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CANCER ASSOCIATION OF SOUTH AFRICA

STRIVING FOR A CANCER SMART SOUTH AFRICA

CANCER DETECTIVES

The very real prospect of eradicating liver cancer in southern Africa

CANCER ASSOCIATION OF SOUTH AFRICA

STRIVING FOR A CANCER SMART SOUTH AFRICA

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Special thanks to Professor Michael Kew for telling his story and sharing his records, research and graphics.

CANSA is proud to have been a funder of Professor Kew's Research for over 30 years.

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Fortunately, as a result of the intervention of the Bill and Melinda Gates' Global Action for Vaccination Initiative (GAVI), the World Health Organization and other non-governmental organizations, the vaccine coverage is set to increase in Africa and other resource-poor countries. These organizations are meeting the cost of immunization in countries with a defined low level of per capita income, provided that the government of the country agrees to take over the costs of the immunization programme after five years. This intervention has already led to a 35% increase in the rate of immunization in sub-Saharan Africa, and it is hoped that the percentage of children immunized will reach the levels achieved in the Asian-Pacific region in the near future.

In Taiwan different vaccine schedules are used, depending upon the status of the carrier mother. With e antigen-positive carrier mothers the first dose of the vaccine is given shortly after delivery and it is now accompanied by a dose of hyper-immune hepatitis B immunoglobulin (HBIG) to provide immediate passive immunization. The second and third doses are given at one and six months of age. With e antigen-negative carrier mothers and non-carrier mothers the first dose of the vaccine is given alone in the baby's first 24 hours and the second and third doses at one and six months of age.

In sub-Saharan Africa and other countries in which horizontal infection is the major form of infection, the first dose can be given later (usually at 6 weeks) and the second and third doses at 10 and 14 weeks (to fit in with the remainder of the infant immunization schedule).

Hepatitis C virus infection

There is, unfortunately, another hepatitis virus, the hepatitis C virus, also capable of causing hepatocellular cancer. Approximately 170 million people worldwide are chronically infected with this virus. It is far less common than the hepatitis B virus as a cause of hepatocellular cancer in sub-Saharan Africa and the Asian-Pacific region. The hepatitis C virus is the main cause of hepatocellular cancer in industrialized countries (which have a much lower incidence of hepatocellular cancer). It has not yet been possible to develop a vaccine against this virus, but when this is achieved it will be possible to prevent more than 80% of hepatocellular cancer in southern Africa and as much as 90% of this cancer worldwide.

Due to the foresight, diligence and brilliance of Dr Kew, with continued vaccination against hepatitis B in southern Africa, we can expect the eradication of hepatitis B virus-induced hepatocellular cancer over the next 30 years. This is a major triumph for research and advocacy in which CANSA played a major role.

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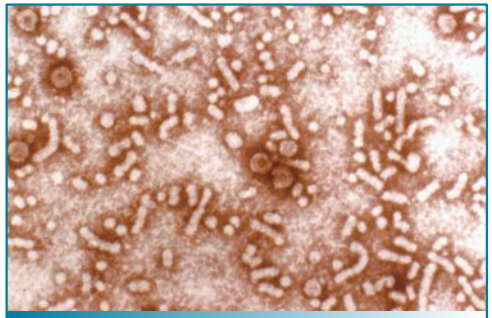
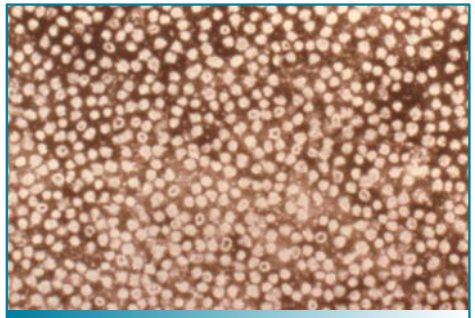


This slide shows the hepatitis B viral particles (large circular structures) together with small spherical and cigar-shaped particles



The vaccine consists of a pure preparation of the small spherical particles

Highly encouraging results

Because there is a long time interval between the original infection with the virus and the chronic carrier developing hepatocellular cancer, it will take many years before the rate of hepatitis B virus-induced cancers decreases in sub-Saharan countries. However, the extremely encouraging news is that in the Asian-Pacific countries where universal immunization was started in 1984, there has already been a 75% decrease in cases of hepatocellular cancer in children, adolescents, and young adults in the age groups that were vaccinated. These results give promise that in time it will be possible to prevent the great majority of the 560 000 new cases of hepatocellular cancer that occur worldwide each year.

One of a kind

The hepatitis B virus vaccine is the first and, at present, the only anti-cancer vaccine. Because the hepatitis B virus is the cause of as much as 70% of global hepatocellular cancers, this breakthrough is of great importance to global public health. Since 1991 the World Health Organization has recommended that the hepatitis B vaccine is part of the routine immunization services in all countries, and the vaccine is currently part of the Expanded Programme of Immunization in 151 countries.

The immunization programme

In Asian-Pacific countries, where universal immunization is already in place, between 80 and 90% of babies are currently receiving the vaccine. This is not the case in sub-Saharan Africa where until recently less than 10% of children were being vaccinated. This is because of financial constraints, competing health care priorities such as HIV/AIDS, tuberculosis, malaria, measles and childhood diarrhea. There are also physical difficulties in reaching remote regions in some countries, and in some countries, a lack of political will.

CANCER DETECTIVES Booklet 1

The very real prospect of eradicating liver cancer in southern Africa

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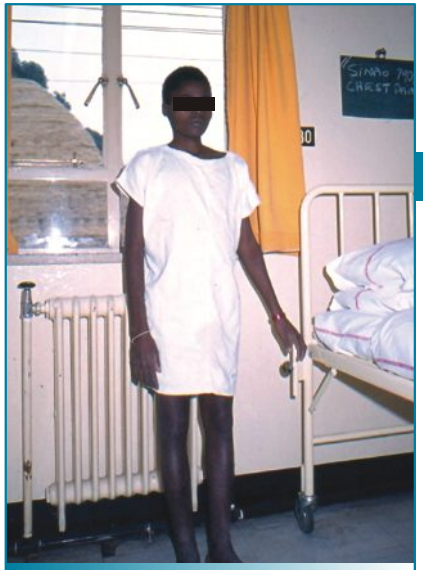
What intrigued Dr Kew

In the late 1960s and early 1970s, a young doctor, Michael Kew, working in Johannesburg's teaching hospitals, was struck by the large number of young black patients he saw with cancer of the liver and the very poor outlook for these patients. On average, the patients lived for only 11 weeks from the time they noticed that something was wrong and only six weeks from the time that liver cancer was diagnosed. By the time that he saw most of these patients, their cancer was already at an advanced stage, their liver was grossly swollen and the cancer had often spread to the lungs or elsewhere. The cancer was so advanced that curative surgery was rarely possible and cancer drugs and radiation therapy did not help.

There are two types of liver cancer: primary liver cancer which begins in the liver, and secondary liver cancer which arises elsewhere in the body and spreads to the liver as a late complication. The people Dr Kew was seeing were suffering from primary liver cancer. The tumour he was seeing originates in the most common of the liver cells, the hepatocytes, and is called hepatocellular cancer. It is the most common type of liver cancer.



An 18-year-old mineworker diagnosed with liver cancer at a hospital in Johannesburg

The start of a long journey

At that time data published by the International Agency for Research on Cancer, a branch of the World Health Organization, confirmed the high incidence of hepatocellular cancer among sub-Saharan black Africans and Chinese in the Asia-Pacific region.

The infection rate for black Africans ranged from 29 to 113 people out of every 100,000 of the population each year. In most of the rest of the world, the infection rate was less than three people of every 100,000 of the population each year and this figure was the same for the white population in sub-Saharan Africa.

These figures also showed that hepatocellular cancer was among the five most common cancers in the world and was the third most common cause of death from cancer. Clearly, hepatocellular cancer was one of the most devastating forms of cancer in the world.

Dr Kew noticed that most of his patients with hepatocellular cancer either lived in the country-side or were city dwellers who had been born and raised in the country-side. He was also struck by the young age of many of the patients. His patients were on average between 33 and 40 years of age, whereas in most other parts of the world hepatocellular cancer affected people ranging in age from the late fifties to early seventies. In addition, he noticed that men were approximately four times more likely to develop this cancer than women.

The hepatitis B virus vaccine was first made by harvesting the excess surface antigen particles from the serum of people chronically infected with the virus. Great care was taken to inactivate any viruses or other organisms that may have been present in the serum. More recently the vaccine has been synthesized in laboratories using molecular biological techniques.

Testing the vaccine

Working with Dr W Szmuness and Dr C Stevens from the New York Blood Transfusion Service, Professor W Prozesky of the National Institute for Virology (now the National Institute for Communicable Diseases) and Dr Kew ran trials to test the effectiveness of the vaccine in preventing infants and young children from becoming infected with the hepatitis B virus.

After being vaccinated, the serum of 97% of newborn black babies became positive for antibodies against hepatitis B surface antigen. This showed that these babies were immune to infection by this virus. This highly encouraging result held true even if the serum of the mothers of the babies had high levels of the protective antibody against the surface antigen because of being themselves previously infected with the virus and the antibody having crossed the placenta into the unborn baby's circulation. Trials in other countries confirmed these positive results.

Government reaction

The excitement in the medical world at having successfully developed a vaccine that could protect against a devastating cancer affecting large numbers of people was not shared by the then South African government. Successive ministers of health failed to respond positively to news of the vaccine against the hepatitis B virus and the need to introduce the vaccine into the Expanded Programme of Immunization in South Africa. In the meantime several Asian-Pacific countries had started universal programmes of immunization of newborn babies. With the first democratically elected South African government coming to power in 1994, there was a new mindset. Within a year, in 1995, the hepatitis B virus vaccine was included in the South African vaccine schedule.

Results achieved by the vaccine to date

The introduction of the vaccine has already had a profound effect on the health of millions of sub-Saharan children. The number of these children carrying the hepatitis B virus has already decreased by about 10-fold and is now less than 1%. These results parallel those in other countries where hepatitis B virus infection is endemic and the vaccine has been universally introduced. In Asian-Pacific countries where perinatal infection of the virus is the most common route of infection with the hepatitis B virus, the percentage of infected babies born to highly infectious mothers has decreased from 90% to 15%. The more recent addition of hyperimmune gamma-globulin (HBIG) vaccine, given shortly after birth, provides immediate passive immunity at the same time as the first dose of the hepatitis B vaccine. These two interventions working together should in future prevent all cases of perinatal infection.

The family of viruses to which the hepatitis B virus belongs infects humans, woodchucks, ground squirrels and ducks but only the first three get liver cancer

The search for a vaccine

With the major role of hepatitis B virus infection in causing hepatocellular cancer firmly established, there was an urgent need to develop a vaccine against the virus to prevent children from being infected. Luck was again with the researchers because at this time a vaccine against the virus was developed by scientists at Merck, Sharp & Dohme laboratories in the U.S.A.

Production of the vaccine

The vaccine produced was the first 'component' vaccine. A component vaccine is one in which immunization is achieved not by injecting the whole virus but, just one antigenic component of the virus. Because the whole virus is not injected there is no danger of the recipient being infected with hepatitis B virus.

For some unknown reason the surface antigen of the hepatitis B virus is produced in far greater quantity than is needed to coat the core of the virus. The excess surface antigen circulates in a patient's blood in a very large number of small spherical particles. Because these particles contain no viral DNA they are not infectious. But, the fact that they contain the surface antigen means that they can be used to immunize people against hepatitis B virus infection.

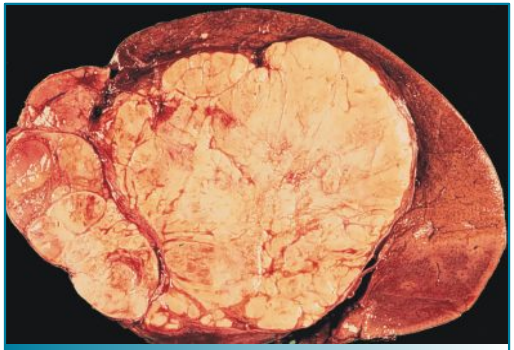
The way forward

Dr Kew and his colleagues were faced with a cancer for which there was virtually no hope of successful treatment. They had to find a way of preventing this cancer. To do this, they had to discover the cause or causes of hepatocellular cancer.

Unfortunately, at that time little was known about the causes of liver cancer either in sub-Saharan Africa or anywhere else. He knew that the most common of the few known causes of cancers were infectious agents and that this was particularly true in low-income countries. He reasoned that in resource poor sub-Saharan Africa, infectious agents needed to be investigated first as possible causes of the cancer, and viruses seemed to be the most likely suspects. Dr Kew began searching for a virus that might be causing hepatocellular cancer.

A possible suspect

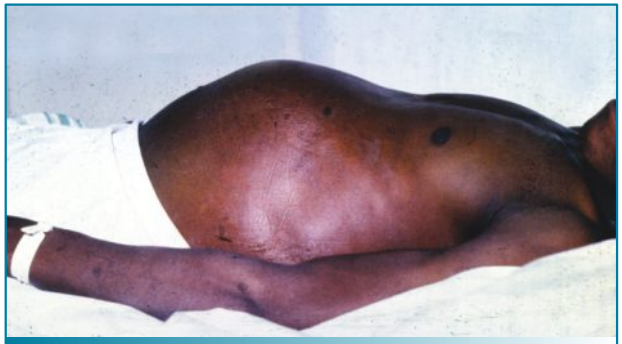
The hepatitis B virus was at that time known to cause acute inflammation of the liver (acute hepatitis). More importantly, the infection sometimes persisted and when it did, the resulting chronic inflammation (chronic hepatitis) often developed into cirrhosis. There was also evidence that the hepatitis B virus could survive in people for many years without causing any symptoms or any apparent disease. The key question was: could chronic hepatitis B virus infection also cause hepatocellular cancer?



Liver cancer in a patient. The tumour is the lighter colour while the liver is the darker strip at the top and right

As a first step in finding out if the hepatitis B virus might be a cause of liver cancer, Dr Kew needed to know how common the viral infection was in the general black population and, more importantly, in patients suffering from hepatocellular cancer.

Then Dr Kew got a lucky break. Laboratory tests became available for the first time that made it possible for the hepatitis B virus to be detected in the blood of people infected with the virus.



This photo shows a patient whose anterior abdominal wall is displaced by the underlying massively cancerous liver

Investigations begin

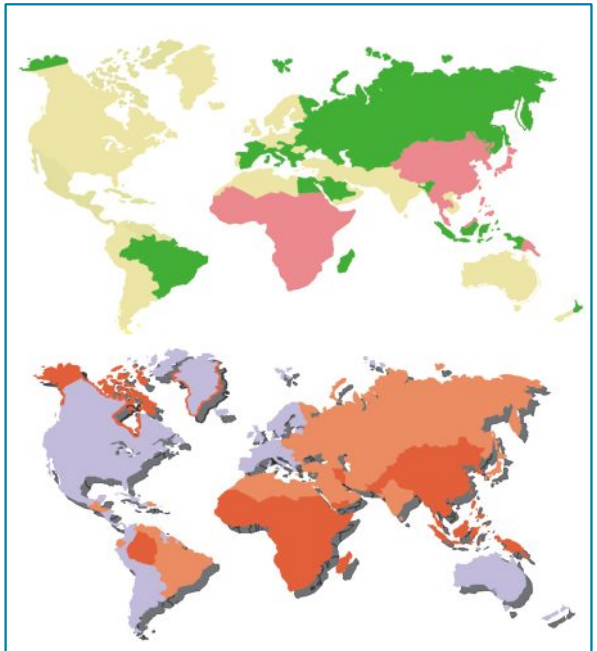
Dr Kew joined forces with Dr Bersohn and Dr Macnab of the South African Institute for Medical Research (now the National Health Laboratory Services) and they began to test the blood of large numbers of people throughout South and southern Africa for the presence of the hepatitis B virus.

The results were surprising and, from the point of view of being a possible cause of liver cancer, encouraging. The tests showed evidence of chronic infection with the hepatitis B virus in as many as 15% of the black adult population in South Africa and neighbouring countries. The highest rates of infection were among rural dwellers or newly urbanized rural dwellers, and approximately twice as many men as women were infected.

On the basis of these figures, the doctors estimated that between 3.5 and 4 million black adult South Africans (and many more people throughout sub-Saharan Africa) were chronically infected with the hepatitis B virus. They also found that along with the low incidence of hepatocellular cancer in white South Africans, chronic infection with the virus was rare (only 0.2%) in this population.

The presence of the virus was recognized by finding in people's blood, viral antigens and antibodies produced by their defence mechanisms in response to the antigens (an antigen is the part of the virus that the body reacts against in the person infected). A person's defence mechanism mounts an immune response to the antigen to prevent its harmful effects. Part of this response is the production of antibodies against the viral antigen. Both the antigen and the antibodies can be detected in serum by laboratory tests.

Although the early diagnostic tests were relatively insensitive, with time more sensitive tests were developed and these showed an even closer association than was originally thought, between the presence of the virus and the development of hepatocellular cancer.



Note the parallel geographical distribution of liver cancer above and the hepatitis B virus infection below

Dr Kew was able to show that as many patients with hepatocellular cancer did not have cirrhosis as those who did have cirrhosis. This showed that the virus could directly cause the cancer.

Other authorities argued that the virus could be merely a passenger in the liver cells and was not playing any role in the cancer-forming process. This idea was disproven when Dr Shafritz at the Albert Einstein College of Medicine in New York and Dr Kew first showed that hepatitis B virus DNA was integrated into the human DNA of almost all patients with hepatitis B virus related hepatocellular cancer.

Exactly when hepatitis B viral DNA integrates into human DNA is not known, but the available evidence suggests that it happens during the course of chronic rather than acute hepatitis B infection. Dr Kew and his colleagues have recently shown that this integration of hepatitis B virus DNA into cellular DNA may rarely occur in patients with acute hepatitis. However, this early integration is not necessarily followed by clonal expansion of liver cells and the other changes necessary for cancer growth.

Collecting further evidence

When extremely sensitive molecular methods for detecting hepatitis B virus DNA became available in recent years, Dr Kew and his colleagues showed that as many as two thirds of patients whose serum was negative for the virus with the original relatively insensitive tests did contain hepatitis B viruses, although in very low concentrations. Low levels of the virus could also be shown in the liver and cancer tissue of these patients. These low level viral infections were referred to as “silent” or “occult” hepatitis B virus infection. The association between chronic hepatitis B virus infection and the development of hepatocellular cancer was shown to be even stronger than had originally been thought. Almost all hepatocellular cancers in sub-Saharan Africa and also those in the Asian-Pacific region are caused by chronic infection with this hepatitis B virus.

Those most at risk

Most chronic carriers of the virus in the world live either in the Asian-Pacific region or in sub-Saharan Africa. A quarter or more of these people will develop hepatocellular cancer. Their risk of developing the cancer may be as high as 102 times that of people not infected with the virus (by comparison, the risk of a heavy cigarette smoker developing lung cancer is 20 times higher than people who don't smoke).

The hepatitis B virus causes as many as 70% of all hepatocellular cancers worldwide. This makes hepatitis B virus the single most important environmental risk factor for this cancer. The hepatitis B virus is now believed to be second only to tobacco as an environmental cancer-causing agent in humans.

Further evidence that the hepatitis B virus causes liver cancer is the fact that other members of this family of viruses infect certain mammals such as woodchucks and ground squirrels and they too get liver cancer. By contrast, Peking Ducks infected by this family of viruses do not get cancer of the liver.

The e antigen difference

In the Asian-Pacific region, the hepatitis B virus e antigen stays in the blood of people infected with hepatitis B virus for a much longer time than it does in people in sub-Saharan Africa. The reason for this difference is not known, although it might be related to differences in the subtypes of the virus in the two regions or to the difference in the main way that the infection is acquired in the two populations. It does, however, mean that many more women in the Asian-Pacific region who are infected with the virus when they become pregnant will be highly infectious and are very likely to infect their babies during the process of childbirth. In sub-Saharan Africa the e-antigen in women has almost always disappeared from their blood by the time they become pregnant and so they are much less likely to infect the baby perinatally. So, the same culprit, but with different patterns of infection.

Although far fewer African babies are born to e antigen mothers, these babies are at risk of becoming infected after six months of age when their immunity, acquired from their mothers, ceases to protect them from infection. The same is true of Chinese babies born to mothers who do not have the e antigen in their blood.

The likely suspect

Dr Kew and his colleagues began investigating how many people in the general black population were chronically infected with the hepatitis B virus. They tested serum from large numbers of patients with hepatocellular cancer for the presence of the virus. The majority of these patients were actively infected with the virus, but, patients suffering from a number of other forms of cancer were rarely, if ever, infected with the virus. This strongly supported other evidence that hepatitis B virus plays a causal role in hepatocellular cancer. Also, almost all of the patients not actively infected showed evidence of having been infected with the virus in the past.

In these patients, the virus could have started the cancer-forming process before it was eliminated by the person's immune response to the virus. Younger patients with hepatocellular cancer were even more likely to be infected with the hepatitis B virus than older patients (82% of patients under 30 years as compared with 30% of those older than 50 years). The children Dr Kew was seeing with hepatocellular cancer were, almost without exception, chronically infected with the hepatitis B virus.

Dr Kew and colleagues also studied liver and cancer tissue from patients with hepatocellular cancer for evidence of viral infection. These studies showed hepatitis B viral surface antigen in the cytoplasm (the material or protoplasm within a living cell, excluding the nucleus) and the viral core antigen in the nuclei of normal liver cells and in cancerous liver cells.

False trails

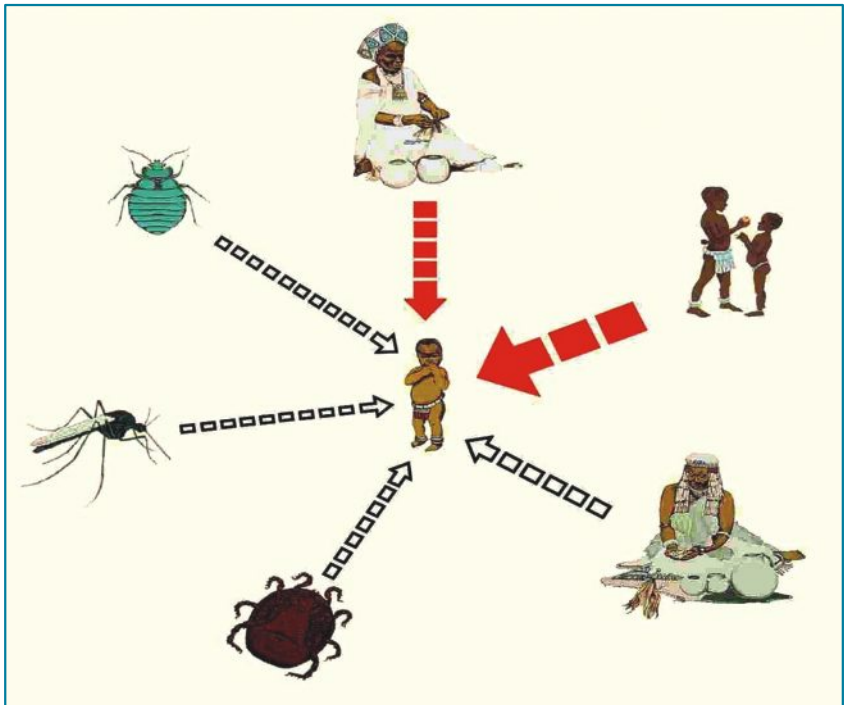
Many patients with hepatocellular cancer, particularly those in industrialized countries, also suffered from cirrhosis. This led some authorities to believe that the hepatitis B virus caused cirrhosis and that it was the cirrhosis rather than the virus itself that caused the cancer.

At the same time, scientists working in a number of other countries showed that chronic hepatitis B virus infection was also endemic in the Asian-Pacific region but was uncommon in most other parts of the world. There was a remarkable similarity between the geographical distribution of chronic hepatitis B virus infection and the occurrence of hepatocellular cancer. It was calculated that about 2 billion people worldwide were infected with the virus at some time in their lives. But more importantly, about 350 million people worldwide, that is 5% of the global population, were chronically infected with the virus. Now, Dr Kew and other scientists had a suspect. But there were more investigations to be done.

When were people infected?

To find out at what age people were infected with the hepatitis B virus, two large studies were undertaken in rural areas of southern Africa. These studies showed that the viral infection that resulted in many people becoming chronic carriers almost always occurred in infancy or early childhood.

Infection occurred in two ways. A relatively small percentage of babies who became chronic carriers were infected by the virus being transmitted from their chronically infected mother to her baby during childbirth. This form of transmission is called perinatal infection. Many more babies and young children were infected with the hepatitis B virus a little later in life.



Ways in which children in Africa are infected with the hepatitis B virus

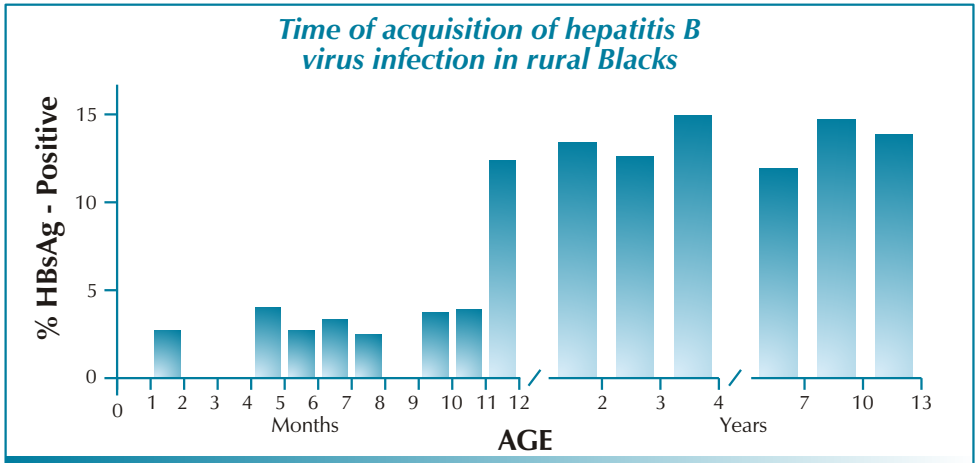
These children were most often infected by already infected family members. Particularly by young sisters and brothers under the age of five, who had themselves been recently infected and were highly infectious. Infected young playmates were also an important source of infection. Infection acquired from other people is referred to as 'horizontal infection'.

Many black women, particularly those living in rural areas, had already been infected by the virus, usually in early childhood, and had recovered completely long before they became pregnant. These mothers carried antibodies against the virus in their blood which protected them from being infected with the virus again.

When these women became pregnant these protective antibodies were passed via the placenta to the developing baby in the womb. At birth, these antibodies protected the baby from infection with the virus. However, these protective antibodies lasted only about six months in the baby's blood and then the baby became vulnerable to infection from other people. The usual incubation period of hepatitis B virus infection is approximately six months. This explains why there was a sharp rise in the infection rate starting at about 12 months of age. After one year of age, the number of infected babies increased progessively, reaching adult rates of chronic infection at about five years of age.

How were children getting infected horizontally?

The exact routes of horizontal hepatitis B infection are uncertain. It is important to remember that hepatitis B is an extremely infectious virus. It is 100 times more infectious than the HI Virus which causes AIDS. And, that very small amounts of blood or, to a lesser extent, other body secretions can transmit the virus from person to person. The virus could be transmitted to a baby or young child by simple daily accidents like already infected children having nose bleeds or cuts or weeping sores on their skin.



This graph shows that the majority of infections take place in the first few years of life. A small proportion of babies are infected in the first few months of life due to mother-to-child transmission. Most children get infected between age 1-5 by horizontal transmission of the virus from young siblings and playmates.

Some authorities thought that the virus could be transmitted by blood-sucking insects like mosquitoes, bed bugs and ticks, but this has been difficult to prove. One source of infection that Dr Kew and his colleagues identified was the use of unsterilized equipment by traditional healers performing minor surgery.

What they now knew was that the great majority of people chronically infected with the hepatitis B virus had been infected when they were babies or young children. They also knew that children infected at an early age very frequently became chronic carriers. It also became obvious that it was these early infected children who were at very high risk of developing hepatocellular cancer later in life. This contrasted with infection in older children, adolescents, and adults which rarely progressed to a chronic carrier state of the virus and so did not cause hepatocellular cancer.

A rural problem only?

A study was done to find out whether the rate of chronic infection differed between rural and urban dwellers. The results showed that only about 1% of children born in Soweto were chronic carriers of the hepatitis B virus. This rate of infection is considerably less than that in rural children. Also, only 7% of urban black children aged 13 had ever been infected with the hepatitis B virus compared with about 50% of rural children of the same age. Dr Kew showed that the dramatic decline in hepatitis B infection rates occurred in the first generation of black children born in an urban environment.

The Asian experience

At the same time as Dr Kew was trying to determine if chronic hepatitis B virus infection was a cause of hepatocellular cancer in sub-Saharan Africa, scientists in the Asia-Pacific region were pursuing a similar programme. These scientists were filled with a passion; to prevent this common and devastating cancer. They showed that the ways in which Chinese children in the Asian-Pacific region get infected differ from the ways in Africa. Most of the Chinese children were infected during childbirth by their mothers, who were themselves chronically infected with the virus, (perinatal transmission of the virus). Fewer Chinese children were infected later by horizontal transmission of the virus.

At first they were baffled, but then they discovered differences between the pregnant mothers in the two populations: the presence of another hepatitis B viral antigen, the e antigen, in their blood. The presence of the e antigen in the blood of a person infected with the hepatitis B virus is a sign that the virus is still actively dividing in that person, resulting in a great many viral particles in their blood stream and a high level of infectivity of the blood. The disappearance of the e antigen from the blood signaled much lower levels of infectivity of that patient's blood.