical advances in their spheres.

During my Paediatric journey I've been interested in several aspects of Paediatrics. The advances in many of the specialities have been breath-taking, but in some the changes have been limited. Unexpected and unwelcome new diseases have also emerged.

Paediatric cardiology

In our student days Rheumatic Heart Disease and Paediatric Cardiology were virtually synonymous. We soon became skilled in auscultation, able to distinguish the murmurs of mitral and aortic valvular disease. We were taught about congenital heart disease and ‘Blue Babies’ and their poor prognosis, but hardly saw any patients. Paediatric cardiac surgical success was limited to ‘extra-cardiac’ conditions. The successful ligation of patent ductus arteriosis (PDA) in the late 1930’s, marked the ‘birth’ of Paediatric Cardiology. During the 1940’s more complicated extra-cardiac procedures followed, including surgery for Tetralogy of Fallot, Coarctation of the Aorta and Pulmonary Stenosis.

In the year we started Medical School the first successful repair of an intra-cardiac defect was achieved in the USA using Cardio-Pulmonary bypass. As a Resident in New York in 1962, I was given the dubious honour of assisting the Paediatric Cardiologist at his 6:00 am Friday cardiac catheterisation sessions. Diagnostic catheterisation is now almost redundant in Paediatric Cardiology, following the introduction of echocardiography, colour flow Doppler and MRI.

The high mortality rate of Paediatric Cardiac Surgery has dropped dramatically following the contributions of cardio-pulmonary physiologists, greater knowledge about the cause and pathogenesis of cardiac malformations and referral to specialist cardiac centres. Prevention is coming to the fore; children at risk for adult cardio-vascular disease are being identified and appropriate preventive strategies are being followed.

Bacterial meningitis

When we were students intensive care units did not exist in the hospitals in which we trained. Several of our fellow graduates became intensivists. Andre Van As was involved in the development of Intensive Care at The Gen. Avroy and Jeff, as indicated earlier, have made major contributions in Neonatal Intensive Care. In the UK, Paediatric Intensive Care followed the introduction of Paediatric Cardiac and Neonatal Intensive Care, resulting in major improvements in the treatment of children with acute respiratory and neurological diseases as well as sepsis.

Meningitis has always been one of the major acute illnesses that General and Neonatal Paediatricians have had to treat. We have been fortunate to train and work in the antibiotic era. With the introduction of antibacterial Sulphonamides in the 30’s and the antibiotics in the 40’s, it became possible to cure children with Meningococcal, Pneumococcal and Haemophilus meningitis. Nevertheless, when we were students and trainees the mortality and morbidity rates remained high. Improvements followed as new intravenous antibiotics were developed. Despite early diagnosis and prompt antibiotic treatment many children, particularly those with meningococcal septicaemia, continued to die

After antibiotics, the next major breakthrough was the introduction of vaccines for Haemophilus B, Pneumococcal and Meningococcal C infections and in 2015 Meningococcal B and MenACWY (which protects against 4 strains of the meningococcal bacteria A, C, W and Y). Although the incidence of meningitis is at an all-time low, cases of meningococcaemia still

occur. The mortality and mortality rate has fallen as a result of the early and vigorous management of sepsis in Paediatric and Neonatal ICU's. In the UK the incidence overall in 2017/2018 had fallen to 1/100,000. In infants there has been an increase from 11/100,000 in 2016/17 t0 16/100,000 (MenB is the most common pathogen). In children there has been a decrease from 5/100,00 to 4/100,000. In 2020 a Paediatric Houseman could spend 6 months in a busy children's ward without seeing a child with meningitis; unthinkable in the 60's!

Cancer

When we were students and trainees, the diagnosis of cancer in children was usually a death warrant. In the 70's improvements in chemotherapy, radiotherapy and surgery brought incremental improvements in the outlook. Between the 70's and the 90's life expectancy increased by almost a decade. Over the past 30 years the five year survival rate has increased to more than 80% of the children treated for cancer.

The greatest advances have been made in the treatment of leukaemia and lymphoma. Younger people have a better prognosis. Over 90% of children aged 14 or less will survive Acute Lymphoblastic Leukaemia for 5 years, compared to 70% of patients between 15 and 24. The 5 year survival rate for Acute Myelogenous Leukaemia is lower (60-70)%) Despite these advances adult survivors of childhood cancer have an increased risk of long term morbidity and premature death. A recent study showed as much as a 28% gap in life expectancy for survivors of childhood cancers diagnosed between 1970 and 1980. Recent advances in treatment, based on DNA analysis, bone marrow transplantation, and tailored and targeted treatments are leading to improved cure rates and life expectancy.

Preventive measures

Although the emphasis during our training was on the treatment of children's illnesses, the focus now also includes preventive measures. Over 60 years we have witnessed dramatic breakthroughs in the prevention of disease. This has been achieved by

1. I**MMUNISATION**. As students we learnt about the use of vaccines to reduce the incidence of smallpox, rabies, whooping cough, diphtheria and tetanus. The adverse effects of some of the early vaccines limited their use. During the period we were medical students, the Salk vaccine was introduced, leading to a dramatic reduction in polio. Since graduating we have seen improvements in DPT vaccines (Diptheria, Pertussis and Tetanus) and the introduction of vaccines for common diseases such as measles, mumps, rubella, hepatitis A and B, chicken pox, rotavirus.

2. **SCREENING**. Screening has also helped to change the face of Paediatrics. In my early years as a Neonatal Registrar, I spent considerably more time doing exchange blood transfusions for Rhesus incompatibility than ventilating neonates. The injection of anti-D immunoglobulin to Rhesus negative mothers had an immediate and major impact. (This breakthrough is detailed in Jack Kussel's article, below)

Pre-natal, intra-uterine and neonatal screening (clinical and blood spot) has led to the early detection and treatment of many conditions including congenital heart disease, congenital dislocation of the hip, hypothyroidism, sickle cell disease, cystic fibrosis and a number of rare metabolic diseases, which have fatal outcomes without early intervention.

3. **IMPROVING MATERNAL HEALTH** Steps mothers take to stay healthy before and during pregnancy increase the chances of them having a child without a birth defect. A striking example is the reduction in the incidence of spina bifida in infants whose mothers take folic acid. The foetus can be harmed by other nutritional deficiencies, as well as smoking, alcohol, drugs and harmful substances

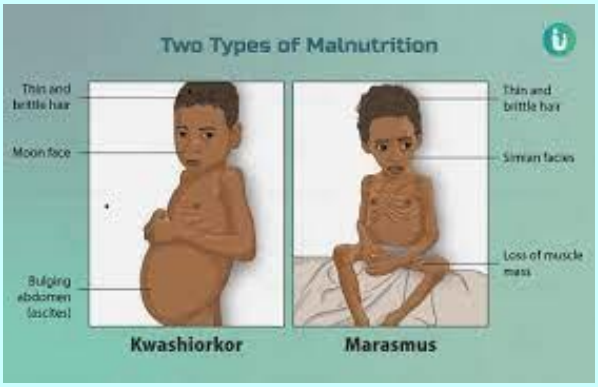
W**hat about other changes and what does the future hold?**

Major breakthroughs have occurred in many other specialities. The outlook for children with surgical, respiratory, gastro-enterological, haematological, neurological, metabolic and locomotor disorders has improved significantly. Specialities such as immunology and transplantation surgery, which did not feature in our curriculum, play a major part in 2020 Paediatrics. Relatively simple measures have had striking benefits. The incidence of 'Sudden Infant Death' fell dramatically when the sleeping position of infants was changed from prone to supine.

Death as a result of car accidents in infants fell by 70% after the introduction of car seats and by 45% in children aged 4-8, using booster seats. In older children, as with adults, seat belts have significantly reduced the risk of death or serious injury. Clinicians have been challenged by a number of viral infections that did not exist in 1960 such as HIV, Ebola and Zika and I am sure others. Antibiotic resistance is now a major problem. Covid has demonstrated how international collaboration between scientists can result in the development of an effective vaccine in less than a year and bodes well for future developments.

What about the downside?

The major causes of childhood mortality when we were students were malnutrition, TB and Malaria. Sadly, these remain the major causes in Africa, Asia and Latin America. Malnutrition still causes 3.1 million deaths a year in children under 5. That is 45% of all deaths in this age group; The survivors of malnutrition are likely to be stunted, wasted and/or underweight. In so-called developed countries food poverty and obesity are growing problems. Nearly 250,000 children still die of TB annually. BCG does not prevent TB, although it does protect children from major complications. A truly effective vaccine is urgently needed. The anti-microbial drugs that were developed in the 50's and 60's are still the ones in use today but are less effective because of drug resistance. Malaria is still responsible for 400,000 deaths a year. The Oxford Vaccine Research Group that speedily developed an effective Covid vaccine, hope to have a suitable vaccine available for Malaria in 2021/22.



Mental health

Although the progress in this branch of Paediatrics has not matched the rapidity of the advances we have seen in other Paediatric specialities, Child Psychiatrists and Psychologists have worked tirelessly to improve the mental health and welfare of children and adolescents. The teamwork that now exists between Psychiatrists, Psychologists, Paediatricians and Social Workers has led to a major improvement in the psychological needs of children and adolescents in hospital and the community in contrast to the provisions we witnessed in our student days.

The tasks that lay ahead are nevertheless daunting. Our newspapers highlight issues on a daily basis. Despite attempts at 'Safeguarding' physical, sexual and emotional child abuse, sadly it is rife. Eating disorders have increased in developed countries and there is worldwide child extortion and slavery. I am optimistic that the efforts of Child and Adolescent Psychiatrists, Psychologists, Paediatricians, Social Workers will ensure that in time these issues will decrease significantly.

Advances in General Paediatrics, **Gary Katz, London**, May 2021

(Read Gary's biography here Katz, Gary)

Edited by Geraldine Auerbach MBE, London,

Jack Kussell of Johannesburg writes

Highlights of the changes that have occurred in my career over the past 50 years.

I practiced general Paediatrics with Neonatology as a sub-speciality in my career and here are some of the marked changes I have witnessed.

A**. Neonatal Jaundice**

The management of severe Haemolytic Jaundice of the new-born was exchange transfusion. It was not uncommon for up to 5 exchange transfusions to be performed per week on different babies. At times as many as 3 transfusions would be performed on the same baby over a period of three days. Over the past 10 years I have not performed any exchange transfusions. What has brought about the change?

- Recognising sensitised mothers after the birth of their first infant and giving them antiserum postnatally.
- The monitoring of antibody titres in sensitised infants during pregnancy.
- The checking of blood group status of every baby at birth born of an Rh negative or Group O mother.

- Bilirubin must be fractionated into indirect or direct bilirubin rather than just relying on the total level of bilirubin. The serum proteins must be adequately maintained and at times neonatal plasma given.
- Photo-therapy has now become one of the main factors in managing all forms of neonatal jaundice.
- Finally, the introduction of Polygam (intravenous human Gobulin) therapy early on in badly sensitized infants has further reduced the need for exchange therapy.

These factors completely changed my approach to the management of haemolytic jaundice of the newborn.

B. Neonatal Respiratory Distress.

The changes in the management of both Hyaline Membrane Disease as well as PFC (Persistent Foetal Circulation) have seen marked changes in management over the years.

In Hyaline Membrane Disease the advent of surface tension lowering factors such as Surfactant and Curosurf used early on by intubation have certainly decreased the need for prolonged ventilation and, according to some experts, claims have been made as to why ventilation would be necessary at all in a great majority of cases

My early experiences of treating Hyaline Membrane ranged from giving oxygen and intravenous therapy. Then came the “Bird ventilator” and with further advances in ventilation therapy the introduction of intermittent positive and negative pressure ventilation.

As the realisation dawned on us that too much pressure or ventilation for too long could be a factor in contributing to subsequent broncho-pulmonary dysplasia, we started to introduce oscillation with or without nitrous oxide therapy.

Now finally the pendulum has gone full course and we are managing many of our cases of Respiratory Distress with the quick introduction of intubation and the administration of surface tension lowering factors eg Survanta or Curosurf, followed by detubation and possibly no need for ventilation at all.

The management of the PFC infant with Respiratory Distress has also undergone many changes. The previous practice was administering oxygen as almost a routine part of the resuscitation. Today the practice is rather withholding oxygen and allowing the saturation levels to fall in the first one or two minutes, thereby allowing the circulation to become balanced following the closure of the ductus.

We have changed from the previous practice of withholding fluids, to now even giving bolus’s of saline in the shunting infant.

How dramatically the management has changed in both Hyaline Membrane and PFC over the past 50 years.

Vaccinations.

I will quote a radio and TV advertisement regarding one specific type of vaccine. "Don't hesitate – vaccinate". The slogan should really be amended to "hesitate before you vaccinate". No one will argue that if we use vaccination to prevent mortality or severe morbidity there can be no contra indication to that type of vaccine. I refer specifically to:

- Polio
- TB(BCG),
- Diphtheria
- Whooping cough (Pertussis)
- Tetanus
- Meningitis including meningococcal (Menactra vaccine)
- Hepatitis
- Measles.

However, the grey areas where I believe that we should hesitate before routinely vaccinating are

- 'flu vaccines
- chicken pox
- mumps,
- Rotavirus
- Pneumococcal vaccine

In my opinion, these vaccines are totally over prescribed and should only be used for selective criteria. I believe that vaccines have impacted on the ability of our T-cells and Lymphocytes ability to cope with more serious conditions due to our immune systems being bombarded with vaccines for diseases where it might be better off relying on normal immune mechanisms to cope with the disease processes themselves instead of giving this to every child, and only use these vaccines for children at risk.

With the emergence of wild strains of Polio, Measles and no doubt the constant mutations of many of the severe viral infections eg Covid-19 it may be prudent in the less compromised child to allow their own immune systems to take over and thereby also breed herd immunity.

Chicken Pox in our youth was considered an illness that we should all get in childhood so that we could then be conferred with lifelong immunity. Today Chicken Pox vaccine is routinely administered in some children as part of the vaccination programme. The result is cases are now being reported of chicken Pox and Herpes infections in adults that have been immunised and some are becoming seriously ill.

To conclude, I have no argument against the first group of vaccines that I mentioned, but in my practice, I "hesitate before I vaccinate" in the second group.

Advances in General Paediatrics.Jack Kussell Johannesburg, April 2021

(Read Jack's biography here Kussel, Jack Josiah)

Edited by Geraldine Auerbach MBE, London August 2021

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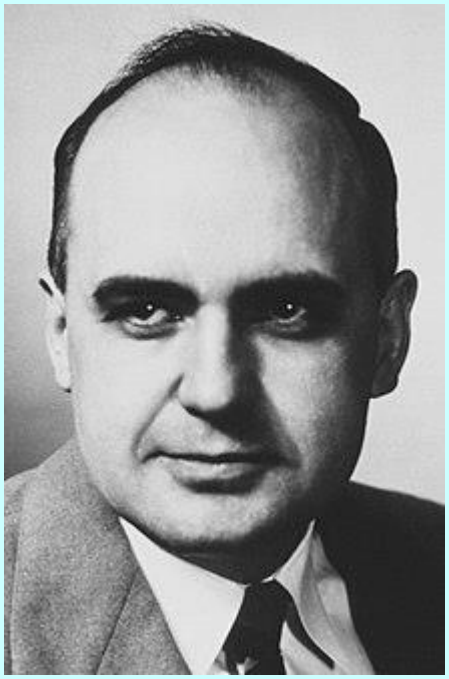
Avroy Fanaroff has added some paragraphs on immunization

Immunization is one of the most cost effective and life-saving interventions preventing over 2.5 million deaths annually. Unfortunately, over 20 million children living in under-developed countries still do not have access to vaccines or are under-immunized. Hepatitis B is a chronic infection that ultimately leads to cirrhosis, liver failure and hepatic carcinoma. Mothers can pass the hepatitis B virus to their baby during childbirth without knowing it, since it is passed through blood and bodily fluids. Immunization, starting at birth, is very effective, protects the baby from hepatitis B; protects others from the disease and protects the child from developing liver disease and cancer. The hepatitis B vaccine is very safe, and it is effective. Greater efforts need to be made to ensure that this vaccine is available throughout the world.

Hilleman's role



Today, few people outside the immunology field recognize Maurice Ralph Hilleman's name. Unlike Louis Pasteur, who developed vaccines for rabies and anthrax, or Jonas Salk, who created one for polio, Hilleman (pictured right in about 1958) never basked in fame's limelight, but he is credited with saving more lives than any one person in modern history. He created more than 40 vaccines, including the staple trio of measles, mumps and rubella (MMR), hepatitis A and B, influenza and chickenpox, to name a few. Experts estimate that Hilleman's vaccines save about 8 million lives a year. He was motivated by one thing — he wanted to try and make vaccines for every disease that could possibly hurt or kill a child."

Some Hilleman history from Wikipedia

After joining E.R. Squibb & Sons (now Bristol-Myers Squibb), Hilleman developed a vaccine against Japanese B encephalitis, a disease that threatened American troops in the Pacific Ocean theater of World War II. As chief of the Department of Respiratory Diseases at Army Medical Center (now the Walter Reed Army Institute of Research) from 1948 to 1957, Hilleman discovered the genetic changes that occur when the influenza virus mutates, known as *antigenic shift* and *antigenic drift*, which he theorized would mean that a yearly influenza vaccination would be required.[2][18]

In 1957, Hilleman joined Merck & Co. (Kenilworth, New Jersey), as head of its new virus and cell biology research department in West Point, Pennsylvania. It was while with Merck that Hilleman developed most of the forty experimental and licensed animal and human vaccines with which he is credited, working both at the laboratory bench as well as providing scientific leadership.

Hilleman served on numerous national and international advisory boards and committees, academic, governmental and private, including the National Institutes of Health's Office of AIDS Research Program Evaluation and the Advisory Committee on Immunization Practices of the National Immunization Program.

Asian flu pandemic

Hilleman was among the first to recognize that a 1957 outbreak of influenza in Hong Kong could become a huge pandemic. Working on a hunch, after nine 14-hour days he and a colleague found that it was a new strain of flu that could kill millions.[6][19] Forty million doses of vaccines were prepared and distributed.[20] Although 69,000 Americans died, the pandemic could have resulted in many more deaths in the United States. Hilleman was awarded the Distinguished Service Medal from the American military for his work. His vaccine is believed to have saved hundreds of thousands of lives.[7][11]

In 1968, during the Hong Kong flu pandemic, Hilleman and his team also played a key role in developing a vaccine, and nine million doses became available in 4 months.[7][21]

SV40

Hilleman was one of the early vaccine pioneers to warn about the possibility that simian viruses might contaminate vaccines.[22] The best-known of these viruses became SV40, a viral contaminant of the polio vaccine, whose discovery led to the recall of Salk's vaccine in 1961 and its replacement with Albert Sabin's oral vaccine. The contamination actually occurred in both vaccines at very low levels, but because the oral vaccine was ingested rather than injected, it did not result in infections or any harm.

Mumps vaccine

In 1963, his daughter Jeryl Lynn came down with the mumps. He cultivated material from her and used it as the basis of a mumps vaccine. The Jeryl Lynn strain of the mumps vaccine is still used today. The strain is currently used in the trivalent (measles, mumps and rubella) MMR vaccine that he also developed, the first vaccine ever approved incorporating multiple live virus strains. Like many other vaccines and medications of that time period, the vaccine was initially tested in children with intellectual disabilities who lived in group homes—this was because, given the poor hygiene and cramped quarters of their accommodations, they were at much higher risk of infectious disease.[23]

Hepatitis B vaccine

He and his group invented[4] a vaccine for hepatitis B by treating blood serum with pepsin, urea and formaldehyde. This was licensed in 1981, but withdrawn in 1986 in the United States when it was replaced by a vaccine that was produced in yeast. This vaccine is still in use today. By 2003, 150 countries were using it and the incidence of the disease in the United States in young people had decreased by 95%. Hilleman considered his work on this vaccine to be his single greatest achievement. Liver transplant pioneer Thomas Starzl said "...controlling the hepatitis B virus scourge ranks as one of the most outstanding contributions to human health of the twentieth century...Maurice removed one of the most important obstacles to the field of organ transplantation".[24]

Later work and life

In his later life, Hilleman was an adviser to the World Health Organization. He retired as senior vice president of the Merck Research Labs in 1984 at the mandatory retirement age of 65. He then directed the newly created Merck Institute for Vaccinology where he worked for the next twenty years.

At the time of his death in Philadelphia on April 11, 2005,[16] at the age of 85, Hilleman was Adjunct Professor of Pediatrics at the University of Pennsylvania in Philadelphia.
