

The Inheritance of Sickle Cell

Starting from this month, Dr Felix I. D. Konotey-Ahulu, the award-winning Ghanaian physician, will write a page of "Clinical Medicine Made Simple" for New African every two months.

For Africans who are said to come from a "hopeless continent", Dr Konotey-Ahulu is a revelation. He qualified MB BS(London), MRCS(England), LRCP(London) at London University's Westminster Hospital School of Medicine in 1959, and later obtained his Doctorate in Medicine (MD Lond) followed by Membership and Fellowship of two Royal Colleges of Physicians, FRCP(London) and FRCP(Glasgow).

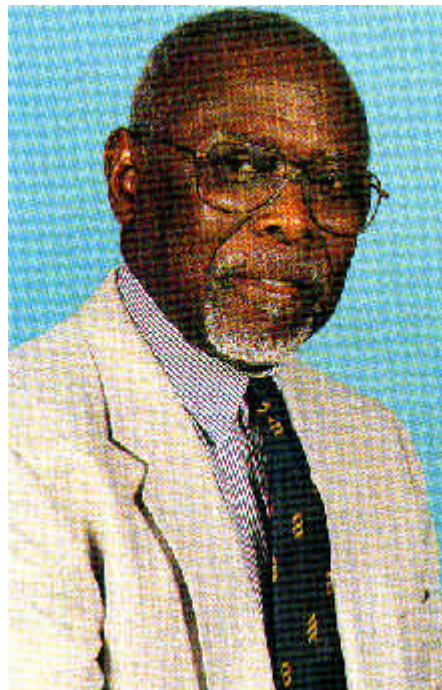
He has a diploma from the oldest School of Tropical Medicine and Hygiene in Liverpool, he is a Fellow of the West African College of Physicians (FWACP), and a Fellow of the Ghana Academy of Arts and Sciences (FGA). In 1974, Dr Konotey-Ahulu won the Academy's Gold Medal "for the most outstanding contribution to knowledge in the medical sciences by a Ghanaian between 1952 and 1973". In 1972, he was one of the recipients in Philadelphia of Dr Martin Luther King Jr Foundation Award "for outstanding research in Sickle Cell Anaemia", and in London in 1976 he received the Guinness Award for Scientific Achievement (GASA) in the Commonwealth "in recognition of his work in applying science to the service of the community".

>From Trieste, Italy, he won the 1998 Third World Academy of Sciences (TWAS) Award in Basic Medical Sciences. The prize was presented to him in 1999 in Dakar by the then Senegalese president, Abdou Diouf.

Before his illustrious foreign adventures, Dr Konotey-Ahulu had been consultant physician at the Korle Bu Teaching Hospital in Accra, Ghana. He was also the director of the erstwhile Ghana Institute of Clinical Genetics. While teaching at the University of Ghana Medical School, together with the Hungarian professor Bela Ringelmann and the Cambridge University professor Hermann Lehmann, Dr Konotey-Ahulu was involved in the discovery of several new haemoglobins including Haemoglobin Korle Bu.

He is currently a consultant physician at two famous London medical landmarks, Harley Street and Cromwell Hospital.

He was recently appointed the "Dr Kwegyir-Aggrey Distinguished Professor of Human Genetics" by the University of Cape Coast in Ghana. The appointment is based in the Faculty of Science at Cape Coast, with duties that include familiarising Ghanaians with genetic epidemiology and, among other things, explaining how the Human Genome Diversity Project (HGDP) could help West Africans trace long



lost relatives across the Atlantic, and vice versa. When the Aids epidemic first burst upon the world, Dr Konotey-Ahulu became the first African to go round the continent to obtain grassroot epidemiological and clinical information. He has published extensively on Aids in the international medical press. His books, *The Sickle Cell Disease Patient*, and *What Is Aids?* have been universally acclaimed. With respect to Sickle Cell Disease, Prof Helen Ranney of the Medicine and Haematology Department at the Albert Einstein College of Medicine, New York, once published this comment: "There is no single clinical experience in the United States comparable to that of Dr Konotey-Ahulu's."

Prof Thomas Mensah, the first Ghanaian high commissioner to South Africa, and the first president of the International Tribunal for the Law of the Sea, reviewing Dr Konotey Ahulu's book, *What is Aids?*, said:

"It takes a truly first-rate expert to make a highly technical subject understandable to laymen... This is what Dr Konotey-Ahulu has managed to do in a highly admirable way... He has set the problem of Aids in a totally different context by giving the individual African man and woman, as well as African governments and the world community in general, the information and perspectives on which to formulate a strategy for the future. For this he deserves the gratitude

of us all."

This is the expertise and medical experience that Dr Konotey-Ahulu brings to New Africa. His column will deal with various medical issues every other month. And what better way to start than hereditary disease - "The Inheritance of Sickle Cell Disease". Hopefully, "acquired disease" will come later.

The Sickle Cell Phenomenon: Are You "Norm/Norm", "Norm/Ache", or "Ache/Ache"?

This question should never be brushed aside. I shall explain. Many a parent has been puzzled to find that while there is no cold-season rheumatism in the family (father does not ache, mother is rheumatism free, the first lot of children are perfectly healthy), suddenly a child arrives who is plagued by ill health. Why should this be so, when no one else has the problem? Why is it that only Kwesi or Femi has been suffering from severe bone and joint pains in the rainy season?

The answer lies in the fact that, if we are West African, or Ugandan, or are from some parts of Zambia, and perfectly healthy, one in three (yes 1 in 3) of us on average has inherited from one of our parents a "rheumatism gene" that can be passed on to a child and we are not aware of this.

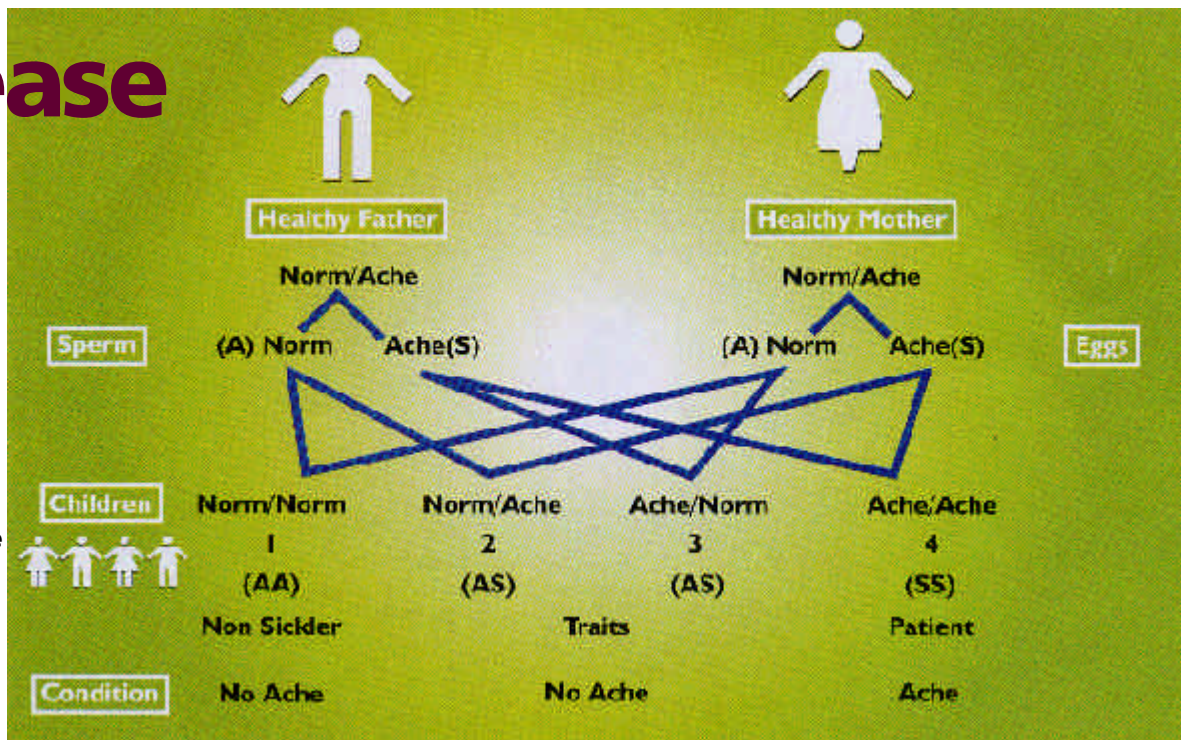
Unaware of it because we have at the same time inherited a matching gene, a "non-rheumatism gene" from our other parent. The "non-rheumatism gene" cancels out the effect of the "rheumatism gene" and we remain unaware of the fact that we are carrying a "rheumatism gene".

The very important thing to remember is this: If we, as parents, are the possessors of a "rheumatism gene", we can pass it on to an offspring. If the child received no such "rheumatism gene" from the other parent, then cold-season rheumatism would not manifest itself in the child.

Remember that each of us needs a pair of genes for every characteristic we possess. Yes, two genes for any characteristic: a pair of genes for skin colour, shape of nose, brilliance, type of voice, facial looks, and so on. True, one gene may be more pronounced than the other half of the pair. "He has got his mother's nose" does not mean his father did not give him a gene for nose. Sometimes, as happens with skin colour, the pair of genes may produce a mixture effect [mother black, father white, so child brown]. With "Haemoglobin type", however, it is very

Disease

Dr konotey-Ahulu's original sickle cell chart explaining how the 'disease' and 'traits' are inherited.



easy through laboratory tests, to find out where the so-called "Abnormal Haemoglobin" which is produced by the "rheumatism gene" comes from. The 1 in 3 of us with a "rheumatism gene" also possesses from the other parent a "non-rheumatism gene" which nullifies rheumatism.

It requires two "rheumatism genes" (one from mother, the other from father) to produce "Hereditary Rheumatism Disease" in the recipient. I have nicknamed the rheumatism gene "Ache", and the non-rheumatism gene "Norm". So the 1 in 3 perfectly healthy parents may be called "Norm/Ache". My own father was "Norm/Ache", and my mother also "Norm/Ache", and did not know the fact until I tested their blood.

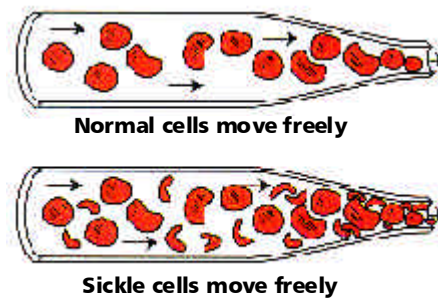
The wonder of the hereditary process is that, a parent never passes on both parts of the pair of genes to a child. It must be one or the other. Looking at the chart above, a Norm/Ache father's millions of sperm each contain either an Ache code, or a Norm code, never both. Similarly, the Norm/Ache mother's egg (ovum) which must be fertilised by a sperm to produce a child, contains just one or other of the "Ache/Norm" combination (or genotype). If that were not the case, conception would give the child four genes for each characteristic rather than two. Now pause a little, and read that again. It may help you to understand what happens with inheritance of cold-season rheumatism if you ponder the case of my own parents.

Papaa Norm/Ache and Mamma Norm/Ache who never suffered from cold-season rheumatism had 11 of us. Papaa passed on his Ache gene to five of us and his Norm gene to

six, and Mamma also did exactly the same. Three of those who had Mamma's Ache gene also received Papaa's Ache gene as well, and became Ache/Ache and suffered from rheumatism.

Two of the rest received Ache from Papaa and Norm from Mamma and were unaware of this until they were tested. Two more received Norm from Papaa and Ache from Mamma, and again did not know they were carrying a Rheumatism Gene until they were tested. Four of my parents' children had Norm genes from both parents and became Norm/Norm, and again did not know their true genotype until their blood was tested.

So, perfectly healthy Norm/Ache parents can have a Norm/Norm child (no rheumatism), a Norm/Ache child (no rheumatism), an Ache/Norm child (no rheumatism), and an Ache/Ache child with rheumatism, depending on which sperm fertilises which egg. This child will suffer from aches and pains. This partially explains the situation of Olu and Kwesi. Please read the above statement again, and again. Now what is the nature of this Ache Gene?



We will concentrate only on the inheritance of the gene.

Blood protein called haemoglobin

The type of blood protein we possess, like every human characteristic, is coded in our genes. Normal adult haemoglobin, the red protein in red blood corpuscles, designated Haemoglobin Type A, (nothing to do with Blood Group A), remains "fluid" even in the absence of oxygen. Sometimes we find genes coding for haemoglobins which differ from normal haemoglobin in certain respects. The best known non-A haemoglobin has been designated Haemoglobin S because, in the absence of oxygen, this haemoglobin solidifies, distorting the red cell membrane, turning it sickle shape (a sickle is a curved agricultural tool). This S gene, inherited with Normal Haemoglobin A, produces the "AS" genotype which I have called the Norm/Ache phenotype and which looks exactly like AA phenotype (Norm/Norm).

In other words, when you look at people with the "AA" and "AS", it is impossible to say what phenotype they have. They can only be distinguished through a blood test - the Sickle Cell Test. The AS person tests positive, and the AA negative.

You often hear people who have just been found to test positive for sickle cell Haemoglobin-S exclaim: "But I have never been sick like my brother has been!"

True, if you are "AS (Norm/Ache), you are no

different in "ache-health" from the one who has "AA" (Norm/Norm'. It is the one who inherits S from both parents (SS, or 'Ache/Ache') who will not only test positive on the Sickle Cell Test, but will also be found on examination to have anaemia (Sickle Cell Anaemia), yellow eyes (jaundice) and other effects of the red cells turning sickle shape in the body. Haemoglobin S is not the only 'Ache' Haemoglobin gene known.

West Africa

The next commonest Ache gene is Haemoglobin-C, prevalent in West Africa. Indeed, in southern Ghana, 20% of people have inherited a Normal Haemoglobin-A from one parent, and the 'variant' Haemoglobin-S from the other, giving them the "AS" phenotype (Norm/Ache, known as the 'Sickle Cell Trait'. I repeat: The Sickle Cell Trait person is not aware of any inherited trait because no disease occurs. Another 10% of southern Ghanaians are found on special tests to have the "AC" phenotype ('A' gene from one parent, and 'C' gene from the other). In northern Ghana the reverse is the case: 10% have the Sickle Cell Trait ('AS') while 20% have Haemoglobin-C Trait ('AC'). It is very important to note that the Sickle Cell Test on a person with Haemoglobin-C trait (AC) will be negative because the test detects just 'S' and nothing else. Because the 'C' gene (Ache) combined with the 'S' gene (Ache) in a child also produces Ache/Ache disease, it is possible for a 'Sickle Positive' father 'AS', and 'Sickle Negative' mother 'AC', or vice versa, to have a child with Sickle Cell Disease.

Read that again, because I have seen serious family disruption and quarrels arise because one parent is not a "sickler" on blood testing, the partner is positive, and a child is born with rheumatism and other sickle cell problems. Question: "If it takes two Ache genes to produce illness in my child, where did the other Ache come from when I am Sickle Negative?" asks a suspicious husband.

Answer: Sickle Negative does not mean Abnormal Haemoglobin Negative! Please do not rush to divorce your wife simply because one of you does not have the Sickle Cell gene. Other Ache genes which, combined with the Sickle Cell gene ('S') can produce Sickle Cell Disease are beta-thalassaemia, Hereditary Persistence of Fetal Haemoglobin (Haemoglobin-F or Fhereditary), Haemoglobin-D, etc. These Haemoglobins cannot be discovered through the Sickle Test, but through a procedure called Haemoglobin Electrophoresis.



Normal cells are round; sickle cells are curved

The Ache/Ache Person with Genius

Remember that a gene producing an Ache haemoglobin is but one of scores of thousands of genes that the Ache/Ache person possesses. We must not judge people by just one pair of genes.

I have seen families where the person with the Ache-from-father/Ache-from-mother pair of genes is also the person who inherited a Genius-from-father/Genius-from-mother phenotype. I can identify these families to anybody.

This is why in the management of people with sickle cell disease we should aim at making it possible for these Ache/Ache persons (or patients) to achieve their full potential. They may not be international footballers, but they can come top of their class and become university lecturers, professors, nurses and midwives, surveyors, bankers, lawyers, businessmen and women, professional singers and pianists. We shall come to the "Achievements of Sickle Cell Disease Patients" in a later article. Please look again at the diagram. There is always a 1 in 4 chance of each pregnancy ending up with an Ache/Ache child. It never should be interpreted to mean that if the first child is SS, then the second child can never be SS. Or that if a couple have four children all of whom are AA, then it is proof that the parents can never be Sickle Cell Trait carriers ('AS'). I have seen a consultant physician, whose wife is also a doctor become greatly puzzled when their "unplanned" fifth child turned out to be 'SS'.

That was the first time they tested themselves and found that they both had been Haemoglobin-S carriers "all these years". They had, for more than 15 years, enjoyed a 3 in 4 chance of not having a sickle cell disease child in spite of being 'AS' parents.

I have also known the TS Family in Ghana, Sickle Cell Trait (AS) parents, whose first child was 'SS', second child 'SS', third child 'SS', and fourth child 'SS'. For those interested in Elementary Mathematics, the chances that it did happen were $(1 \text{ in } 4) \times (1 \text{ in } 4) \times (1 \text{ in } 4) \times (1 \text{ in } 4) = 1 \text{ in } 256$. Relatively infrequent, but it did happen!

Now work out the chances of sickle cell disease in the offspring when one parent has sickle cell trait (AS or Norm/Ache) and the other has sickle cell disease (SS or Ache/Ache). Would you agree that the chances of sickle cell disease in the offspring would be 50%, ie, every other child born could be Ache/Ache?

What about a sickle cell disease person marrying another sickle cell disease person? Well, Prof Bela Ringelmann and I found such a couple in Ghana. They had 13 children. The Ache/Ache father (SC) and Ache/Ache mother (Sbeta-Thalassaemia) produced 13 Ache/Ache children (100% abnormal haemoglobin incidence). They gave permission for their photograph to be published on the cover of my book, The Sickle Cell Disease Patient, with the advice that people should take genetic counselling and family planning seriously.

TERMINOLOGY

Sickle Cell Trait:

A person who has inherited a Normal Haemoglobin-A from one parent, and a 'Mutant' Haemoglobin-S from the other parent ('AS' phenotype, also called Heterozygote or Sickle Cell Carrier). Can only be identified through blood test (Sickling Test).

Before the age of 4, the Sickle Cell Trait ('AS') withstands the lethal complications of Falciparum malaria. It is not true to say Sickle Cell Traits do not suffer from malaria. They do, whether young or old, but the disease in them is not as serious as in the 'AA' (Norm/Norm) or 'SS'.

Sickle Cell Traits never suffer from Sickle Cell Disease. Indeed, they have run at Olympic Games in Mexico and beaten the whole world. It is not true to say Sickle Cell Traits (the



Dr Konotey-Ahulu's website

Norm/Ache) have died climbing mountains. It is also not true to say that the "Sickle Cell" is a "black people only" phenomenon. It is found in whites in Greece, Turkey, Cyprus, etc, and the highest incidence in the world is in India and Saudi Arabia. It is less common in the Kikuyus of Kenya than in Greeks.

Sickle Cell Anaemia:

A person who has inherited Haemoglobin-S from both parents (SS phenotype, also called homozygous-S, or S-homozygote). The SS state is Sickle Cell Disease, but because anaemia (low blood level) is the main feature with this phenotype, it is specially designated "Sickle Cell Anaemia".

Sickle cell anaemia patients fare very badly against malaria. Textbooks of science and genetics that state that sickle cell anaemia patients are resistant against malaria are dangerously and hopelessly wrong. When sickle cell anaemia patients go from Europe, Canada, or America on holiday in Africa or other malaria-prone countries in the Far East and elsewhere, they must protect themselves with anti-malarial tablets like anyone else. On their return, should they develop joint pains, headache, fever, or what they think is 'Flu', they should tell ask their doctor to test them for malaria, or they would be in trouble.

Sickle Cell Disease:

Inheritance from both parents of abnormal haemoglobin genes at least one of which is the 'S' gene. So 'SS', 'SC', 'Sbeta-Thalassaemia', 'Sfhereditary', 'SD', 'SKorle-Bu', 'SOsu-

Christiansborg', 'Sibadan', etc, are all sickle cell disease phenotypes with their own peculiar behaviour.

The AS phenotype, or Sickle Cell Trait or Carrier State must never be called Sickle Cell Disease. I do not use the term "Sickle Cell Disorder" partly because people think (wrongly) that the term extends to Sickle Cell Trait too, and also because I never talk of "the diabetic disorder", or "the tuberculosis disorder".

Nor do I encourage the phrase: "I have sickle cell". It must always be spelt out: "I have Sickle Cell Trait (AS)", or "I have Sickle Cell Anaemia (SS)", or "My child has Sickle Cell Disease (SC)",



Top - normal cells; above - sickle cells

or "My wife has sickle Cell beta-Thalassaemia". I know that many doctors and nurses display ignorance on such terminology, so I make it a point of educating my patients in order that they may in turn educate their health carers.

Wrong terminology:

A doctor across the Atlantic was reported telling a distraught mother about the sudden death of her daughter in hospital: "Her Sickle Cell Trait suddenly worsened overnight and became Sickle Cell Disease, and she died".

A copy of this article should be sent to that doctor. Another wrong terminology I read on a website was: "I have the Sickle Cell Anaemia Trait". If the reader of my article here does not see that this is also a genetic nonsense, then I have failed as a teacher.

Africans knew it for centuries:

Because both of my parents were Ache/Norm and they had three Ache/Ache children out of 11, I became the first to point out in the medical textbooks that what was called Sickle Cell Disease had in fact been known by Africans for centuries. It was, and still called, Chwechwechwe (by the Ga of Ghana), Hemkom (Krobo/Dangme-Ghana), Ahotutuo (Twi-Ghana), Nwiiwii (Fante-Ghana), Nuidudui (Ewe-Ghana/Togo), Amosane (Hausa-Northern Nigeria), Aromolegun (Yoruba-Nigeria), etc. (For further information, please see my website: www.sicklecell.md).

In subsequent articles I shall deal with the signs of this hereditary disease, and what can be done to help patients achieve their full potential. Meanwhile let's go interactive - you could supply some feedback information. Readers could write to me, care of New African, or direct to me at konotey-ahulu@sicklecell.md

Self Assessment

1. I understood what I have just read.
2. I did not fully understand what I read.
3. I have never been tested for Sickling.
4. I have been tested for Sickling and I know my phenotype.
5. I have been tested for Sickling but I don't know my phenotype through Haemoglobin Electrophoresis.
6. I would like to find out what my true haemoglobin phenotype is (AS, AC, AA, Abeta-Thal, SS,SC, etc).
7. I would like to find out my children's phenotype and learn more about genetic counselling.
8. I now realise how important it is to know whether I am Norm/Norm, Norm/Ache, or Ache/Ache.