The Future of Medicine from the Standpoint of the Practising Paediatrician†

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From the time of recorded history of medicine, the doctor whether he be the ancient healer or the modern medical practitioner, the doctor had practised the art and science, on the basis of curing the patient when he has an illness. The doctor is sought out when the patient is ill. The so-called Hippocratic Oath refers to the codes the doctor should abide by when he practises his vocation,[1] in such a manner that is honourable and that he should in no way harm his patient. This behaviour of the doctor towards his ill patient is further strengthened by numerous extensions to the 'original' Hippocratic oath through the ages till the present day to bring the oath to deal with changing social times. It emphasises the relationship between the doctor and the ill human being, i.e. the patient. Therefore, the doctor 'waits' till the human being becomes diseased, before he practises his art. His job is done when he cures the patient, or when the patient succumbs as a result of the disease, as not all diseases are curable.

Gradually, doctors came to realise that instead of waiting for the disease to affect their patients, it was often possible to prevent diseases in human beings, the classic example being Jenner's observation that vaccination with cowpox could prevent human smallpox. Smallpox vaccination is so successful that it has been eliminated as an infectious disease throughout the world, so that smallpox vaccination is no longer practised as there is no smallpox to deal with. When smallpox was rife, there was (and still is) no treatment for smallpox so that prevention of smallpox is an example of a true medical triumph. The new generation of human beings, being born after the eradication of smallpox, cannot appreciate this medical triumph as he does not experience the illness. He does not seek out his doctor for management of smallpox as his parents, grandparents and great grandparents did. When the latter survived, they were grateful to their doctors, and of course, they willingly paid their fees for the services of their doctors. They had experienced smallpox and they can compare the situation previously and now, and appreciate what vaccination had achieved. The present generation cannot as they had not seen or experienced smallpox. I would like to refer this phenomenon of experience and appreciation as the syndrome of experience-appreciation (or SEA).

Because of SEA, the human being will seldom see his doctor when he is well, much less pay him a fee by seeking his advice to prevent him getting a disease, which he now has not got. This attitude affects the doctor also and he is unenthusiastic in advising his patients how to behave to prevent him falling ill. Even when the patient gets this advice from the doctor, he tends not to follow the advice which often involves a sacrifice on the part of the patient as he often has to forego some aspects of his life style. Obvious examples include advice on cessation of smoking or men ceasing visiting female sex workers. However, as doctors we should not give up so easily and we should educate our patients when they visit us for illnesses which they suffer from in order to prevent them getting other diseases in themselves or members of their family. They do not now suffer from these illnesses, but with time, they might. Many of these are incurable and these illnesses cause severe suffering not only in the patients but also in non-affected family members who have to take care of them. This group of illnesses usually has a genetic component which may be the total cause of the disease, e.g. Mendelian and chromosome diseases, or the diseases are caused by a combination of not one genetic cause but many genetic factors, all working with environmental factors and finally resulting in the individual getting the disease. This third group of diseases is termed multifactorial as both genes and environment are needed for the surfacing of the diseases. The majority of diseases are in this group such as infection, malignancy and others.

I would therefore like to discuss with you some of these diseases and their prevention in Singapore and the results that have been achieved and the impact that has been made to the health of the Singaporeans.

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Mendelian Diseases

The commonest Mendelian diseases encountered in Southeast Asia are the thalassaemias and erythrocytic glucose-6-phosphate dehydrogenase deficiency.

(A) b Thalassaemia

The thalassaemias were first described in America by Cooley[2] who wrote about a form of chronic haemolytic anaemia seen in immigrants from Southern Europe, viz. Greeks, Italians and settled in America. Patients died if not given blood transfusions from infancy and this caused haemosiderosis of the organs and these complications arising from the repeated transfusions finally killed the patients when they reached the age of 10 to 15 years. The liver and spleen were enormously enlarged with compensatory erythropoiesis causing widening of the medullary cavity of bones and often resulting in a typical facies and fractures of the long bones. There was no effective treatment and even now there still is no simple effective treatment. The patients were first referred to as Cooley's anaemia, and later the term Mediterranean anaemia or thalassaemia (thalos = the sea, meaning the Mediterranean Sea, referring to the origin of these patients from Southern Europe bordering the Mediterranean Sea).

When I was a medical student, we saw identical cases in Chinese and Malay patients and we referred to them as Cooley's anaemia as we could not find any difference in their disease from that described by Cooley in the Meditteranean races. However, when we showed these patients to visiting Caucasian haematologists, they said they could not be examples of Cooley's anaemia because they were Asians and not Southern Europeans. As I worked in the Paediatric Wards (Wards 11 and 12) in General Hospital, we doctors had to spend a lot of time getting intravenous access in these patients for their monthly blood transfusions; there was always one or two patients in the wards. When the splenomegaly became enormous, the organ was not only a mechanical impediment, it also became hypersplenic with further haemolysis, thrombocytopenia and neutropenia and the patients became more ill and needed more frequent transfusions. At this point, splenectomy was performed and they improved temporarily and finally died of cardiac and liver haemosiderosis.

It was only later that Cooley's anaemia was designated a globin chain inherited autosomal recessive disease and affected the production of the b chains, and the term b thalassaemia was applied to Cooley's anaemia. It was at this point in time that with the gold standard of diagnosis established, that it was proved beyond doubt that our cases of Cooley's anaemia are identical to the cases of Mediterranean anaemia as described in the West.

At that time, there was only one paediatric unit, i.e. the government paediatric unit in General Hospital and I collected and followed these patients up and discovered that annually there were about 15 new cases born with b thalassaemia major and over a period of 10 years, there were easily 150 such patients suffering from this devastating chronic anaemia with no effective treatment except for repeated blood transfusions, which treatment finally killed the patient after years of suffering, not only to the patients themselves, but also to all the members of the family. There were unfortunate families with 2 or 3 patients and one family had 5 such affected children! The suffering of such families did not escape the notice of doctors, nurses and social workers helping these patients and their families to cope. At that time, it was not uncommon for some parents to bring their child with chronic illness, usually with mental deficiency, to be warded in hospital and then absconding without giving details of names, addresses etc. But this never happened to families with b thalassaemia major. In spite of severe anaemia, chronic malnutrition, the complications arising from the disease and from its treatment, the children were bright and such a devastating disease that even in those years, the solution to me was its prevention rather than its inadequate treatment.[3]

When the University Department of Paediatrics was established, I started the prenatal diagnosis of the b thalassaemias. At that time, the only strategy available was obtaining foetal blood and using radioactive leucine, the synthesis of the globin chains with radioactivity was carried out and then the laborious separation of the radioactivated globin chains was achieved by passage through sephadex columns. The amount of b globin chains compared to the other chains was then determined and the ratio of b and g chains gave an indication of the normal foetus, the b thalassaemia trait carrier and the foetus with b thalassaemia major. Besides the labour intensity and the use of radioactive material, the obtaining of pure foetal blood uncontaminated with maternal blood was always a problem. Initially, foetal blood was obtained by placental puncture and the blood so obtained was purged of maternal blood and often one could not be certain of the purity of the final blood. Later, when obstetricians became more expert in cordocentesis, under ultrasound guidance, pure foetal blood could be obtained consistently.[4] When the results revealed that the foetuses were affected by b thalassaemia major, the mother was offered termination and almost always the mother agreed.

As knowledge of the b thalassaemias grew, it was soon realised that there are many types of b thalassaemia depending on the type of mutation of the b globin gene. By now, these are as many as 100 different mutations of the globin b gene causing many different combinations and resulting in different phenotypes. Fortunately, the number of globin gene mutations in a particular ethnic group is limited and that each ethnic group has about 5

to 10 types accounting for the majority of b thalassaemia genotypes. Once the common genotypes are known, they can be ascertained directly without chain synthesis and separation. Furthermore, cordocentesis is not required and chorionic villus sampling (CVS) at 12th week can be done and mutations determined from the chorionic villus instead of waiting till the 20th week for cordocentesis. CVS can be done not only earlier but it is done more easily and with less foetal complications compared to cordocentesis. Therefore, at present, in our Department the chorionic villus tissue is subjected to polymerase chain reaction to produce the b globin chains in large numbers using primers for the mutations found in the father and the mother. In this way we can infer what type of mutations are found in the foetus, viz. no mutations, i.e. genotypically perfectly normal, b thalassaemia major when the foetus has both mutations of the parents, and b thalassaemia carrier when the foetus possess only one of the parental mutations. The method used by us is the ARMS, i.e. amplification refractory mutation system.[5] This system obviates the use of radioactive material, is rapid, accurate and results are consistent. We therefore rely on CVS and ARMS so that the genotype can be determined very early in pregnancy, a method parents prefer if they wish for termination. However, if the mother comes late in pregnancy to the obstetrician, then CVS / ARMS cannot be done, as the parents' genotypes must first be determined. Under these circumstances, then cordocentesis will have to be done and the laborious radioactive synthesis and separation method will have to be resorted to.

It will be realised that in spite of adequate methods of prenatal diagnosis, the incidence of b thalassaemia is reduced but not totally eradicated because the cases described above are applicable only in families who have produced one previous affected child with b thalassaemia, i.e. the parents have selected themselves for prenatal diagnosis because they have given birth already to one affected child with its tragic consequences. You only reduce the repeat cases in the family but NOT the first affected. Therefore, if we with to reduce the incidence of b thalassaemia effectively, we must prevent the birth of the first affected child. About 10 years ago, I talked to and discussed with the obstetricians here how to identify dual parental carriers before the birth of their first child. The strategy is for the obstetrician to obtain blood from the wife before she is pregnant or when she is pregnant with the first child when she makes the first visit to her obstetrician. The blood of the wife is screened for b thalassaemia carrier status and if she is normal, i.e. not a carrier, the exercise stops here, as she cannot produce a b thalassaemia homozygote if she is not a carrier, no matter what the genetic status of the husband. However, if the wife is a carrier, then the obstetrician must obtain the husband's blood for thalassaemia screening. If he is not a carrier, although the wife is a carrier, all his children will be free of b thalassaemia major. However, if the husband is also a carrier, then both the wife and the husband are genotyped, i.e. the exact type of mutation in the wife and the husband are determined and foetal tissue is obtained for prenatal diagnosis. In this way, we can prevent the first affected child and that is why we seldom see any new cases of b thalassaemia major in Singapore nowadays. Although the strategy is simple, there may be problems, e.g. the obstetrician may not offer screening, or if he offers, the couple may refuse screening. Both these situations have been encountered by me but they are conspicuously uncommon. The other problem is with the screening tests and their interpretation. These can produce real problems as obstetricians may want to economise for their patients and select the minimum of tests. Most obstetricians now offer the complete basic tests. Yet there is no single test or set of tests which is 100% satisfactory except the DNA mutation test which is expensive and takes time. However, a knowledge of the possible deficiencies in the basic tests include the following: (Table I).

TABLE I: EXCEPTIONS TO CRITERIA FOR DIAGNOSIS OF THALASSAEMIA

1. Hypochromic microcytic indices are of course more common in iron deficiency anaemia.
2. Some b thalassaemia carriers show a normal HbA_2 level in electrophoresis, i.e. the normal HbA_2 b thalassaemia carrier, e.g. the d-b thalassaemia carrier.
3. d thalassaemia carriers who interact with b thalassaemia carriers.
4. Carriers of hereditary persistence of foetal haemoglobin
5. Association of a and b thalassaemia
6. Totally silent b thalassaemia

Therefore, screening test results must be examined critically and in some cases, further tests may be necessary.

As patients are tested for their particular mutations, it was soon realised that some mutations produce a more severe type of disease than others, in other words, some genotypes produce more severe phenotypes while others produce less severe disease. The key factor determining the phenotype is the amount of b globin chains produced by a particular mutation. Hence, mutations can be classified into 2 groups, those that produce minimal b globin chains are termed b^o thalassaemia and therefore more severe and those which produce more b globin chains, the b^+ thalassaemias. The genotypes of patients therefore could be b^+b^+, b^+b^o, b^ob^o and so on. In this way, it is possible to correlate the genotype with the phenotype and the terms used can be illustrated in Table II.

It is important to realise that b thalassaemia intermedia may respond to treatment with oral iron chelators, viz.

TABLE II: GENOTYPE PHENOTYPE RELATIONS IN b THALASSAEMIA

Genotype	Phenotype
$b^o b^o$	b thalassaemia major
$b^+ b^+$	b thalassaemia minor
b^+/b^o	b thalassaemia intermedia

Deferiprone and may live beyond 20 years. These b thalassaemia intermedias may be first born without screening and they have a better prognosis than the classical b thalassaemia majors.

Table III shows the common mutations and their severity in the Chinese and Malay ethnic groups.

TABLE III: COMMON MUTATIONS IN b THALASSAEMIA

	Mutation	Severity	Incidence (%)
(A) Chinese	Codon 41,42	b^o	51
	IVS-2 654	b^o	35
	-28	b^+	4
	Codon 17	b^o	4
	Codon 15	b^o	2
	Codon 26 (HbE)	b^+	2
	-29	b^+	1
	Codon 71,72	b^o	1
(B) Malay	IVS-1 5	b^+	46
	Codon 26 (HbE)	b^+	21
	Codon 15	b^o	12
	IVS-1 1	b^o	4
	IVS-1 654	b^o	4
	Polyadenyl	b^+	2
	Codon 35	b^o	1

The only effective new treatment is the introduction of L1, the oral iron chelator-deferiprone. It is cheaper and easier to administer compared to desferal which is given parenterally every night by infusion and is very expensive. Few patients can afford it and many became non-compliant. Many other drugs have been tried and found to be ineffective such as hydroxyurea; sodium butyrate and others. Even erythropoietin has been used and found wanting and bone marrow transplant is not always available and if available, is associated with recurrence or mortality.[6,7]

By June 1997, the number of prenatal diagnosis carried out in foetuses at risk is shown in Table IV.

Because of screening of couples prior to pregnancy and application of prenatal diagnosis of the foetus when both wife and husband are carriers of b thalassaemia with termination of the pregnancy when the foetus is found to be a b thalassaemia homozygote, there has been hardly any new cases of b thalassaemia born in Singapore in the last few years. The present cases are the leftovers born a decade or more ago together with b thalassaemia intermedia patients who usually have a longer life span. Therefore, it is possible to eliminate all new cases of b thalassaemia major in Singapore, a remarkable achievement of preventive medicine by paediatricians, obstetricians, and others. What was a most tragic disease for affected patients and their families will very soon be a thing of the past, a good example of the achievements of the era of the new paediatrics.

TABLE IV: PRENATAL DIAGNOSIS IN b THALASSAEMIA

Globin chain analysis	77
DNA analysis	31
Total	108

(B) a Thalassaemia

The evolution of the story of the a thalassaemias, in contradistinction to the b thalassaemias in Singapore, is remarkably different.[8-11] Initially, we were seeing mild cases of thalassaemia major but with some common features, viz. a chronic haemolytic microcytic hypochromic anaemia with hepatosplenomegaly with typical target cells but without raised HbF and HbA_2 and hardly needing blood transfusions. It was only with the discovery of the globin chains that the concept of a thalassaemia was applied to the form of clinical cases which came to be known as HbH disease because on electrophoresis of the red cells of these patients, a fast Hb band was seen and named HbH. Studies of the globin chains revealed that HbH is a tetramer of b chains, i.e. b_4 without a chains. In other words, HbH disease was one where a globin chains are not produced in normal amounts as b thalassaemia is a disease where b chains are produced ineffectively. Studies of the genes of the a globin and b globin chains revealed that the b globin genes are situated on chromosome 11, one in each chromosome as with most genes. However, the a globin genes are situated in chromosome 16, but there are 2 a b globin genes on each chromosome 16, so that the total number is 4 rather than 2 as with the b globin genes. In other words, in most human races, the a globin gene has undergone a duplication. Most of the mutations of b thalassaemia are due to point mutations, but in a thalassaemia, the commonest mutation is a deletion as encountered in Southeast Asia. Therefore, the a thalassaemias can be graded as to its severity by the number of a globin genes deleted, i.e. the more deleted, the more severe is the disease. Table V shows some features of the 4 graded types of a thalassaemia depending on the number of deleted a globin genes.

Except for Barts hydrops foetalis, the other 3 conditions are compatible with a normal lifespan. Babies born with Barts hydrops foetalis are stillborn or will die a few minutes after birth because no a globin chromosome is

TABLE V: GENOTYPE PHENOTYPE RELATIONS IN a THALASSAEMIA

No. of a globin genes deleted	Term applied to phenotype	Degree anaemia	Hb electrophoresis
One	a Thal-2	Nil	Normal
Two	a Thal-1	Minimal	Normal
Three	HbH disease	Mild	HbH (b_4)
Four	Hydrops foetuses	Severe & lethal	Barts Hb (g_4)

formed so that there is no oxygen carrying Hb, viz. no HbA, HbF and HbA_2, each of which needs a globin chains to be formed, i.e. a_2b_2 (HbA), a_2g_2 (HbF) and a_2d_2 (HbA_2). Patients with HbH disease may need blood transfusions in the first few years of life, but as they grow older, they produce more HbA and do not need any blood transfusions in late childhood and adulthood. Therefore, for practical purposes, HbH does not need prenatal diagnosis. Of course, a thal-2 and a thal-1 also do not need prenatal diagnosis. The b thalassaemias can be easily distinguished from b thalassaemias by rapidly mixing the red cells with brilliant cresyl blue when large inclusion bodies are produced and seen under the microscope in the red cells.

It is only Barts hydrops foetalis which need prenatal diagnosis and this can be done by determining the number of a globin chains that are not deleted. Thus a foetus with Barts hydrops foetalis will reveal no a globin genes. The question may be asked as to why Barts hydrops needs prenatal diagnosis as all these foetuses die anyway before delivery or shortly after delivery as there is no foetal treatment available to prevent affected foetuses from dying. Then why carry out the procedure of prenatal diagnosis and terminate the pregnancy when affected foetuses will in time self-destruct? The reason for prenatal diagnosis is that an affected foetus can produce complications in the pregnant mother who may suffer from hydramnios, pre-eclampsia, antepartum and postpartum haemorrhage and difficulty in vaginal delivery, besides the inconvenience of carrying the foetus to term to no effect as the foetus will die anyway.

So far we have carried out prenatal diagnosis of Barts hydrops foetalis as in Table VI.

TABLE VI: PRENATAL DIAGNOSIS OF a THALASSAEMIA

Chinese	116
Malay	1
Indonesia	1
Filipino	1
Total	120

Of these Barts hydrops foetalis were encountered in 26, i.e. 25 Chinese and 1 Malay.

Besides the classical inherited forms of a thalassaemia described above, 2 other interesting forms of a thalassaemia have been described, both of which showing the phenotype of HbH disease.

1) *Acquired a thalassaemia*: This is sometimes seen in some patients with the myelodysplastic syndromes, and patients showing the acquired HbH syndrome are usually elderly males and often their myelodysplastic syndrome has already progressed to leukaemia.

2) *Mental retardation with HbH disease*:[12] There are 2 varieties, one of which is due to a larger deletion of the short arm of chromosome No.16, so that not only are the a globin genes deleted but also some other contiguous genes nearby which results in the mental retardation. The other variety does not show any deletion of the a globin gene or contiguous genes and the a thalassaemia is mild. This condition is due to a mutation of a gene on the X chromosome and causes a down-regulation of the a globin genes (which are intact) causing a mild form of HbH disease.

(C) Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

Deficiency of the erythrocytic enzyme (G6PD) is probably the most common Mendelian disease recorded world-wide. The deficiency of this enzyme in the monophosphate shunt of the rbc glycolytic cycle was first discovered during World War II when American soldiers fighting the Japanese in the Pacific area of the War were denied access to quinine with the loss of certain Asian tropical countries to the Japanese. Hence, US scientist discovered an anti-malarial drug substitute — pamaquin. Some of the American Negro soldiers came down with an intravascular form of haemolytic anaemia with haemoglobinuria while most of the white US soldiers were not so affected. This led to discovery of the erythrocytic enzyme G6PD and its deficiency among some Negroes. In fact, before World War II, doctors in Europe had described Favism where haemolysis occurred in Southern Europe in Greece, Italy and Spain and it was stated that Greek doctors like Hippocrates knew of favism or "allergy" to the broad bean or Fava bean and it was stated that Aristotle suffered from such a haemolytic episode when he went to a field of growing Fava beans after inhaling the Fava pollen! Anyway, G6PD deficiency was only discovered at the end of World War II.

The story of G6PD deficiency in Singapore stemmed from cases among Chinese and Malays with intravascular haemolysis after certain drugs and the Singapore kernicterus described by me in the 1960s.[13-17] In contrast to Caucasian babies with kernicterus, where the commonest cause was Rh incompatibility, our cases of Singapore kernicterus did not stem from Rh-negative mothers because Rh negativity is rare among Chinese and Malays. Again when we showed these cases to

visiting doctors from the West, many disbelieved that the cases were due to a hitherto undescribed cause and many commented that we were 'missing' cases of Rh or other red cell blood group incompatibility! Be that as it may, we found that the majority of these cases of Singapore kernicterus were due to G6PD deficiency when they were so tested. In fact G6PD deficiency causing kernicterus was the commonest cause of death and / or mental retardation.

At that time among full term infants admitted to the General Hospital Paediatric Unit, it was indeed a significant cause of neonatal death and mental retardation. In those days, mothers after giving birth were discharged on the same day or the day after if there was no maternal or newborn illness. Usually mothers of these Singapore kernicterus babies said that they noticed jaundice on day 3 or 4 and they would give herbs especially a yellow herb to these babies as treatment. These herbs contain berberine and in a day or two, the jaundice was more intense and the affected babies had fits and were rushed to hospital too late for exchange transfusion. The majority died and those who survived had cerebral palsy with mental retardation. Most are males and the G6PD would be deficient as the mutation is in the G6PD gene which is on the long arm of the X-sex chromosome near the gene for colour vision. Hence, G6PD deficiency is sex-linked. I carried out family studies on G6PD deficient babies and found the incidence to be about 3% among Chinese male newborns and slightly lesser Malay male newborns.[13] In females, who inherited the abnormal gene from the mother, the G6PD status could be normal, deficient or intermediate because of Lyonisation.

Besides herbs given to these enzyme deficient males, other triggers found by me include naphthalene in mothballed clothes infection and Western drugs. One infant had kernicterus due to breast feeding when the mother ate fava beans, which are not indigenously grown but imported from Taiwan, an example of favism due to breast-feeding.[18] By this time, other countries where G6PD deficiency was found were also describing kernicterus in their babies confirming our findings.

In 1968, I initiated a preventive strategy applicable to all newborns in Singapore.[16] It was not an easy task as we had to educate not only doctors but laymen about the enzyme deficiency and why and when severe jaundice occurred with subsequent brain damage. This was achieved by utilising the mass media, newspapers and radio as TV was in its infancy. Pamphlets were printed and distributed by the maternal and child health clinics. However, the linchpin of the strategy was the ability to screen rapidly cord blood for G6PD deficiency and this was achieved by a modification of the usual standard method so that we could get the result within one hour. Large numbers of cord blood from newborns born daily in Singapore were collected and our University Paediatric Laboratory was able to deal with this load and transmit the result to the wards. Those whose G6PD were normal were discharged the next day with the mother if both were well, i.e. a continuation of the usual custom in maternity hospitals at that time. However, newborns with G6PD deficiency were held back in the wards while their mothers were discharged so that the serum bilirubin was assessed daily and if it reached a critical level, early exchange transfusion was carried out and thus preventing kernicterus. In spite of warning to parents not to give drugs to the infants, often a few parents brought herbs surreptitiously to the ward and administered them to their G6PD deficient babies. Initially we kept them for 3 weeks but as the parents became convinced about drugs and other triggers, we could discharge these babies much earlier and surveillance carried out in the clinics and outpatients. Singapore was the first country to start this kernicterus surveillance strategy with G6PD estimation at birth and very soon, the incidence of Singapore kernicterus plummeted and kernicterus due to G6PD deficiency was totally eradicated, preventing not only death but also mental retardation. This was noted by the World Health Organization (WHO) and with their assistance other countries started the same strategy.

In Singapore now, all newborns are screened for G6PD deficiency and the status is recorded in the infant's health book and all parents of G6PD deficient children are given education material about the effects of deficiency of this erythrocytic enzyme and parents are also given a list of drugs which are most likely to cause haemolysis in the newborn period as well as during childhood and adulthood so that haemoglobinuria may be prevented. Early work on G6PD deficiency revealed that not all patients with G6PD are "equal". Some deficient ethnic groups do not suffer from kernicterus while others show evidence of haemoglobinuria in later life. Some cases eat fava beans without haemolysis while other suffer from favism and so on. Therefore, work on the chemical characteristics of the type of G6PD were carried out in the hope that the different chemical phenotypes may explain the differences in the genotypes. This was found not to be reliable and recently DNA gene analysis has detected different mutations in the G6PD gene and it is the type of mutation which determines the phenotype. So far about 90 mutations have been characterised in the gene which contains 13 exons and 12 introns. These mutations and their phenotypic expression has been classified by the WHO in Table VII.

The most common type of mutation occurring in Chinese in Southeast Asia comprises those effecting nucleotides in exon 12 and about 80% to 90% of mutations occur at this site. The other 10% occur elsewhere so that very occasionally, chronic haemolytic anaemia has been encountered.

TABLE VII: CLASSES OF G6PD MUTATIONS

Class 1	Non-spherocytic chronic haemolytic anaemia
Class 2	Severe acute haemolysis with triggers
Class 3	Mild haemolysis with triggers
Class 4	No haemolysis in spite of mutation
Class 5	Enzyme deficiency in other organs/tissues besides erythrocytic G6PD with different clinical expressions e.g. cataracts, immunodeficiency, muscle weakness, etc

In conclusion, among the commonest Mendelian diseases in the world, i.e. the autosomal recessive a and b thalassaemias and the sex-linked G6PD deficiencies, screening procedures have been firmly established by both doctors and laymen in Singapore. Note that prenatal diagnosis is practised in foetuses where both parents are carriers of the same type of thalassaemia but no prenatal diagnosis is carried out in G6PD deficiency as we are able to prevent diseases arising from the enzyme deficiency so that such individuals live normally and with a normal life span. No prenatal diagnosis and no termination of pregnancy are necessary.

Chromosome Disorders

The next group of genetic diseases arises because of abnormalities in number or structure of the chromosomes. Finally such chromosomal abnormalities affect the genes as the genes 'reside' in the chromosomes. Chromosome abnormalities therefore result in excess genes or diminished genes and as a result the phenotype can be abnormal. It was as late as the 1950s that it was decided that the human cell has 46 chromosomes as prior to that time, there was uncertainty as to the number of chromosomes because of difficulty in culturing human cells for chromosomes. I still remember that day when this was announced in the journals and to me, even at that time, I realised that human genetics would play a large part in the future of medicine. At that time whenever we did a bone marrow aspiration for diagnostic purposes, I would scan the slide for the chromosomes and I was elated to discover that indeed the human chromosome complement was 46 or 23 pairs as one can see human chromosomes in bone marrow without culture. Thus, when the University Department of Paediatrics was established with myself as the Foundation Professor, I started the first chromosome laboratory in Southeast Asia. Initially we prepared cultured chromosomes from peripheral blood and then started chromosome culture from amniotic cells, chorionic villus cells, skin and other tissues. Of all chromosomal disorders, the commonest serious defect is Downs anomaly (DA). DA patients are all mentally retarded and most are unable to attend a normal school nor could they live an independent life in adulthood. Besides the mental retardation, DA patients often suffer from other organ defects such as congenital heart disease, alimentary tract atresia, proneness to infections and leukaemia, and other diseases. Therefore, if those born alive (many die in utero), these physical defects are dealt with and with modern medicine, DA individuals can live up to 50 years, so that the whole family often shares this burden if the patient is not institutionalised. When they reach the age of about 50, nearly all of them also suffer from Alzheimer's disease so that whatever self-care they may possess now totally disappear and the whole family would have to pay more attention to the adult DA patient. It is therefore not surprising that parents would like to seek methods of prenatal diagnosis of DA.

The strategy of prenatal diagnosis depends a lot on the likelihood of a mother bearing a DA foetus depending on her age when conceiving, the likelihood rising precipitously at age 35 years and above. Prenatal diagnosis involves culturing CVS or amniotic cells, the former around 12 weeks and the latter at 16 weeks. As chromosome culture is still a relatively labour-intensive procedure, it is not possible to do amniocentesis and CVS in all pregnant women and also these 2 procedures are invasive and they have their own complications which may cause abortion. Therefore, the initial strategy was to offer these procedures and chromosome culture to mothers 35 years and over. However, mothers younger than 35 years can still produce DA foetuses and in these younger mothers, although percentage-wise they conceive DA foetuses less frequently than older mothers, in totality the number of DA infants born to younger mothers exceed those conceived by mothers 35 years and older especially in the West as most pregnancies occur before 35 years. For example, in the West, mothers older than 35 years comprise 6% to 7% of all pregnancies, whereas in Singapore, this is higher at 16%.[19] Therefore, to reduce the birth of DA babies further, the younger mothers could be selected for amniocentesis by non-invasive tests, and indeed maternal blood screening tests are frequently carried out in the West and in Singapore. Three serum proteins are usually estimated, viz. alpha fetoprotein (AFP), human chorionic gonadotrophin (HCG) and unconjugated estriol (UE_3). These are estimated in the second trimester of pregnancy and the age of the foetus must be accurately determined by ultrasound and cut-off points determined for increased or decreased likelihood of the foetus being a DA. The AFP and UE_3 are lower and the HCG is higher with a DA foetus. Of course, these tests are not 100% accurate as false positives and false negatives occur, so that, at the moment, with amniocentesis of all mothers aged 35 years or over plus all mothers younger than 35 selected on the basis of the maternal serum screening tests, we still cannot prevent the birth of all DA infants. We can reduce substantially the incidence. Some laboratories use 2 rather than 3 screening tests leaving out UE_3, and others use 2 but with free b HCG rather than total HCG.

In Thomson Medical Centre prenatal diagnostic centre, we use AFP and HCG. HCG has 2 subunits, the a and the b. It is the b subunit which is more accurate in determination of DA foetuses.[20] The free b HCG levels rise quickly during the normal course of pregnancy to a peak at 8 weeks gestation and then fall to reach a plateau around 18 weeks, so that its rise in a DA foetus can be more discriminatory.[21-23] The use of AFP and free b HCG as a screening test in TMC, gives a detection rate of 86% with a false positive rate of 7.2%. The false negative rate is 14.3%. Therefore, if we assume that all mothers 35 years and over in Singapore are offered amniocentesis and all of them accept the offer, and those less than 35 years are offered dual AFP and free b HCG screening and all of them accept the offer, we will detect all cases of DA in mothers 35 years and older and 86% of mothers less than 35 years. This, of course, is the ideal state and acceptance rates may not be 100% in each of the two age groups above. Assuming that acceptance rate is 100% and all parents with a DA positive result after amniocentesis, opt for termination of pregnancy, how many DA will still be born in Singapore yearly and how many cumulative DA patients after a period of about 50 years will still have to be taken care of by the families or the state?

To try and answer that question, we will have to determine how many DA babies are born alive annually in Singapore at the present moment. Unfortunately, there are no accurate figures because DA is not a notifiable condition. It is very important to get as accurate a figure of the incidence of DA live births in Singapore so that the country can make plans for the care, education, and later assist them to be as independent as possible and even able to work under supervision, and furthermore, with this accurate figure, we will then be able to forecast how effective the preventive methods discussed above have been and how effective it will be in the future when the strategy for screening and chromosome culture is accepted by all doctors as well as by all citizens in Singapore.

Since no official count of the number of DA individuals in Singapore has been made at the moment, i.e. in 1997, we can only estimate this number by indirect means. One estimate is to take the usual figure of DA in live births being approximately 1 in 800. For a 40,000 live birth figure annually for Singapore, the number of DA live births is 50 per year. Since 1993, all laboratories carrying out chromosome culture work, were invited to report to the Birth Defects Registry of the Ministry of Health whenever the laboratory detects a baby born alive with chromosome culture of trisomy.[24] The figures obtained from 1993 to 1996 are shown in Table VIII.[24]

The average for the 4 years works out to 59 births per year. If we assume that 50% of DA born alive are still living by 10 years of age and that 25% are still alive by 32 years of age,[25] we can estimate the number of DA individuals (born from 1950 to 1997) to be approximately 2700. Even if this is an overestimate, half of this will give 1350 at any one time. This is a large number but it is only an estimate. We need actual figures and in this regard, the DA Association of Singapore should be able to give us more accurate figures in the future and we should assist the Association to achieve this by encouraging parents with DA children to register with the Association.

TABLE VIII: NO. OF BIRTHS WITH DOWN'S ANOMALY REPORTED BORN ALIVE

Year	Number
1993	60
1994	50
1995	52
1996	45

No matter what the actual figure is for the prevalence of DA cases in Singapore at the moment, it is certain to be overwhelmingly large and serious attempts must be made to reduce the birth of DA foetuses so as to prevent further increase in the numbers. It is important to realise that the percentage of mothers 35 years and over in the West is different from that existing in Singapore. The percentages are demonstrated in Table IX together with the percentages of DA live births in the West and in Singapore.

It can thus be seen that more DA are being born to mothers 35 years and over in Singapore compared to such births in mothers younger than 35 years, which is the opposite in the case in US and UK. It is thus logical that in Singapore, all mothers 35 years and over should be offered CVS or amniocentesis without maternal blood screening while mothers below the age of 35 years should be offered maternal blood screening and on the basis of a positive result be then offered amniocentesis.

Because maternal blood screening will always result in some false positives (i.e. unnecessary amniocentesis which will show that the foetus is not a DA) and also some will result in false negatives (i.e. the foetus is a DA but screening misses it), the addition of ultrasound studies of the foetus will diminish these false results. In this connection, the determination of the size of nuchal

TABLE IX: PERCENTAGES OF BIRTHS AND DA LIVE BIRTHS

	Mothers Under 35 Years	Mothers 35 Years & Over
US and UK births	95	5
Singapore births	84	16
US and UK DA live births	67	33
Singapore DA live births	34	66

DA: Down's Anomaly

translucency may point towards a DA foetus, as may lengths of femur, presence of echogenic bowel, etc. The ideal solution to this dilemma in screening may eventuate in the future when we will be able to recover foetal cells in the mother's blood and submit such interphase cells directly to fluorescent in situ hybridisation (FISH) using DA probes but without the labour intensive chromosome culture and also bypassing invasive procedures such as chorionic villus sampling, amniocentesis or cordocentesis to obtain foetal blood for chromosome culture.

Multifactorial Disorders

Finally, we come to the third category of diseases, after Mendelian and Chromosome diseases, viz. multifactorial diseases. This third and last category of diseases need both genetic factors as well as environmental influences before the disease state takes hold of the patient. Both the genetic factors and the environmental factors are not single but multiple. Very often we only know some of the relevant genetic factors but not all, so that they are not as overwhelming like the Mendelian and chromosome disorders. Because these genetic factors are multiple, it is difficult to carry out prenatal diagnosis of these genes and even if we did know which these genes are in a particular child or infant, he will not suffer from the disorder as environmental factors are necessary to bring the effects of these genes to their 'fulfilment'. Yet, much can be done to prevent these diseases from achieving the genetic potential by controlling the environmental factors. For example, Type I diabetes mellitus or IDDM can be prevented by breast-feeding the baby from birth for as long as possible because cow milk could be one of the precipitating factors while in NIDDM or Type 2 diabetes obesity is definitely one of the major environmental factors precipitating the onset of the disease in adulthood no matter what the genetic potential may be. So it is with the cancers e.g. nasopharyngeal carcinoma is common among Southern Chinese due to their genetic response to E-B virus infections and their dietary habit of eating salted fish. Avoidance of such a diet from birth would prevent the adult from NPC and so on. Many of the multifactorial diseases can be avoided in individuals with certain genetic potentials and the paediatrician is in a unique position to give advice to parents of babies and children who are so genetically predisposed. Avoidance of smoking and certain moderation in the dietary can all be taught by parents when their children are young, and it behoves the paediatrician taking care of such families to be aware of these environmental factors acting in these members of the family and give such advice that is necessary to keep the children and adults as healthy as possible. These are examples whereby doctors should go beyond Southeast Asia, as mentioned above so as to serve their clientele better.

Recent new knowledge about some of these multifactorial diseases has come to hand and I consider some of them as extremely important advances in medicine. One of these is the so-called Barker's Hypothesis.[26,27] Barker and his group of workers analysed the birth characteristics in Hertfordshire and followed these babies till they reached adulthood and found a correlation between low birth weight at term, i.e. IUGR, and hypertension, glucose intolerance and Type 2 diabetes mellitus and insulin resistance as well as coronary ischaemic heart disease, especially if these babies become obese in adulthood. In other words foetal malnutrition produces a state which may result in the above adult diseases. It seems that there can be a programming of diseases in adult life starting as early as the foetal state, and in this case, foetal malnutrition. Others have extended these findings to the opposite situation, i.e. infants with large birth weights.[28] American workers in the Children's Cancer Group (CCG) examined 3711 children suffering from paediatric cancers and compared them to 816 control subjects with regards to their birth weights. They found that large birth weights, i.e. those born with a birth weight more than 4 kg were more likely to suffer from cancer before the age of 2 years compared to those with lower birth weights with regards to acute lymphoblastic leukaemia ($P = 0.006$), Wilms tumour ($P = 0.003$) and neuroblastoma ($P = 0.001$). However, there was a reduced risk for soft tissue sarcoma ($P = 0.04$). With regard to acute myeloid leukaemia diagnosed before 2 years of age there was an increased odds ratio of 2.5 with higher birth weights but there was no such increase if the leukaemia occurred after the age of 2 years. Similarly, increased dietary energy intake in childhood could result in death from cancer in adulthood after taking into consideration confounding factors for cancer.

The importance of these observations for the practising paediatrician is that the paediatrician should be cognisant of these early environmental factors when they examine newborns, infants and children so that he will give adequate preventive advice and also look for possible signs of disease arising from these early programmable factors.

But what about these early factors which are not created by the parents but created by doctors themselves? A possible recent example is the Vitamin K problem first brought to light by the epidemiologic studies of Golding[29,30] and her colleagues in Bristol. They found that there could be an increased incidence of acute leukaemia in those newborn babies given intramuscular vitamin K as a routine to prevent haemorrhagic disease of the newborn, both early and late, especially in some totally breast-fed babies with occasional devastating incranial haemorrhage. Understandably, the epidemiologic studies created a storm and very soon other paedia-

tricians showed that no such significant relationship between intramuscular vitamin K and leukaemia in their own countries.[31-33] Golding did another study and confirmed the significant association of paediatric cases of acute leukaemia and intramuscular vitamin K.

However, I started giving 1 ml of oral vitamin K to newborns who are totally breast-fed at one week of age and weekly till 3 months of age or till breast-feeding stopped whichever is earlier. For those who are bottle-fed with or without breast-feeding, they are given 1 ml of oral vitamin K at one week of age and again at one month of age. Since 1994, more than 10,000 newborns have been given oral vitamin K instead of intramuscular vitamin K and none of them had any symptoms of bleeding. Besides Thomson Medical Centre using oral vitamin K, I could not persuade the other hospitals to switch to oral vitamin K. If indeed there is an association between intramuscular vitamin K and cancer, what could be the mechanism? We do not know the cause, but the plasma concentration of vitamin K after intramuscular injection of 1 mg exceeds endogenous levels by a factor of 10,000! The reason for mentioning vitamin K now is that recently 4 new studies have been published and although 2 of them did not find an increase of cancer or leukaemia after intramuscular vitamin K, 2 others did find such an association.[34-37] Under the circumstances, it is best to give oral vitamin K for prevention of haemorrhagic diseases of infancy as vitamin K given by this route is effective and it does not carry any risk for cancer or leukaemia.

In Singapore, there is only one supplier of oral vitamin K, a pharmaceutical company from Japan. Recently, they have informed me that 2 other paediatricians have started using oral vitamin K. If indeed future further epidemiologic studies confirm that intramuscular vitamin K does produce a greater paediatric risk for cancer and/or leukaemia, parents of such affected children may take medico/legal measures.

One more example of a multifactorial disease will suffice to convince doctors that it is possible to prevent the birth of such affected foetuses. I refer to congenital heart diseases which is probably the most common significant lesion among multifactorial diseases affecting newborns. The estimated prevalence of congenital heart disease (CHD) in newborns is 8 per 1000 livebirths.[38] Although some CHD can be satisfactorily 'cured' with surgery, many are not and residual morbidity and mortality still occur in spite of surgery. Hence, greater effects should be made for prenatal diagnosis of CHD. Not all CHD can be diagnosed prenatally but a significant proportion can, and some obstetric units carry out a 4-chamber view of all foetuses during routine foetal ultrasound studies between 14 to 18 weeks of gestation. The lesions which can be detected with 4-chamber view are shown in Table X.[39]

TABLE X: 4-CHAMBER DIAGNOSIS OF FETAL CONGENITAL HEART DISEASE

1.	Total anomalous pulmonary venous drainage
2.	Mitral, tricuspid and aortic atresia
3.	Pulmonary atresia with intact ventricular septum
4.	Atrioventricular septal defect
5.	Ebstein tricuspid anomaly
6.	Critical aortic and pulmonic stenosis
7.	Coarctation of aorta
8.	VSD and cardiomyopathy

However, some lesions may be missed with a 4-chamber view and this includes transposition of great arteries, double outlet RV, Fallots, pulmonary atresia with VSD, truncus and absent pulmonary valve syndrome. However, some of these may be detected with ultrasound studies other than the simple 4-chamber view. CHD which may be overlooked with prenatal ultrasound cardiac studies are shown in Table XI.

TABLE XI: FAILURE OF DIAGNOSIS WITH PRENATAL ULTRASOUND

1.	Persistent arterial duct
2.	Secundum ASD
3.	Milder forms of pulmonary, aortic stenosis, and coarctation
4.	Some forms of VSD

Thus, a sizeable proportion of CHD can be diagnosed by prenatal ultrasound studies and except for the milder lesions which can be easily and effectively corrected by surgery with hardly any morbidity or mortality, the other lesions are often either not correctable or associated often with a high mortality and morbidity rate.

In conclusion, paediatricians should play a more active role in preventing significant diseases in individual patients. When we examine a child who is brought to the paediatrician by his parents for what they think is a disease which they feel the paediatrician could help them, e.g. upper respiratory tract infection, the paediatrician should be on the look out for other lesions which the parents have not noted or signs which may point to a disease which could be more serious than the one the parents feel should be dealt with by the paediatrician. The history elicited should not only include that of the particular child but also the siblings and even the history of the parents themselves. The present illness is only one of the factors which need the assistance of the paediatrician.

Genetic Screening

I have given you examples of those illnesses often with a high genetic load often with ineffective treatment in spite of the advances in medical science and how we can prevent the birth of such children by prenatal diagnosis if the parents so wish. However, genetic screening and

diagnosis are not straightforward issues. Some parents need help in not regarding such genetic diseases as evidence of social stigmatisation and they certainly need help in dealing with insurance companies as well as foreign embassies.[40] I had the misfortune to tell the mother of one of my child patients with a b thalassaemia carrier status that she herself is a carrier and she has passed the genetic trait to her child but her husband is not a carrier, so that they cannot produce b thalassaemia major children. Her family subsequently applied to migrate to Australia and in the application, she mentioned the b thalassaemia carrier status of herself and her child. Her application was turned down by the bureaucrat in the Australia Embassy in Singapore, on the grounds that she might produce a b thalassaemia major child who may then need expensive health care to which he would be entitled if the application is approved. I explained to the official that the carrier status is asymptomatic and would not need any special health care and the parents cannot produce a b thalassaemia major child, but to no avail. The family's application was turned down because the mother decided to reveal her carrier status and that of her child.

Some genetic tests are extremely useful to the family e.g. newborn screening for G6PD deficiency in Singapore for all newborns, so that kernicterus and haemoglobinuria may be prevented. Local families now understand this and freely agree for such screening and the use of preventive measures to keep the child and the adult as healthy as those who do not possess the G6PD deficient gene. They are also happy that there is no necessity for prenatal diagnosis. However, homozygous a and b thalassaemia states are totally different as methods for their adequate treatment are still lacking and under these circumstances, screening of parents and prenatal diagnosis is necessary if both parents are carriers. With prenatal diagnosis, termination of pregnancy is offered. Of course, the decision finally rests with the parents—similarly with prenatal diagnosis for Downs' anomaly. After years of education, the majority of Singaporeans accept the fact that some individuals are born as carriers and others are born with the full effects of the disease and they do not feel stigmatised. They accept all this as part of normal life and normal living. But what about insurance companies? There does not seem to be common agreement among the companies to request genetic testing, to ask for results of any genetic tests and to deny any insurance totally or to increase the premium and if so by how much. Even in the West, these problems remain and we doctors are also involved as to whether to reveal the results of such tests when requested by insurance companies. This problem must be tackled in the very near future. Many of the multifactorial diseases involve not one or two genes but a large number and not only that, there are also environmental factors which will have to interact with the many genetic factors before the final outcome can be determined, if at all. How do you therefore decide on what premium would be adequate for a particular person with such multifactorial influences?

Conclusion

I have touched on some but not all diseases for which there are certain effective preventive measures which we must inform our patients so as to keep them as healthy as possible, and not to wait until they fall sick with the disease and try to treat them. Doctors will have to be more preventive in their approach besides being therapists even if the recompense from the patients will be far below compared to when you allow them to be ill and then treat them. Often, there is no adequate therapy. Looking at diseases in this light, it would be useful to take an overview of the different diseases which affect mankind to determine which ones are more common and thus should receive more of our attention as doctors. The World Health Organisation has summarised these disease incidences as at 1997 (Table XII).

Thus, vaccine development and delivery are a priority together with healthy lifestyles to prevent cancers and circulatory system diseases. Perinatal diseases also should receive priority. Finally, earth resources are finite and we should also try and reduce family size as the following WHO figures for birth by every hour shows (Table XIII).

TABLE XII: CAUSES OF DEATH WORLDWIDE 1997 (WHO)

Infectious diseases	33%
Diseases of circulatory system	29%
Cancers	12%
Perinatal and neonatal causes	7%
Diseases of respiratory system	6%
Maternal causes	1%
Others	12%
Total	100%

TABLE XIII: POPULATION CHANGES WORLDWIDE BY THE HOUR

Year	Births	Deaths	Natural increase
1955	11,500	5800	5700
1975	13,800	5300	8500
1995	15,100	5900	9200
2025	15,500	7500	8000

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