The Role of Heredity and Environment in the Causation of Cancer

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INTRODUCTION

There are at least three reasons why it is a great honour for me to deliver the 6th Oluwakayode Osuntokun Memorial Lecture. First, Professor Osuntokun, a foundation student of the MBBS Ibadan course, the first professor of neurology of the University of Ibadan, a former dean of the University of Ibadan Medical School, was one of the most distinguished scholars amongst those born and educated in this country, as well as a world leader in clinical neurology. A talented, enthusiastic, eminently competent clinician, he was at the same time a charismatic teacher; his mind was always focused on the progress of medical science. I will never forget my first encounter with him. He had just returned from Newcastle and was setting up his major, now historical epidemiological and clinical study of tropical neuropathies. I was struck by Kayode in part because of his solid background and specialized expertise; but even more because I could perceive in him a marvellous blend of youthful spirit and intellectual maturity. It took me a bit longer, but not too long, to learn the secret of that blissful blend: the secret was called Bopo, and having her here today with their children is the next best thing to having dear Kayode himself with us.

Second, I am aware that I have been preceded by far more prestigious lecturers, and I am a bit awed by that notion. It is a testimony to the regard in which Professor Osuntokun was held, that people from different parts of the world have come here to honour him, and to share their memories of him with you. I

cannot help being partial to Sir Keith Peters, former Professor of Medicine at the Royal Postgraduate Medical School, now Regius Professor of Medicine in Cambridge, a mutual colleague and friend, a great supporter of Professor Osuntokun and of his family. From Sir Keith I learnt many anecdotes about Kayode, even before I met him. One of them was about the time the two of them were waiting to take the *viva* for the MRCP exam. Keith recalls being somewhat nervous. Whether Kayode was also nervous is not on record: what he said instead was that he did feel some fright, but on behalf of the examiners, in case they came to realize fully how much he knew!

Third, I am honoured because I feel loyal to the University of Ibadan. Having had the privilege of holding positions in haematology and in genetics elsewhere, I cherish in a very special way the ten memorable years I spent in the Haematology Department in Ibadan. These years are special because of the exceptionally stimulating academic environment and the pleasant cosmopolitan community on a lovely campus; because of the medical students, with whom I shared what I knew of haematology while I was learning English from them; and probably most of all, because I was young, and this is where my family got started. I shall be forever grateful for the wonderful experiences we had living in Nigeria, particularly at the University of Ibadan.

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My topic today is complex, and in some ways esoteric, yet, it touches upon issues that affect us all. Cancer is such a common disease that it may be hard to find any family that has not been touched by it directly. It is not surprising, therefore, that we are afraid of cancer. Of course there are other dreadful, potentially deadly diseases about which we have every reason to feel frightened: malaria, or HIV/AIDS, just to mention two examples. Yet, it must be admitted that for most people the emotions associated with the word *cancer* are much stronger. Indeed, when we know someone has cancer it affects the way we talk to them. At one extreme, there may be denial; at the other extreme, there may be harshness, or even anger. I feel great respect for these sentiments, and if I am stirring them up in some of you, I crave your indulgence in advance: as this lecture is going to consider the scientific aspects of the subject.

The word *krebs*, corresponding to the Latin *cancer* (also used to indicate one of the signs of the Zodiac), simply means 'a crab'. This word was used in the early description of various types of tumours by German pathologists, and it conveyed the message – whether intended or not – that a foreign creature equipped with claws was attacking an organ of the patient; and often, the aggressor seemed to greedily claim more and more of the patient's body as the tumour spread, eventually resulting in death. The loss of weight associated with advanced cancer (called *cachexia* when it becomes extreme) further reinforced the notion that the unwelcome guest was literally overwhelming the host.

I cannot claim any thorough knowledge of the concept of cancer in traditional Nigerian medical culture, but I have no doubt that the *babalawo* was able to recognize certain growths as malignant. It is very likely that some traditional doctors had learnt to appreciate the ominous nature of jaw lesions in children, long before Dennis Burkitt had painstakingly defined that unique type of lymphoma which we now call the Burkitt's tumour, and of which we now know the precise basis at the molecular level. Indeed, when the babalawo applied certain liniments to these lesions he was attempting to introduce a form of treatment not very different from what we call hyperthermia therapy today. It appears that the treatment of malignant tumours is part and parcel of medicine in all cultures.

A bit of history

Although one might wish to imagine that cancer is an outside aggressor, or a foreign invader, the current evidence is that cancer originates from inside, from the very cells that compose our normal tissues. In fact, despite the colourful description of the crab, it was Rudolf Virchow, the father of 19th century pathology, who delineated the 'cellular theory' of cancer. In essence, Virchow's idea was that a normal cell can change in some way to become a cancer cell: he used the word 'degeneration' to indicate this process. Today we prefer to say that a normal cell *transforms* into a cancer cell.

In 1914, it was Wilhelm Boveri, following Virchow's trail, who first expressed the notion that a person with cancer had something wrong with his/her chromosomes; thus pinpointing the origin of cancer not just to the cell, but to its most sacred interior part. It was not until 1973, however, that it became possible to

point the finger not just at the chromosomes, but at individual genes: this was the dawn of oncogenes, for which Michael Bishop and Harold Varmus were subsequently awarded a Nobel prize.

The Current View on the Nature of Cancer

Another thirty years have passed since Bishop and Varmus were able to pinpoint individual genes, and we now have a fairly clear idea of how a normal cell transforms into a cancer cell. This transformation results from a precise sequence of genetic events that take place within individual cells inside our body. This is not to imply that external factors cannot play a role, but invariably they do so by causing, or favouring the transformation of a normal cell into a cancerous one.

Normal development is based on the well orchestrated function of the genes

In order to understand how this happens, we must first recall some basic facts about how cells are programmed in the tissues of our body. This also ties up with the development of the embryo, and with the wonderful way in which organs bud and tissues differentiate within the embryo, and further on in adult life. Although we should not presume that we now understand fully how a fertilized egg becomes a baby, some fundamental features of this regularly occurring miracle are clear.

1. The plan to build a highly complicated organism is entirely encoded in the fertilized egg in the form of a DNA sequence.[1]

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[1] Artists are often ahead of scientists. When Michelangelo was asked to explain how he conceives a statue, he replied with a poem. "*Non ha l'ottimo artista alcun concetto/ che un marmo solo in sè non circoscriva/ col suo*

2. The plan is implemented through the development of an embryo; and through the differentiation of organs within the embryo, and of different cell types within each organ and throughout the body.
3. Cells vary widely in their features and functions by virtue of the different sets of proteins they contain. Proteins are encoded in individual genes, and by reading the sequence of a gene we know the sequence of the protein.
4. Development and differentiation are actuated and finely controlled by turning on and off individual genes or sets of genes at the right place at the right time.
5. The control of the expression of certain genes by others and by regulatory (non-coding) elements within DNA is critical for development and differentiation.

A beautiful performance is not necessarily a perfect performance; mistakes can happen in any kind of manufacturing process. Human development is so complex that one may well wonder why something has not gone wrong (for instance, a misplaced vessel in the heart; an extra toe; an incompletely sealed palate midline). But how come most babies are flawless? In some cases abnormal development may result from an abnormal gene passed on by either parent; in other cases the abnormality may be acquired, either during embryo development or subsequently. It turns out that some of such changes, subtle yet potentially devastating, are capable of causing cancer.

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soverchio: e solo a questo arriva/ la mano che obbedisce all'intelletto", ie, 'Even the best of artists cannot conceive any shape that a marble boulder does not already encompass within the part that is redundant: and towards this only reaches the hand that obeys the mind'.

Cell growth or, more precisely, cell division continues actively even after the growth of the body as a whole appears to have ceased. Populations of cells are somewhat analogous to populations of organisms, and so are many of the issues they confront. If the population density has reached an optimum, or a maximum, it better be controlled. From early times in evolution, cells have evolved mechanisms able to exert strict control on their own growth. Such controls are both internal and external.

The cell cycle

Cell division is a very complicated process. Imagine having an object consisting of thousands of different parts, say a motorcar; imagine making another identical motorcar, not by using a separate assembly line in a factory, but rather by allowing the original motorcar to double its size and then splitting into two; and imagine doing all this in about 24 hours. In order to pull off this remarkable feat, a cell must proceed in a very orderly fashion. First, all components of the cell, except the nucleus, grow in size; then the DNA within the nucleus replicates. This is of course a critical step: it involves copying the entire length of DNA, consisting of some 3 billion bases, in the cell's 46 chromosomes. The replication process is based on the famous double-stranded structure of the DNA molecule, whereby each strand acts as the template for a new strand. To make replication faithful the copying process is continuously monitored for mistakes: ie, there is a true 'proofreading' going on all the time, and the mistakes detected are immediately repaired. In spite of all this, no physical process can be perfect. If a typist copying a manuscript were to slip once in every million characters nobody could say that he or she is sloppy; but since we are dealing with 3 billion characters, this would mean about 1000 errors. Most of

these errors do not matter, because we know that much of the DNA is non-coding; but occasionally an error, which we call a *point mutation*, may have serious consequences, as we shall see later. Once the DNA is replicated there is another period of time during which the cell again grows in size. Finally, we have the most spectacular act of this play. The nuclear envelope breaks down, and the material within the nucleus called chromatin, (which consists of the DNA bound to proteins called histones) condenses and makes its chromosomes visible. Since the DNA has already replicated, there are in fact now 46 x 2 = 92 chromosomes. In the meantime, the cell produces a complex system of filaments called the mitotic spindle, which spans the distance between the two poles within the cell. The 92 chromosomes form a beautiful crown across the equator of the spindle; then one chromosome of each pair gradually moves towards either pole. Once each set of 46 chromosomes has reached one pole, two nuclear envelopes form and eventually the two daughter cells segregate.

We now understand the phrase *cell cycle*. It is a cycle because it starts and it ends with a complete cell. Once the two daughter cells are on their own, each one can go through a new cycle. Although the cell cycle is a continuum, it is convenient to identify discrete phases within this process. The phase of DNA replication, or DNA synthesis, is called the *S* phase. The two phases of growth before and after *S* are called *G1* and *G2* respectively. The segregation of the chromosomes along the spindle and the separation of the two daughter cells is called the *M* phase, for mitosis. When cells divide at a high rate they will always be in one or the other of these phases of the cycle: this is largely the case, for instance, at early stages in embryonic development. On the other hand, cells may exit the cycle, and

they are then said to be resting, or in *interphase*, or in *G0*. This is the case, for instance, for most of the nerve cells in the adult brain.

The cell cycle must be carefully controlled

A process as sophisticated as the one we have outlined cannot have evolved overnight. In fact, it is remarkable that the basic features of the cell cycle are already fully present in unicellular organisms like yeast. Because yeast is a much more simple organism than a human being, it has been easier to elucidate factors that control the process. From these studies two sorts of controls have emerged. On the one hand, the cell must decide if and when to divide; on the other hand, once the cell activates the division programme, it wants to make sure that the programme is implemented correctly. This latter control is exerted by having 'check-points'. For instance, if a cell in *G1* is not ready for *S*, the process is aborted. The same happens if the chromosomes do not segregate correctly in *M*. The significance of these checks is clear: they tend to prevent at all costs the production of abnormal cells: indeed, in human cells the checks are even more rigorous than in yeast cells.

It is not possible to present all the details of how the cell cycle is driven, actuated, and controlled here. Suffice it to say that a large number of proteins are required for and involved in the cell cycle: some of them are appropriately called *cyclins*, others are called by the more awesome phrase of *cyclin-dependent kinases*, or *cdk*. Others have a variety of names or they are simply identified by their size, or molecular weight, for instance protein 27 or p27 (meaning that the molecular weight is 27,000 daltons).

This nomenclature is pertinent because we can already imagine that these proteins may be important in cancer.

Cell multiplication is also subject to control

Thus, it appears that the choice between resting and cycling is a major decision for a cell, especially because, once a cell has committed itself to dividing, the commitment is irrevocable. If we now consider a whole population of cells, it is clear that whether the population remains stationary or instead grows in number will depend on how many cells will commit themselves to cycling. Once again, under normal circumstances the behaviour of different cell populations in the body will vary depending on time, location and cell type (for instance, in the embryo and in the child, most cell populations are growing); and it is also obvious that excessive growth is the essence of cancer. Therefore regulating the growth of individual cells in all parts of the body is of critical importance for the body's development, survival and well-being.

It is clear that for cells as well as people, growth requires an enabling environment, which must include adequate provision of nutrients. These can be regarded as necessary conditions, but they may not be sufficient. In most cases, cells proliferate when they meet special protein molecules generally called *growth factors* in the environment. A great variety of these molecules exist in the body; they are said to be specific, in the sense that they stimulate growth of a certain type of cell. One prototype is the nerve growth factor (NGF): this was discovered and characterized half a century ago by Rita Levi-Montalcini and Stanley Cohen, who, for this reason, were awarded the Nobel prize in 1986. At about the same time, Eric Goldwasser found a

growth factor for the production of red cells in the urine of anaemic people, this has become known as *erythropoietin*. This is now used in the treatment of certain types of anaemia. Unfortunately, this substance has also been abused by some athletes in order to give themselves the advantage of supra-normal hemoglobin levels. In addition, we now know the growth factors required for white blood cells (several), for cells of the mammary glands, for liver cells, for skin cells, and so on.

In essence, where growth factors are absent, cells will tend to stay at rest. However, when cells of a certain type see their favoured growth factor, which is usually produced by other cells, they start cycling, and their numbers increase. When this happens it may send a signal, directly or indirectly, to the cells producing the growth factor, and they will stop. As the concentration of growth factors decreases, cells will gradually stop cycling. Through this feedback mechanism growth is promoted, but it also remains under control.

Cells can receive signals from other cells

It is not only growth factors that control cell growth. In many tissues the physical arrangement is also very important, For instance, if we lose a small piece of skin, keratinocytes and other cells will start cycling to repair the damage. When the cycling cells have filled the gap, they will get signals from the neighbouring cells to tell them that the job is done, and they will exit the cycle. This type of feedback is called *contact inhibition*; without it, we would form an excess of skin every time we have a small lesion.

Growth factors and contact inhibition are not the only factors which control cell growth. The story is more complicated: for

instance, there are also factors that inhibit cell growth. However, the oversimplified outline given here may be sufficient for us to understand how control can be lost in cancer.

Cells can commit suicide: What are the motives?

Up to this point, we have an idea of how a cell population can grow, or how it can remain stationary when growth is not needed. We must also consider that cells can be damaged through an accident, such as a wound, or even killed, for instance as a result of aggression by a virus. What is perhaps more surprising is that a cell can deliberately choose to die. There are at least two kinds of situations in which this happens. First, during embryonic development the shaping of certain body structures requires trimming as well as growing. A rather spectacular example is the formation of fingers and toes. The bud of a hand is a sheet of tissue; then certain cells selectively die, and the gaps between fingers are thus produced.[2] This example illustrates how sophisticated this process can be: cells must die or persist according to a very precise plan. For this reason the process is also referred to as *programmed cell death*, or by the Greek word *apoptosis*. Another situation is when the cell suffers non-lethal damage, particularly to its genome. Since the damage is non lethal, the cell retains the ability to divide, and thereby it would generate more cells that are equally damaged. Before this happens, the cell commits suicide, thus preventing the formation of a set of abnormal cells, which might get out of control and thus do harm to the entire organism. It is tempting to infer that such a cell is really sacrificing itself, unselfishly, for the common good,

[2] Interestingly, this happens in chickens but not in geese, which therefore have palmed extremities.

but we should not project our emotions on a cell. The biologically-minded observer would infer that this phenomenon has been selected in the course of evolution, because in this way the organism, rather than the cell, can survive and reproduce. But there is something else we can certainly infer: for the cell to know when to commit suicide, there must be an internal surveillance mechanism. We now know at least one such mechanism. A protein called p53 constantly scans the DNA (p53 has been called a patrolman of the genome): when it detects damage it activates cellular self-destruction pathway, or apoptotic pathway. Now we understand the phrase programmed cell death.

Once again, we have a striking example of similarities between the behaviour of people and the behaviour of cells. Among people, it is terribly sad when somebody is driven to suicide; and certainly this is not a sensible way to control population size. Indeed, even when it comes to cells, in general we should not think of apoptosis as a means to control population size: this is best done by fine-tuning the shift from cycling to resting. But for individual cells apoptosis is a fine safeguard against the emergence of abnormal cells, which could become a cancer.

Somatic mutations modify genes in a permanent way

It is clear that cell growth is tightly controlled. Correct growth requires the appropriate supply of growth factors, the precise operation of the cell cycle, the timely transition of cells in and out of cycle: and sometimes the activation of the death program. Every one of these processes requires the intervention of several proteins, encoded by as many genes. We don't know the total number of genes involved, but we can estimate that they may total

several hundreds. We now must examine what may happen if something goes wrong with one of these genes; and before that we must consider what can go wrong in any gene.

We have seen exactly how a gene encodes a protein. If the sequence of a gene in a single cell changes, due to a replication error, the gene is said to be a *mutant* gene. The mutant gene is still a gene, and therefore when it replicates at the time of cell division – this time without errors – the daughter cells will have the mutant gene: and so on. After some time there will be a set of cells, all of which have the mutant gene: since all the cells derive directly from the cell in which the mutation took place, we call this a mutant *clone*. In all cells belonging to the clone the protein encoded by that gene will be altered. Often the alteration in the protein will have minor consequences, and therefore it will not cause any problem. However, this depends critically on the type of mutation. An extreme example, for instance, is when a G mutates to A in the sequence UGG. UGG codes for the amino acid tryptophane; UGA instead, codes for no amino acid at all: it is called a STOP codon, because it dictates for the protein sequence to be terminated. If the UGG corresponded, for instance, to amino acid 101 in a protein of 495 amino acids, the protein produced (after the mutation) will be only 100 amino acids long, instead of 495, and it will be almost certainly a non-functional, or useless protein.

In the example above, let us imagine that the mutation took place in a gene that controls the exit from the cell cycle. The protein in the mutant cells is unable to do its job: as a result, the cells belonging to the mutant clone will have trouble in the transition from cycling to resting, and they will cycle too much. Thus, the clone will tend to grow excessively.

Somatic mutations inevitably accumulate in time

We emphasized earlier that DNA replication is highly accurate and therefore mutations are relatively rare: those having adverse consequences are even more rare. In contrast to the deterministic nature of DNA replication, the occurrence of a mutation is a chance event: we have not used this word yet, but we can see that in mutation there is an element of randomness. Yet, given enough time, mutations will happen again and again. Our body consists of some 10^{18} somatic cells (that is to say, about one billion billion cells)· it is inevitable that mutations accumulate as we age.

Several somatic mutations may change a cell from normal to malignant

If the clone we have just described had already become a cancer, we would all probably be victims of this disease by the age of 5. However, the control of cell growth is so critical that several back-up control mechanisms have evolved; therefore, in order to escape from the normal controls of cell growth, the cell must break through the rules not just once, but more than once. In other words, the process of transformation from a normal cell into a cancer cell is not at all trivial, and it certainly *requires more than one mutation*.

Genes that affect cell growth, once mutated, are prime candidates for being involved in producing cancer

The finely-uned control of cell growth has been compared, perhaps a bit crudely, to the smooth running of a car: we need an accelerator, and we need the brakes. Since a tumour is an abnormal growth, we can presume that a mutation will favour its development in one of two ways: either by causing a growth-

promoting gene to overdo it (like pressing on the accelerator); or by causing a growth-inhibitor gene to fail (like brake failure). In the first case we call the mutated gene an *oncogene*, because we see it as a generator of cancer (the normal, non-mutated gene would then be called a *proto-oncogene*). In the second case we call the gene a *tumour-suppressor gene*. Since genes are always in pairs, it is important to note that in the case of an oncogene one mutation will be enough to cause trouble: the mutant gene can effectively press on the accelerator, even though the other partner is still intact. By contrast, if a tumour suppressor gene is mutated, the other partner will still act as a brake: therefore, *both* genes of the pair have to be mutated before the braking power is lost. We have not yet identified all the oncogenes and all the tumour suppressor genes that exist: but it is interesting that until now the list of the former is much shorter than the list of the latter.

Other genes, not just those controlling the cell cycle, can be involved in the transformation of a normal cell into a cancer cell

In the previous paragraphs we have seen that mutations in individual genes are critically implicated in producing cancer. Although mutations are rare events, they are part and parcel of our existence. Therefore we must now consider on the one hand factors that may influence the probability of mutations taking place (in technical jargon, the *mutation rate*); and on the other hand, how the cell deals with the consequences of mutation. Taking the second point first, it turns out that the cell is endowed with devices of surveillance, that are able to monitor the occurrence of mutations, particularly those associated with relatively major changes, such as the loss or the gain of a whole chromosome. When such damage to the genome is sensed, a well-behaved cell ought to activate what we have called the death

programme, or apoptosis. But what will happen if one of the genes responsible for surveillance is itself mutated? What may happen in this case, is that the cell will fail to apoptose. As a result, not only will a cell with a major damage to its genome survive: it may also still be able to proliferate, thus giving rise to a whole population – a clone – of damaged cells, each one of which is a potential target for further mutations that might eventually become malignant.

As for mutations that may in turn affect the mutation rate (this sounds almost like a pun, but it is probably a common event in tumour formation), some authorities think indeed, that it may be the rule rather than the exception. The DNA replication machinery is very complex, because some parts do the copying, but others do the proofreading and on-the-spot repairs. It is easy to visualize that any mutation affecting one of these parts risks reducing the fidelity of the copying: in other words, it may increase those copying errors that we call mutations. Thus, in addition to the oncogenes and the tumour suppressor genes, we have encountered earlier, we must include two other groups of genes on the list of those that, if mutated, can favour the production of cancer: repair genes, and the genes that are required for the cell death programme.

Different types of cancer arise through different sets of mutations

Whether cancer is one disease or many diseases has been keenly debated for a long time: some have regarded it as an important distinction, others as just a matter of semantics. Molecular analysis now gives us a picture that perhaps can reconcile the controversy. In essence, the general pattern is the same in all cases: a sequence of somatic mutations transforms a normal cell

into a cell which is abnormal in a variety of ways, but always with dysregulated growth. This supports the notion of cancer as one entity. On the other hand, for each type of tumour it is different genes that are involved: in this respect, ie, at a much more refined or detailed level of analysis, each tumour is a distinct entity, supporting the notion of the multiplicity of cancer. Thus, both notions are correct at certain levels of resolution, and it is important to understand both sides of the argument if we want to progress. On the one hand, the fundamental unity of cancer means that what we learn from one type of cancer can be useful for other types of cancer; on the other hand, the distinct pathways in the transformation to cancer rationalize to some extent why we must tailor preventive measures and therapeutic measures to each type of cancer individually.

There is a close link between disturbed differentiation and the development of cancer

There is a close link between cell division and cell differentiation: indeed, cells can divide before they differentiate, they continue to divide hand in hand with the progress of differentiation, and they stop dividing when they have reached the terminal stages of differentiation. In contrast to these normal situations, a cancer cell is defined, in a way, by its commitment to unrelenting cell division. How does this come about? We don't yet have a complete answer to this question, which is currently the subject of advanced research. However, we can visualize in a fairly simple fashion at least some of the relationships between differentiation and cancer growth. Let us say that, as a consequence of a mutation in a gene that controls cell differentiation, the cell becomes unable to differentiate beyond a certain stage. Let us also assume that the link between

differentiation and cell division has remained intact: ie, the cell does not stop dividing because it has not reached the terminal stage of differentiation. The result will be that the cell continues to divide, retaining the degree of differentiation it has reached: in practice, we have indefinite growth, which meets the definition of neoplastic growth. Thus, we must add the genes involved in differentiation to those that, when mutated, can contribute to the formation of cancer.

The Role of Heredity

Inevitably, as soon as a baby is born, the family begins to debate its likeness to either parent, or sometimes even to a great-aunt. The notion that parents transmit all sorts of characteristics to their children has emerged in every human culture: in fact, it must be as old as the emergence of humans from the primate world. Children, as they grow up, may wonder what abilities or liabilities they have inherited from their parents, long before they even think of the material items they may subsequently inherit.

Yet, we have been slow in working out a scientific understanding of the mode of this transmission. Indeed, while the main laws of physics were conquered by the 17th century, the laws of biological inheritance discovered in about 1850 by a Bohemian monk, Gregorius Mendel, were not incorporated into the mainstream of science until the early 20th century. Mendel's contribution was not just his careful quantitative analysis of how physical characteristics are transmitted;[3] even more important was his notion that in each organism the characters of the parents are

[3] Mendel did his work on green peas in a vegetable garden in a monastery, but the essence of his findings are applicable also to animals, including humans.

combined, but not forever blended together. Rather, these characters somehow retain their discrete individuality; therefore, even when they are not seen in an individual member of a family, they may once again segregate and thus re-appear in a subsequent generation. In other words, it became clear that what is inherited was not a continuum: instead, it seemed to consist of very small particles or units. Mendel did not give these units a specific name, and he could not have any idea of their chemical nature: today it is clear that he meant genes, and today we know the genes are made of DNA.

Mutations generate a variety of genes that are at the heart of human diversity

As we know already, genes can undergo mutations, and mutations in germ cells can be passed on to our children. Over thousands of generations, since the emergence of the human species, many mutations have accumulated, and they have caused the marvellous diversification of human beings all over the world: in technical jargon, we say that there is a lot of genetic polymorphism in the human species. We know now that genes operate by making proteins: different genes will make different proteins, and these may cause visible diversity.

While mutations as such are not necessarily a bad thing, harmful mutations do exist. Considering that we have some 40,000 genes, it may appear surprising, at first sight, that a mutation in a single gene may cause major trouble: but there is abundant evidence that this is true. For instance, we all know that a mutation that causes a single amino acid change in the molecule of haemoglobin in red cells produces the serious form of anaemia called sickle cell anaemia; a mutation that causes a loss of DNA

(called a *deletion*) within a gene encoding a muscle protein called *dystrophin* produces a serious progressive loss of muscle power in children with muscular dystrophy; a mutation in the gene encoding coagulation factor VIII produces haemophilia; and so on. The first diseases due to single gene mutations were discovered a century ago; and since 1960, Victor McKusick has carefully catalogued all diseases that we call Mendelian, or monogenic, precisely because each one is caused by a mutation in one specific gene. The catalogue, now available on-line,[4] comprises nearly 2000 individually numbered diseases.

Why are disease-causing genes not eliminated?

We have already remarked upon the fact that normal genes, such as those for skin pigmentation, can be subject to natural selection: this process, first explored in depth by Charles Darwin in the middle of the 19th century, is therefore referred to as Darwinian selection. But what about the fate of genes that cause disease? Since many of these diseases manifest early in life, and unfortunately may cause death in childhood, ie, before reproduction, one might expect in principle that they will be quickly eliminated from the population. However, there are at least three possible (and not mutually exclusive) reasons why these inherited diseases persist. First, since mutations keep taking place, mutant genes that are eliminated may be replaced by those that newly arise. Second, remember that many diseases are recessive, and many of them are rare. Selection will operate against the patients affected by a serious disease, who have two mutant genes in the respective gene pair (they are called *homozygotes*). On the other hand, people with only one of those

[4] <http://www3.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>

mutant genes (they are called *heterozygotes*) are perfectly normal: selection will not operate against them, and therefore heterozygotes will persist in the population. When two heterozygotes marry,[5] they may produce a homozygous child: and this will keep happening, more or less frequently depending on how common the gene is, as long as there are heterozygotes in the population.

The third mechanism is more subtle: it applies only to recessive diseases and it can be powerful. It will be recalled that heterozygotes for recessive diseases do not, by definition, suffer from the disease (it is only homozygotes who are affected). It may happen that in a certain environment heterozygotes are actually at an advantage. The best studied example comes from Africa, namely the heterozygotes for the sickle cell gene. As we know, this turns out to be a plus when the red cells are infected by the malaria parasite *Plasmodium falciparum*.

The example we have outlined is well known: there are probably many more yet to be discovered because they may be more subtle. At any rate, one cannot help noticing a parallel between biology and sociology: we are more accustomed to socio-economic situations where some people have it good, whereas others pay the price.

Cancer as such is never inherited; but certain mutant genes predispose to cancer

How does heredity apply to the development of cancer? We have previously represented cell transformation as a kind of pathway, leading from N to M: the pathway may consist, for instance of 5

[5] This is particularly prone to happen if two related people, for instance first cousins, marry each other.

genetic events. In this parable an increased risk of cancer means a higher probability of getting from N to M during a lifetime; or, to get there faster. What would a runner do if he wants to win a race from N to M? In essence, he has two options: first he could run faster; second, he could cheat, by reducing the distance he has to run, Let us see what this means once we move back from the parable to a real cell.

1. To run faster means a higher probability of going from one stage to the next along the pathway. Remember that each step is a mutation, and that a mutation is a small error in DNA replication. In general the mutation rate is very low, but any factor that increases the mutation rate will increase the risk of cancer. We know several mutant genes that do so when inherited in double dose (the homozygous state), and indeed the diseases they cause (for instance Fanconi's Anaemia, Bloom's syndrome, *xeroderma pigmentosum*) are associated with a high rate of cancer.[6] Other genes may increase the mutation rate even when only one of the pair is mutated: and some of them are associated with increased risk of colon cancer. While these cases are clear-cut, there may be subtle but extensive variability in mutation rate from one person to another even in people who do not have any identified disease: and this may be important in determining, for each person, what is the life-time risk of developing cancer.

2. To cheat means to skip one step along the pathway. The most direct way to visualize this is to consider that, if it takes four mutations to go from a normal cell to a certain type of cancer, the first mutation might have been inherited. Thus, it would be present in all cells of the body to begin with: the

[6] DNA repair genes can also be mutated somatically.

implication being that now only three more acquired mutations will be required, rather than four, for cancer to arise. One might think that this is a small difference, but don't forget that each mutation in a critical gene is a very rare event: therefore, based on probability theory, to have one mutation ready-made has a major impact on our estimate of the risk that the pathway to cancer will be completed.

A childhood tumour, retinoblastoma, often has a strong inherited basis

Perhaps the most dramatic example of the transformation of a normal cell into a cancer cell which involves cheating (in the sense we have just defined) is that of a tumour, called *retinoblastoma*, which unfortunately affects the back of the eyes of very young children. It had been suspected for a long time that this tumour had an inherited basis; but it was H. Knudsen in the early seventies who carried out a thorough analysis of many cases and came up with a specific hypothesis. Knudsen pointed out that children who had retinoblastoma, and in whom there was also a family history of retinoblastoma, almost invariably developed the tumour in both eyes (and sometimes more than one tumour in each). By contrast, children who had retinoblastoma but no family history of it almost invariably had a single tumour, and in one eye only. (We generally refer to the former group as having *familial* retinoblastoma, and to the latter as having *sporadic* retinoblastoma). Knudsen suggested an explanation, which will probably seem by now obvious to the reader, although at the time it was published, in 1975, it was rightly hailed as a very imaginative new departure. In essence, Knudsen thought that, if we indicate by *Rb* the normal form of the gene that is mutated in retinoblastoma, and by *rb* the mutated form found in retinoblastoma, a cell must have both genes of the *Rb* pair

mutated to *rb* before it becomes a tumour cell. On this assumption, it seemed likely that sporadic retinoblastoma, like any other tumour, arises through two successive independent mutations, each one of which happens to hit one of the two *Rb* genes in succession. The tumour is solitary because the probability of these two independent genetic events is very low.[7] In contrast, in familial retinoblastoma the child has unfortunately inherited a mutant *rb* gene, which will therefore be present in every cell of his or her body. In this case, all it takes is one hit, *ie,* the mutation of the other *Rb* gene, for a retinal cell to become a tumour cell: it is not surprising that this may happen more than once, and therefore multiple tumours are seen.

Just as in the case of retinoblastoma, a number of other genes increase the risk of specific types of cancer

Taking a family history is a must in good medical practice, whatever the patient's complaint may be. But in the case of cancer, people often do not even wait to be asked before they express their own concern that 'it runs in the family'. Needless to say, this feeling can generate a high degree of anxiety, and therefore it is important to state right away that in many cases this anxiety may not be justified. Indeed, cancer is a relatively common disease: therefore, the fact that it has already occurred, say, in an uncle and in a second cousin could be due merely to chance. Another common problem relates to the nature of the information that is available, which is often hearsay: my aunt may have told me that her father died of renal cancer, but it is not

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[7] This notion became known in jargon as the *two-hit hypothesis* on the origin of this type of tumour, and it was very influential in the thinking on the origin of cancer in general. Indeed, there are many other cases where both genes of a pair are mutated in cancer. We can now regard the two-hit hypothesis as subsumed in the more general multi-step model of the origin of cancer.

certain that the diagnosis was correct. It is also important to know not only the site of the cancer, but also its exact type.

Once the information has been compiled as best as possible, the next thing to do is to draw a proper family tree, or pedigree. Even when a reliable pedigree is available, it is never easy to determine whether or not there is a genetic link among several cases of cancer in a family: in first approximation, we must estimate probabilities rather than aiming for an immediate certainty. For this purpose, there are set criteria, some of which are fairly obvious. The first point is how many cases of cancer have occurred in the family; the second point is how many members of the family had the same type of cancer. A third point that turns out to be quite important, is the age of onset: a cancer in a young person, say below the age of 40, is more likely to have a strong inherited basis than a cancer that arises at the age of 80.

We have already considered how an inherited mutant gene can increase the risk of cancer: either by running faster – we could call such a gene an *accelerator* of the cancer pathway; or by cheating – we could call such a gene a *skipper* of one of the steps leading to cancer. These two different mechanisms may produce different clinical situations. In the case of an accelerator gene there may be no warning before the cancer develops; in the case of the skipper gene, because the inherited gene has already poised the organism since birth one step closer to cancer, there may be detectable indications that this is so. The two situations are best illustrated by familial breast cancer and by familial colon cancer respectively.

Breast cancer may run in families

The bond between a woman and her daughter is strong in more ways than one; and the breast that nourished that daughter is certainly part of that bond. Perhaps for this reason the inheritance

of breast cancer, whether true or perceived, is especially distressing. In fact, families with 'clustering' of breast cancer have been observed for a long time; but it was only in 1994 that intensive studies of these families, aided by advances in the human genome map, led to the identification of two specific genes, which were called breast cancer 1 and 2 or *BRCA1* and *BRCA2*. It should be clear that these are normal genes present in all people; but many inherited mutations in either of them put them at a higher risk of developing breast cancer. The mechanism and modalities are still under investigation, but here are some key points.

a. Breast cancer is eminently a disease of women: but the mutant gene is transmitted to and by males as well. It is the *consequences* of the mutations that are mostly manifested in women; although, rarely, a *BRCA1* mutation can give rise to breast cancer in a male as well.

b. As repeatedly emphasized, one never inherits cancer, but the risk of cancer. In the case of *BRCA1* and *BRCA2* mutations, the risk is estimated to be between 50-90%. Unfortunately women with any of these mutations are also predisposed to, or have a higher risk of ovarian cancer.

c. In first approximation, breast cancer in women who have *BRCA1* or *BRCA2* mutations is no different from breast cancer as it occurs in other women: except for the fact that, *on the average*, the age at which they develop cancer is younger. What is especially noteworthy is that, before they develop breast cancer, there is no hint of any abnormality in these women. Indeed, sometimes a woman with one of these inherited mutations may sail through life without ever developing cancer: unless one did a genetic test, one would never know she had the mutation.

What do these features tell us about the mechanism whereby a mutant *BRCA1* or *BRCA2* gene predisposes one to cancer? The absence of pre-cancerous manifestations suggests that we are dealing with an accelerator gene. There is nothing wrong yet with the cells of the mammary gland or of the ovary in women who are born with a *BRCA1* or *BRCA2* mutation. Recent studies have shown instead that both of these genes are involved, directly or indirectly, with DNA repair. What is more, these women have inherited one mutant gene, but the other gene of the pair is still intact: therefore, the DNA repair is not seriously compromised. However, just like in the case of retinoblastoma, sooner or later the other gene of the pair may undergo a mutation (this time a somatic mutation). From this time on, DNA repair is compromised, and the probability of additional mutations increases sharply; the pathway to cancer is now potentially accelerated. This model explains all the features we have listed, including the early onset of cancer, and the possibility that cancer may never develop, because the occurrence of the somatic mutations required to complete the pathway has an element of chance in it. This, we will see, is a recurrent theme in the development of cancer.

Colon cancer may also run in families

In familial adenomatous polyposis (FAP) the lining of the large intestine (called the mucous membrane or *mucosa*) is abnormal: on top of its normally smooth surface one sees formations that have the shape of very tiny fingers: these are called *polyps*. In each one of the patients who are affected by FAP shown in the pedigree there may be dozens, or sometimes hundreds or even thousands of polyps. The pattern of inheritance of the polyps is characteristic: about one-half of sibs are affected in each generation. The pattern of inheritance is called dominant: indeed,

FAP is number 175100 (starting with the digit 1) in McKusick's catalogue.

Polyps are not cancer. In this family, once again, there is no inheritance of cancer. Unfortunately, however, within each polyp there is a chance that a somatic mutation will occur, that will make it grow further. This may be followed by further mutation(s), until a polyp has become a small cancer. We do not yet know exactly why a polyp is more prone to become cancer than the normal mucosa; and for each polyp the probability of this happening is still low. However, the number of polyps is so great in FAP, that this small probability, multiplied by the large number of polyps, gives a product of 1 or more, which becomes almost a certainty. Perhaps the only reason why cancer develops in patients with FAP is that the number of cells in the upper layer of the mucosa, called the *epithelium*, is so much greater than in the normal gut.

Just like for breast cancer in women who have a *BRCA1* or *BRCA2* mutation, the colon cancer that develops in patients with FAP is not much different from the 'sporadic' colon cancer that may develop in any other person who does not have FAP. In fact, there is more to the similarity. It turns out that in the latter case the development of cancer is regularly preceded by the growth of a polyp: in other words, a polyp is the regular precursor of colon cancer. Thus, we can look at the patient with FAP as one who, because of the mutations he or she has inherited, has already prepared the ground for cancer.

In terms of what we said in a previous section, here we have a prime example of the skipper gene. In a patient with FAP the first step in cancer formation is skipped, because that step has already been accomplished in the inherited genome of the person. From this point of view we must admit that having been born with a mutated FAP gene is really bad luck. As doctors committed to

curb human scourges, we have a double obligation to patients who have this burden. In fact, certain steps can be taken to prevent cancer in these patients, albeit at a considerable cost, since extensive surgery may be involved.

In some families we can obtain direct proof, by a genetic test, that a mutant gene associated with cancer is present

Until now we have considered the general evidence indicating that at least in some families there is an inherited basis for increased susceptibility to cancer, or in brief an increased risk of cancer. Clearly, from the practical point of view, it is of interest to ask whether there is anything we can do about it.

Since, in some cases, we know the culprit genes, we can determine whether a person harbours one of the mutations that are associated with increased risk: this is referred to as a *genetic test*. For instance, if two sisters both had breast cancer at an early age, we could obtain a sequence of their *BRCA1* and *BRCA2* genes, and we might find one and the same mutation in one of these genes or in both. On the basis of this finding, we would recommend a higher than standard surveillance of these two women with the aim to detect, as early as possible, either a recurrence of breast cancer or the occurrence of ovarian cancer; but one could argue this is hardly the result of genetic testing, since from the clinical data, these women were already considered to be at increased risk. However, the implications are quite novel with respect to any other sisters in that sibship (and possibly with respect to other members of the family). First of all, if any unaffected sisters elect to undergo genetic testing, this will be much easier (and cheaper), because now we know exactly what mutation we are looking for. Secondly, once the results are known, we will have an objective basis on which to recommend a standard surveillance or an increased level of surveillance.

Genetic testing has been criticized because it can cause anxiety

It is clear from the example just given that conceptually, genetic testing is straightforward, however, we must confront two sorts of problems. First, from the purely technical point of view, we have already learnt that several genes are involved, and more will be mentioned later. Thus, to rule out any mutation in any of them is not a trivial task. Conversely, even in one of the known genes we may find a previously unknown mutation, and we may not be sure if it does indeed increase the risk of cancer. Second, there are human and psychological problems. Awareness of an increased risk of cancer is a great burden, which will not be handled by every person in the same way. It is, therefore, imperative that any genetic test be carried out only after one or more counselling sessions with someone who has the appropriate training and experience.

The Role of the Environment

In the city of London that Charles Dickens vividly depicted for us in his novels, the chimney-sweeper was a familiar sight. Even at a time when the average lifespan was much shorter than it is now, it must have been shocking to observe that a boy who started as an apprentice in that profession at 12, might be dead before 30. Carcinoma of the bladder became known as 'the chimney-sweeper's cancer'. We now know that the smoke and the soot in the chimneys have a high concentration of chemicals called aromatic hydrocarbons, particularly antracene and phenantrene. The chimney-sweepers were victims of the continued exposure to these compounds by direct contact and by inhalation.

What proportion of cancer can be attributed to the environment?

In spite of the vast literature on the subject, this question is still difficult to answer. In the first place, we must try and separate impressions from facts. For instance, we have already seen that the general perception that cancer is on the increase in industrialized societies is largely a consequence of the fact that we live longer. Thus, it is important to consider how we can seek evidence that a certain environmental factor, say diet, lifestyle, occupation, can affect the risk of cancer.

In essence, there are two sorts of approaches. On the one hand, one has to analyze carefully and in quantitative terms the development of cancer in human populations; this is the task of *epidemiology*. The dream of a cancer epidemiologist is that every case of cancer ought to be recorded, and that for every case we ought to have information on age, occupation, and all sorts of other circumstances. This is best done by setting up an *ad hoc* database called a *cancer registry*. There are many cancer registries in the more developed countries, and fewer in other countries. However, even in Europe and in North America, cancer registries cover only a fraction of the population. If we find that within a region covered by a cancer registry there is, for instance, a cluster of thyroid tumours near a nuclear plant, one may suspect that there has been inadequate protection from radiation, and that radiation has contributed to producing this type of cancer. Long before cancer registries were set up, it was noticed that radiologists had a higher risk of cancer. Fortunately, this is no longer the case because appropriate protective measures have been put in place.

On the other hand, apart from observing empirical facts, one can carry out experiments with experimental animals. If we suspect, for instance, that tar causes cancer, we can apply tar to the skin of rats, and find out if indeed they develop skin cancer.

Of course there is always a question as to how far we can apply data obtained from rats to humans. However, when we already have epidemiological evidence from human studies, and then we obtain experimental evidence in animals, we can regard the two lines of evidence as corroborating each other.

Cigarette smoke causes cancer

As implied above, one aim of epidemiology is to correlate diseases to lifestyle. As a doctor, I always feel a bit embarrassed about asking a patient how many cigarettes he or she smokes, because I might give the impression that I am setting myself up as a judge of moral character. In actual fact, I am only trying to establish how much exposure the patient has had to a noxious agent that may cause cancer. To buttress that intent, I also ask how much exposure they might have had to the smoke of others (*passive smoke*).

It must be stated here that one of the most impressive results of epidemiological research has been the body of evidence that has linked cigarette smoking with lung cancer; and head and neck cancer; and to a much lesser degree with other types of cancer. It seems pertinent to list some of the features of this link between smoking and cancer.

1. The association is roughly dose-related: the more the cigarettes, the greater the risk.
2. The association is never complete: some people who have smoked heavily for a long time have not developed cancer.
3. Quitting smoking helps, because the risk of cancer will cease growing; but unfortunately quitting does not reverse the risk previously accumulated.

4. It is possible that different types of cigarettes are less harmful than others, but these differences are probably marginal. By contrast, smoking cigars or a pipe is generally less harmful.

5. It has been abundantly proven that being exposed to passive smoke can also contribute to causing cancer.

6. There is little doubt that smoking habits have accounted for a higher frequency of lung and head and neck cancer among men; unfortunately these types of cancer have increased in women, as they now smoke as much as the men.

Smoking cigarettes has many adverse consequences other than cancer, particularly with respect to the respiratory system and the cardiovascular system. A discussion of these problems falls outside our current remit. It should be mentioned, however, that whereas with regard to cancer there is always an element of chance (ie, as stated above, not all heavy smokers develop cancer), all long-term smokers get chronic bronchitis and some degree of lung damage called emphysema. It is difficult for most people to quit smoking, and unfortunately it appears that for many young people it is difficult to resist taking up smoking; but if we respect our body we should take a firm stand on this matter.

The risk of cancer is increased by occupational exposure to a variety of chemical agents

We have already mentioned bladder cancer in the chimney-sweepers; unfortunately this is but one example. A very well-known cause of cancer is exposure to asbestos (which also causes asbestosis, a peculiar reaction of the lung tissue to the tiny fibres of asbestos). An interesting point about asbestos is that it causes specifically a tumour arising from the lining of the lung called the pleura; the name of this tumour is *mesothelioma*. In terms of

human cost, this tumour is rather dreadful, because it is exceedingly difficult to treat and it tends to progress rapidly from the time of diagnosis. In terms of epidemiology, mesothelioma is an important paradigm because, in the absence of asbestos it is extremely rare: therefore, its geographic distribution is almost a sentinel of exposure to asbestos. In Italy, for instance, Genova and Taranto, two harbour cities which are also industrial cities, have a sad placement at the head of the league table of the frequency of mesothelioma. A saving grace is that the lag between exposure and onset of cancer is measured in decades rather than years: thus, the current incidence[8] of mesothelioma reflects exposure to asbestos some 30 years ago. Protective measures have been put in place, so we can hope that the incidence in Genova and Taranto will be much less 30 years from now.

Another example of an industrial culprit of cancer is vinyl chloride (VC), a chemical used in the manufacture of plastic substances, causing a tumour of the liver called *angiosarcoma*. Once again, this tumour is very rare in the absence of this kind of exposure.

Nuclear accidents can cause cancer

We know very well that exogenous agents can increase the mutation rate, for this reason they are called mutagens. Both physical agents (ie, many types of radiation) and chemical agents (a great variety of them) can be mutagenic. It became apparent in

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[8] In epidemiological jargon there are two distinct important measures of the frequency of a disease. *Prevalence* means how many cases of a disease are present, overall, in a certain population: for instance, 1%, or 80 per million. *Incidence* means instead how many *new* cases are diagnosed each year in that population: for instance, 10 per year, or 100 per year in a population of 1.7 million.

the early 20th century, through numerous observations and work on experimental animals, that mutagenic agents could also be carcinogenic. However, the experiment that proved this point with the most devastating power of persuasion was carried out on humans; it was the explosion of nuclear weapons in Hiroshima and Nagasaki in 1946. Apart from all the immediate effects of the bombs, the fallout from the radiation produced, in the population who survived, a tenfold increase in the rate of cancer that lasted for some twenty years.

Unfortunately, even peaceful uses of nuclear energy entail the risk of cancer when accidents happen, as we know from the Chernobyl disaster in Russia in 1989.

Infectious agents can contribute heavily to cancer

The notion that infection can cause cancer is not new, but for a long time this has been couched in rather vague terms. Today, we have very convincing evidence that the notion is correct, and that several different mechanisms are involved. Here we quote several examples, particularly pertinent to Africa.

HIV/AIDS. Currently the most infamous case is the HIV-AIDS epidemic. Although, due to the complexity of this disease, cancer is probably not the main cause of death in AIDS, but it contributes very substantially to its clinical manifestations. The two main types of tumours in AIDS are Epstein-Barr-virus (EBV)-related lymphoma, and Kaposi's sarcoma. The mechanism is indirect; because of the immune deficiency that defines AIDS, the body is unable to respond adequately to attack by opportunistic viruses superimposed on the HIV infection. The EB virus then causes lymphoid cells to proliferate. As we have seen, at each cell division there is a chance of error, and lymphoid cells are particularly error-prone. The mechanism that produces Kaposi's

sarcoma is less clear, but it is probably linked to another virus called HHV8.

Human papilloma virus. The human papilloma virus (HPV) is sexually transmitted. The virus infects the squamous epithelial cells of the lining of the ano-genital mucosa, and it modifies the cell cycle, thus favouring the transformation of the normal epithelial cells into cancer cells. Unfortunately, cancer of the cervix is rampant in many developing countries; its prevention is the same as for other sexually transmitted diseases, including better hygiene.

Hepatitis. There are many causes of hepatitis, including viral infection. Two viruses, called in shorthand Hep B and Hep C, are particularly common causes, and both cause the destruction of liver cells. The liver makes a brave effort of regenerating dead cells; once again, the extra numbers of cell divisions associated with this process entail the risk of malignant transformation. In the case of the Hep B virus, the process is aided by a direct action of the viral genome on the host cell. Another environmental factor that increases the risk of liver cancer is the fungal product aflatoxin, which is a contaminant of foodstuffs in Nigeria and elsewhere.

EB virus. The EB virus has already been mentioned as a major agent in the causation of the Burkitt lymphoma.

Helicobacter pilori. Research on the causes of cancer has been so active over the past century that one might have expected that all major issues had been covered. Therefore, it has come as quite a surprise that in the last decade there could be an entirely new departure in this area. The discovery of the role of *Helicobacter pilori* has changed radically our understanding of cancer of the stomach. It is now quite clear that this micro-organism is a major factor in causing peptic ulcer; and it is already known that peptic

ulcer, if not treated effectively, is frequently a precursor of gastric cancer. Therefore, this devious organism, *H. pilori* can be said to cause cancer of the stomach. Radical treatment of *H. pilori* infection turns out to be the most effective preventive measure for cancer of the stomach.

Concluding Remarks

As I said at the beginning, the topic of my presentation is complex, and I do not presume that in this brief survey I could do justice to its complexity. It is evident that, rather than giving details, I have tried to concentrate on certain core issues, for which I have selected examples. I hope that from this complexity a pattern has emerged. Cancer is a genetic disease of the somatic cells, because it can only arise as a result of a sequence of mutations, most of which are somatic. Some of the mutations which act as a precursor to cancer may be inherited, or the tendency to accumulate somatic mutations may be inherited. The environment, in a remarkably variegated multitude of ways, can favour the accumulation of somatic mutations.

I have focused on how we have progressed on the pathway towards understanding cancer, however, we must never lose sight of the fact that we have a profound obligation to those who suffer from cancer or who may be at risk of developing cancer. In this respect, there are a number of recommendations:

1. For the majority of solid tumours, appropriate surgery is still the mainstay of treatment; but radiotherapy and chemotherapy can be curative for some types of cancer, and both have an important adjuvant role in a large number of cases. The conventional concept of these forms of treatment has been essentially to attack, in a variety of ways, the process of cell growth. Inevitably, the effectiveness of this treatment has

been associated with considerable, and sometimes life-threatening toxicity, because normal cells are also hit hard in their own vital processes. The gradual identification of the mutations that cause cancer can provide a new paradigm in developing anti-cancer drugs. Indeed, the most logical approach is to target those very molecules that are cancer-specific because they are produced by the mutant genes present in cancer cells. The tyrosine kinase inhibitor called *Imatinib*, introduced about two years ago for the treatment of a relatively rare condition called chronic myeloid leukaemia, has been rightly hailed as signalling the dawn of a new era of more intelligent drugs for treating neoplastic disorders.

2. 'Prevention is better than cure' is an old slogan that is still valid today. It has emerged from our analysis that, because of the inevitability of somatic mutations, cancer is not totally preventable: I have the audacity to say that probably it may never be totally preventable, even in the future. We can, however, take measures to prevent the most dire consequences of cancer with respect to both heredity and the environment. In the case of families with a high risk of cancer due to an identifiable mutation, it is now possible to provide genetic testing. This does not in itself prevent cancer, but the finding of a high risk for a particular type of cancer makes it possible to institute surveillance measures that, by enabling us to diagnose cancer at a much earlier stage, may increase the chances of achieving a cure. In some cases, specific (surgical) preventive measures can be taken.

3. It is in the area of environmental agents that increase the risk of cancer – whether by increasing the mutation rate or otherwise – that we have a major scope for prevention. Cigarette smoke and smoking can be avoided; radiation and mutagenic chemicals must be kept at bay; the transmission of

known oncogenic infectious agents can be prevented. All these environmental hazards that increase the risk of specific types of cancer are potentially preventable. Creating awareness about these hazards is a major challenge for public health agencies which cannot be met without important choices being made by communities and by governments.

* * *

I wish to end this presentation by recalling a statement issued, I believe in 1994, to an international body, by Professor B.O. Osuntokun. He said:

> In my part of the world the available expertise concerning the use of gene therapy is currently extremely limited, but if this were not so, there are several fields/areas where therapeutic genetics would be desirable. These would include development of vaccines against malaria and other parasitic diseases, several of which are endemic and to which millions of people are at risk, human immunodeficiency virus infection, very common single gene disorders such as sickle cell anaemia, thalassaemia, and cancer.

Kayode then continued:

> I believe that somatic cell gene therapy does not raise any new ethical issue. It is of course important to ensure that research protocols are carefully evaluated and that such therapy is carried out in centres with adequate facilities both for therapeutic applications and for monitoring of serious adverse effects such as those recently suggested

> in the use of retroviruses, which may cause insertional mutagenesis such as activation of cellular oncogenes.
>
> . . . With regard to the manipulation of animals and plants, there would be no opposition on ethical grounds to the use of genetic research to alter vegetable material or animals for the purpose of contributing to human therapeutic agents and for stable improvement of the nutritional sources of humans, once adequate precautions are taken about safety, etc.

I present these statements because they illustrate that remarkable combination of clairvoyance, insight into innovative approaches to therapy, and commitment to high moral standards for which Kayode has set an example; in a way, a benchmark for us all. Indeed, I think there is an important message in these words. On the one hand, we must try and harness all possible resources for the prevention and the relief of human suffering. There is no contradiction between exploiting old ways and exploring new ones: from traditional African medicine to the use of contemporary molecular diagnostic methods, to hi-tech therapy. On the other hand, the foundation of medicine is in scientific research. We all know that both in medicine and in basic science, the economic situation makes the necessary endeavours exceedingly difficult; yet, there is no life for medicine if we cut it off from research, because research is its lifeline. I believe that to pursue research the hard way, and at the same time with joy, will be bearing good testimony to the memory of our beloved friend and kin, Benjamin Oluwakayode Osuntokun.

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Figure 1. Rudolf Virchow (b. Schivelbein 1821, d. Berlin, 1902)

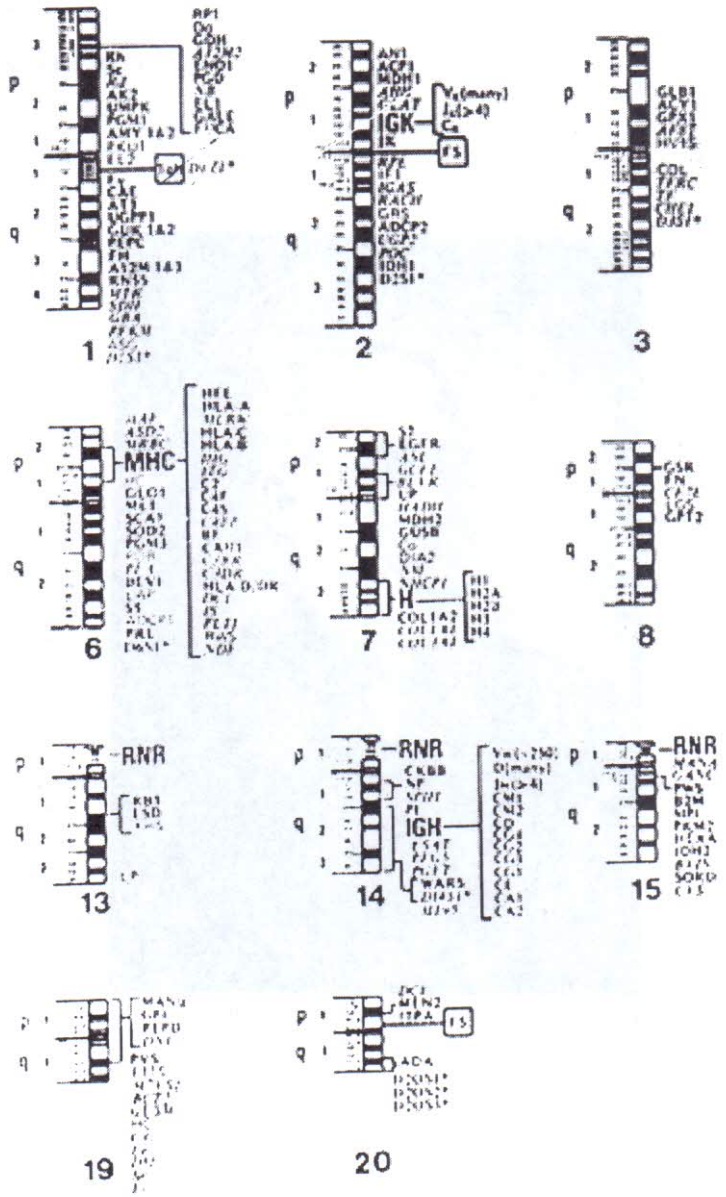

Figure 2a. The Human Genome

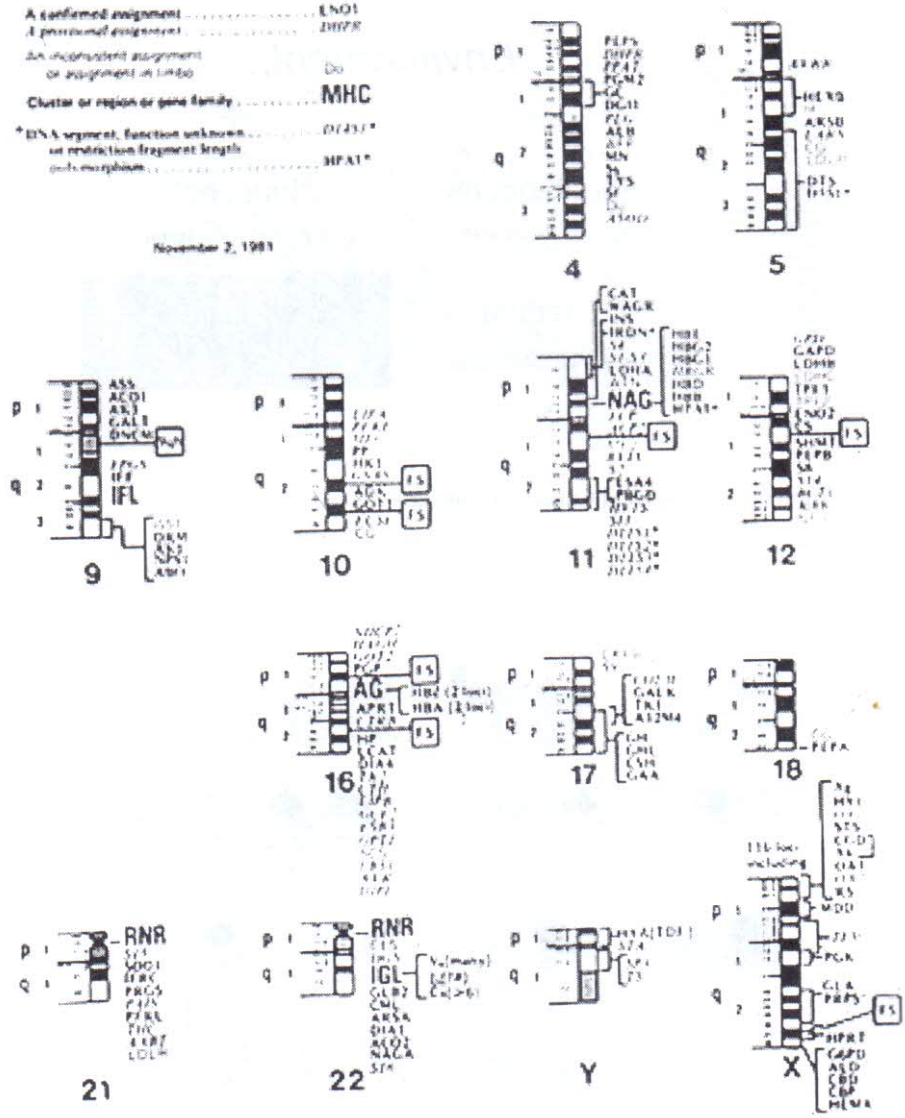

Figure 2b. The Humane Genome

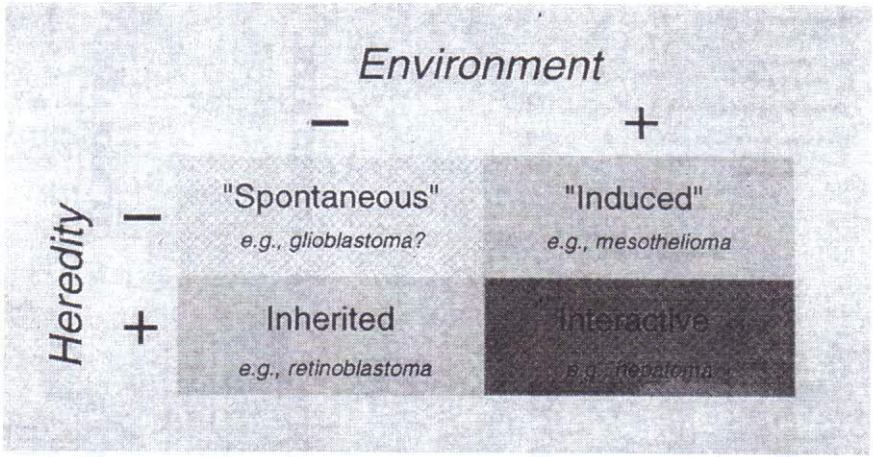

Figure 3a. Types and Causes of Cancer

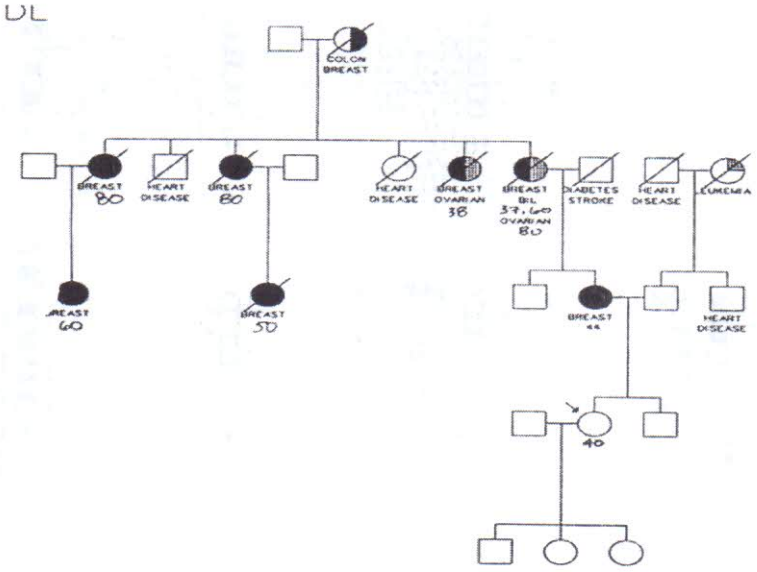

Figure 3b. Mendelian Causes of Cancer

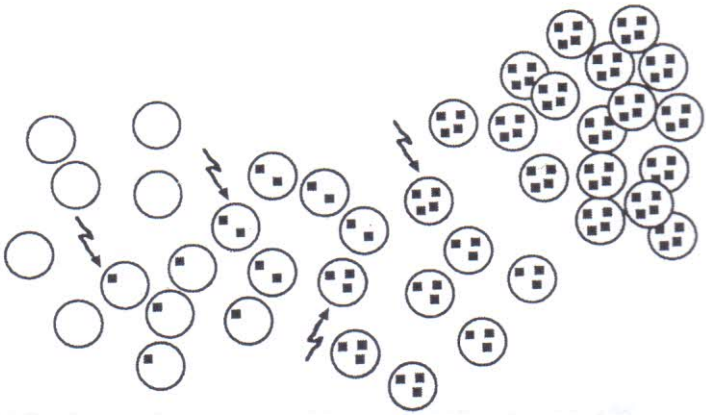

Figure 4. Successive Stages in Neoplastic Transformation

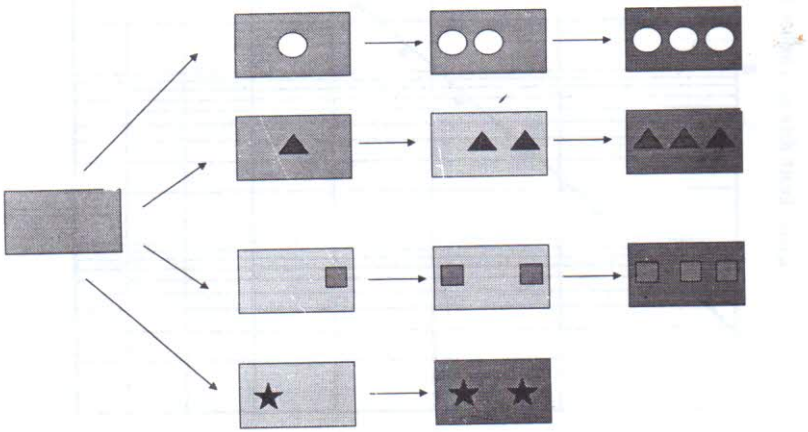

Figure 5. Several Paths to Cancer

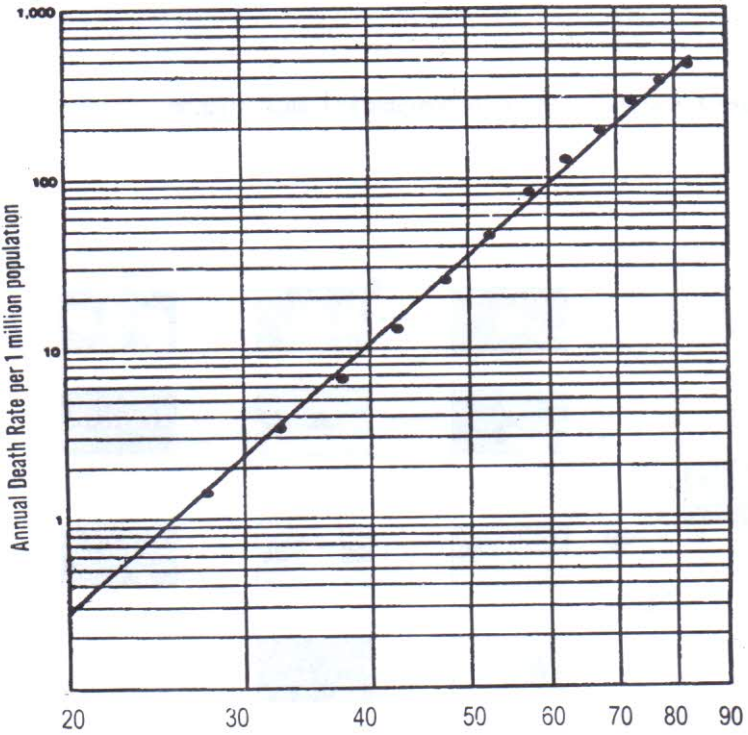

Figure 6. The Incidence of Cancer Depends Strongly on Age

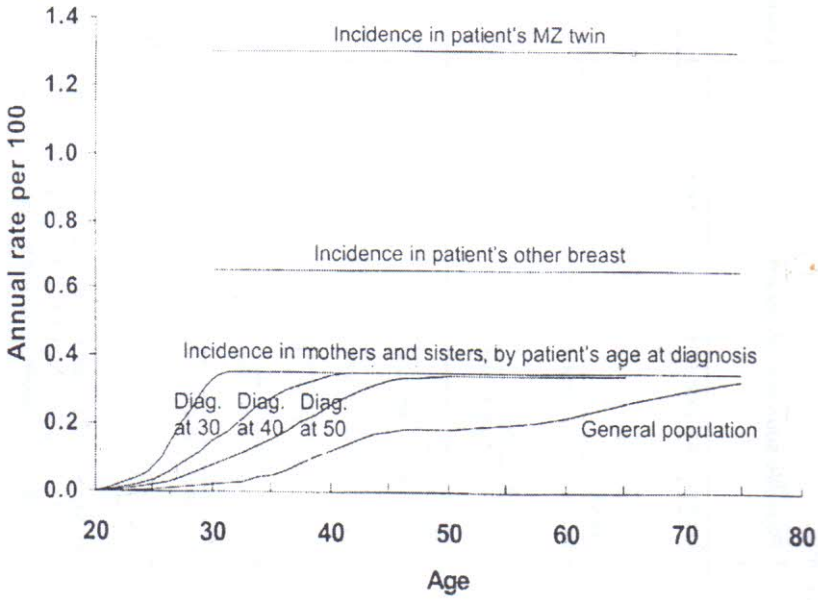

Figure 7. Subtle Genetic Factors in Breast Cancer

Table 1. Cancer Prevention

Agent with carcinogenic potential	*Possible source(s) of hazard*	*Level of risk of cancer*	*Means of prevention*
Ionizing radiation	Occupational exposure of X-ray workers	LOW	Optimize protection
Radiotherapy[1]	MEDIUM		
	Occupational exposure of workers in nuclear plants	LOW	Optimize protection
	Exposure of general population after accidents	LOW	Improve security against accidents
	Nuclear weapons	HIGH	Eliminate nuclear weapons
UV radiation	Over-exposure to sunlight	MEDIUM (melanoma)	Reduce exposure and/or use sunblock
Infectious agents	*Helicobacter pilori*	MEDIUM (stomach)	Appropriate antibiotic
	Hep B virus, Hep C virus	MEDIUM (liver)	Prevent transmission of virus
	Human papilloma virus (HPV): sexually transmitted	HIGH (uterine cervix)	Physical protection; improve hygiene
	Epstein-Barr virus (EBV)	LOW (lymphoma, nasopharynx)	?Delay contact with virus
Aromatic hydrocarbons	Occupational exposure to tar	LOW if protection adequate	Optimize plant construction and protection of workers
	Occupational exposure in chemical industry	LOW if adequately protected	Optimize plant construction and protection of workers
	Cigarettes	HIGH	Stop smoking

[1] It is paradoxical that one of the most powerful weapons we have at our disposal for the treatment of cancer can itself contribute to give rise to another cancer. Unfortunately at the moment this is a calculated risk we have to take any time we use radiation; and it is for this reason that one is constantly improving the techniques to deliver the lowest possible dose and to focus it optimally onto the tumor target.