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1965 TO 2015: IARC, A UNIQUE INSTITUTION FOR A CHANGING WORLD

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Il faut faire le pari que les avancées du bien se cumulent mais que les interruptions du mal ne font pas système. – Paul Ricoeur

A CHANGING WORLD

The world into which IARC arrived in 1965 presented a set of circumstances that without doubt aided its development: a receptive social and political setting, a freshly optimistic view of the potential of medicine to effectively control disease, and the emerging idea that cancer, rather than being considered an almost inevitable companion of ageing, could also be controlled. A journey into the world of the 1960s highlights each of these three circumstances.

The world in the 1960s

In the 20th century, Europe had twice been the origin and the major battleground of wars, called "world wars" for the first time in history because they rapidly spread to involve countries and populations from other continents. Contacts and exchanges – peaceful or violent – between populations had been occurring on a global scale since the beginning of the 16th century, acquiring increasing intensity with the expansion of European colonies on other continents. To these centuries-long exchanges, the two world wars added a tragic unifying experience, which gave rise to a radically new situation at the end of the Second World War, in 1945. First, a perception emerged anew of how the lives of all people in the world had become interwoven. Second, the communality of experiences prompted a movement towards communality of human rights, leading to the end of the colonial era; the colonies, still numerous in the 1940s, progressively became new autonomous countries. Third, major reconstruction efforts began that involved sustained economic growth. In developed countries, the gross domestic product per capita increased by close to 5% per year.

This long aftermath of the Second World War lasted about three decades, until the mid-1970s, and is on record as a golden age of increasing opportunities and well-being for all people, whatever their initial socioeconomic level. Economic growth alone would not have produced this result if it had not been accompanied – and, in several aspects, guided – by a vision and a widespread spirit of solidarity that had been awakened by the harsh experiences and lessons of the war. This vision was a driving force within countries, and internationally it repeatedly succeeded in overcoming deep ideological and political differences. The United Nations was established immediately after the war, in 1945, and its specialized agency for health, the World Health Organization (WHO), followed in 1948.

Europe embarked on an innovative and close cooperation, with the primary aim of preventing the repetition of armed conflict. Beginning in 1951 with a treaty between six countries, this involved the transfer of powers to the supranational level, and through a step-by-step process led to today's European Union with 28 member states. This setting of economic growth and solidarity within a framework of state regulations not only favoured the expansion of scientific research but also stimulated its international development. In 1954, the European Organization for Nuclear Research (known as CERN) was established in Geneva. Today, it is the world's leading facility for experiments and research on subatomic particles. CERN's 12 founding states have been joined by nine more member states, plus several associate members as well as observer states including the USA and Japan. In 1964, the European Molecular Biology Organization (EMBO) was established as an organization of life scientists. Since 1969, EMBO's programme and activities have received support from the governments of European member states (at present, 27) via the European Molecular Biology Conference (EMBC). Related to these initiatives, the independent European Molecular Biology Laboratory (EMBL) was founded in 1974; it is today supported by 21 member states and operates at five sites, including the central laboratory in Heidelberg.

The World Health Organization (WHO) was established on 7 April 1948. Its headquarters were hosted in the Palace of Nations in Geneva until 1966, when the WHO building, designed by the Swiss architect Jean Tschumi, was inaugurated. In 2014, an international design competition was launched to develop a new building and extend the existing one.


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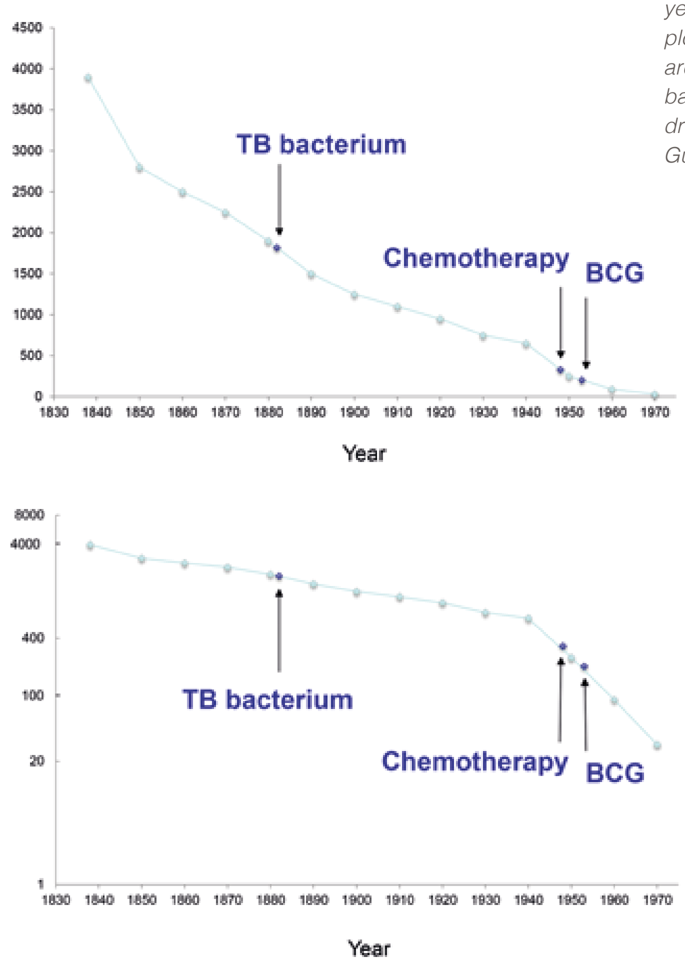
Health and medicine in the 1960s

Health conditions improved remarkably between the beginning of the 20th century and the 1960s. For instance, in 1910 average life expectancy at birth was still low, even in the most economically developed countries: only 47.3 years in the USA and 47.5 years in France. By 1965, these figures had become 70.3 and 71.0 years, respectively. This increase of more than 20 years is all the more remarkable because it occurred during a period that was marked by the massive loss of young lives during the two world wars. The improvement in health was due not only to better nutrition, hygienic measures, and work conditions but also to the fact that medicine "took off" and for the first time started to be regularly effective on a substantial scale.



Decline in rates of respiratory tuberculosis (measured as deaths per 1 million people per year) in England and Wales, with the same data plotted in two different ways. Key dates indicated are the discovery of the tuberculosis (TB) bacterium and the introduction of antituberculosis drugs (chemotherapy) and the bacille Calmette–Guérin (BCG) vaccine.

The two graphs show the decline of respiratory tuberculosis in England and Wales. In the first graph, the rate of decrease appears to be uniform over time, with no change after the causative agent, the tuberculosis bacterium, was discovered by Robert Koch in 1882, and no appreciable change with the introduction of antituberculosis drugs (chemotherapy) and the bacille Calmette–Guérin (BCG) vaccine in the 1940s and 1950s. These results, and similar ones for other infectious diseases and other countries, have been widely quoted as a clear indication that the major improvements in health since the beginning of the 19th century are due to favourable changes in the populations' environmental, hygienic, and nutritional conditions, with advances in medicine playing almost no role.

The second graph, however, tells a different story. The same data are now plotted with a proportional scale on the vertical axis, rather than an arithmetic scale as in the first graph. This representation provides a better insight into changes because in nature, quantities most often change by an amount that is proportional to the quantity present at each moment, rather than by a constant amount. It can be seen that although the discovery of the tuberculosis bacterium did not affect the decline in mortality, the introduction of chemotherapy produced a sharp change in the slope of the decline. Mortality decreased much more rapidly after 1945. This clearly shows that if before the Second World War improvements in health were probably due to better environmental, hygienic, and nutritional conditions, in more recent times advances in medicine have made major contributions.

Senior physicians who were practising in the 1960s and had graduated from medical school in about 1930 had lived through a radical change in medicine. In 1930, only a handful of effective and reasonably safe medications were available: essentially, several vaccines, aspirin, and digitalis. Surgeons could do much more, but with the exception of a few operations, such as those to treat fractures, the short- and long-term outcomes for patients remained variable. By the 1960s, a panoply of new classes of medications had been discovered and made available for clinical use. For example, sulfonamides, the first class of antibacterial drugs, were introduced in the mid-1930s; antibiotics followed, during the Second World War. Cortisone and related compounds were used from 1948 onwards, and safe and potent diuretics and psychotropic drugs since the early 1950s. Alongside therapeutic agents, diagnostic procedures had also undergone a marked expansion, notably based on the development of clinical biochemistry, histochemistry for the microscopic examination of tissue specimens, and physiological function tests suitable for clinical use. These advances fundamentally changed the general perception of what medicine could actually do. In particular, academic teachers shifted their perspective completely: from one in which making correct diagnoses represented the pinnacle of professional skill and achievement (with the disease being left largely to take its natural course) to one in which the cure or control of the disease became the measure of professional success.

Even more impressive and fundamental is the progress that occurred in the understanding of basic biological functions and structures. Artificially produced isotopes became available in the 1930s to label biological molecules and trace their behaviour within the body. The title of a 1942 book by Rudolf Schoenheimer,

In the entrance hall of IARC's tower building, DNA welcomes people. This sculptural representation of DNA by French artist Pierre Mathieu was a gift of the Mérieux Foundation and – as an inscription reads – "expresses the fundamental poetry embedded in the natural DNA structure".

The Dynamic State of Body Constituents, concisely expresses the concept, arising from investigations with tagged molecules, that living organisms are open systems, stable but in a constant state of renewal and exchanging components with the surrounding environment. Tracer molecules revolutionized the study of metabolism and other physiological functions, making it possible to examine both normal and pathological processes in undisturbed in vivo settings.

At the beginning of the 1950s, substantial knowledge had accrued on the chemical composition of nucleic acids, particularly DNA. Thanks to the fundamental discoveries of Oswald Avery, Colin MacLeod, and Maclyn

McCarty in bacteria, DNA was believed to contain the hereditary information unique to each living species and passed from parents to offspring. Consistent with this hypothesis, Erwin Chargaff and co-workers at Columbia University had found that DNAs from different living organisms differ in the proportion of their component molecules, the purine nitrogenous bases (adenine and guanine) and the pyrimidine bases (thymine and cytosine). More crucially, they had shown that independently of the species-specific composition, there was always a 1-to-1 quantitative ratio of adenine to thymine and of guanine to cytosine. Thus, a base-pairing regularity of one purine base to one pyrimidine base appeared to hold.

Also in the early 1950s, the physicist Rosalind Franklin at Cambridge University had submitted DNA molecules to X-ray examination to investigate their spatial configuration. From the X-ray images (diffraction patterns), she inferred that "the results suggest a helical structure (which must be very closely packed) containing probably 2, 3, or 4 coaxial nucleic acid chains per helical unit." By the spring of 1953, James D. Watson and Francis Crick understood that to satisfy the base-pairing regularity, a long helical structure should be composed not of a single strand but of two paired strands. They published an epoch-making two-page paper in *Nature* in which they proposed a DNA structure model rigorously coherent in its chemical and physical features: the soon-to-be-famous double helix, which has stood the test of time. Biology was transformed, particularly genetics. It was now possible to investigate how the hereditary information passed from parents to offspring was coded in the form of distinct units (the genes) in the well-identified DNA structure, the key component of chromosomes in humans. Deciphering the code and how it is translated into instructions that ultimately control human physiology expanded into a vast area of research during the 1960s.

In parallel, knowledge of the DNA structure opened new avenues to the understanding of how the environment may affect genes, producing not only transient, repairable damage but – more importantly – stable and heritable gene mutations. Experiments by Hermann Muller investigating heritable characteristics, such as eye colour, in fruit flies had already shown in the 1920s that X-rays can produce gene mutations. Subsequently, the mutagenic effects of several chemicals, such as mustard gas, had been demonstrated in the 1940s and 1950s, particularly through the work of Charlotte Auerbach, John Michael Robson, and Eric Boyland. Against this background and with the DNA structure now elucidated, by the late 1950s and early 1960s Philip Lawley was able to characterize the binding between specific DNA bases and the molecules of known carcinogens, such as polycyclic aromatic hydrocarbons, the ubiquitous products of incomplete combustion that are found, for instance, in tobacco smoke. Light started to be shed on the paths linking agents present in the environment to cancer: the binding of carcinogens to DNA bases produces mutated genes capable of inducing or permitting the unlimited cell proliferation that is characteristic of cancer.

Combined with the practical results of medicine, all these burgeoning advances in biology fuelled widespread optimism about what biomedical sciences could achieve.

CANCER IS HUNDREDS OF DIFFERENT DISEASES

The term "cancer" describes a diverse group of several hundred diseases, arising from different types of cells and in different organs of the body, in humans or animals. Each disease presents with its own clinical manifestations and evolves with its own course. However, all of them share a common and fundamental trait: the uncontrolled proliferation of some cancer-originating cells ("cancer stem cells"). If left untreated, this inordinate cell multiplication, combined with invasion of neighbouring or distant organs, leads to death after a highly variable period of time; some cancers grow rapidly, others slowly.

The endless proliferation of cells implies that some heritable command to replicate is transmitted from each generation to the next. In fact, it has long been recognized that heritable genetic alterations lie at the core of cancer development, and more recent studies have shown that a typical cancer contains several abnormally mutated "driver" genes that confer a selective growth advantage to the tumour cells. This may result from mechanisms controlled by the driver genes, such as inhibition of senescence, programmed cell death, or immune destruction that would normally prevent the cells from reproducing. It may also derive from genomic instability, favouring the emergence of cells capable of successfully surviving and replicating in different compartments (microenvironments) of the body. This is what makes a cancer a killer: the great majority of patients dying of cancer have multiple colonies (metastases) of the cancer in organs distant from the original site, for instance in the brain, lungs, and bones from a prostate cancer. Unless highly localized, these colonies are usually difficult or impossible to access for surgical removal or radiation therapy, and their variable genetic make-up increases the probability that some of them will prove resistant to anticancer drugs. As a result, the development process is very similar for all cancers, but the biological characteristics, clinical manifestations, course, and opportunities for treatment have distinct profiles for individual cancers.

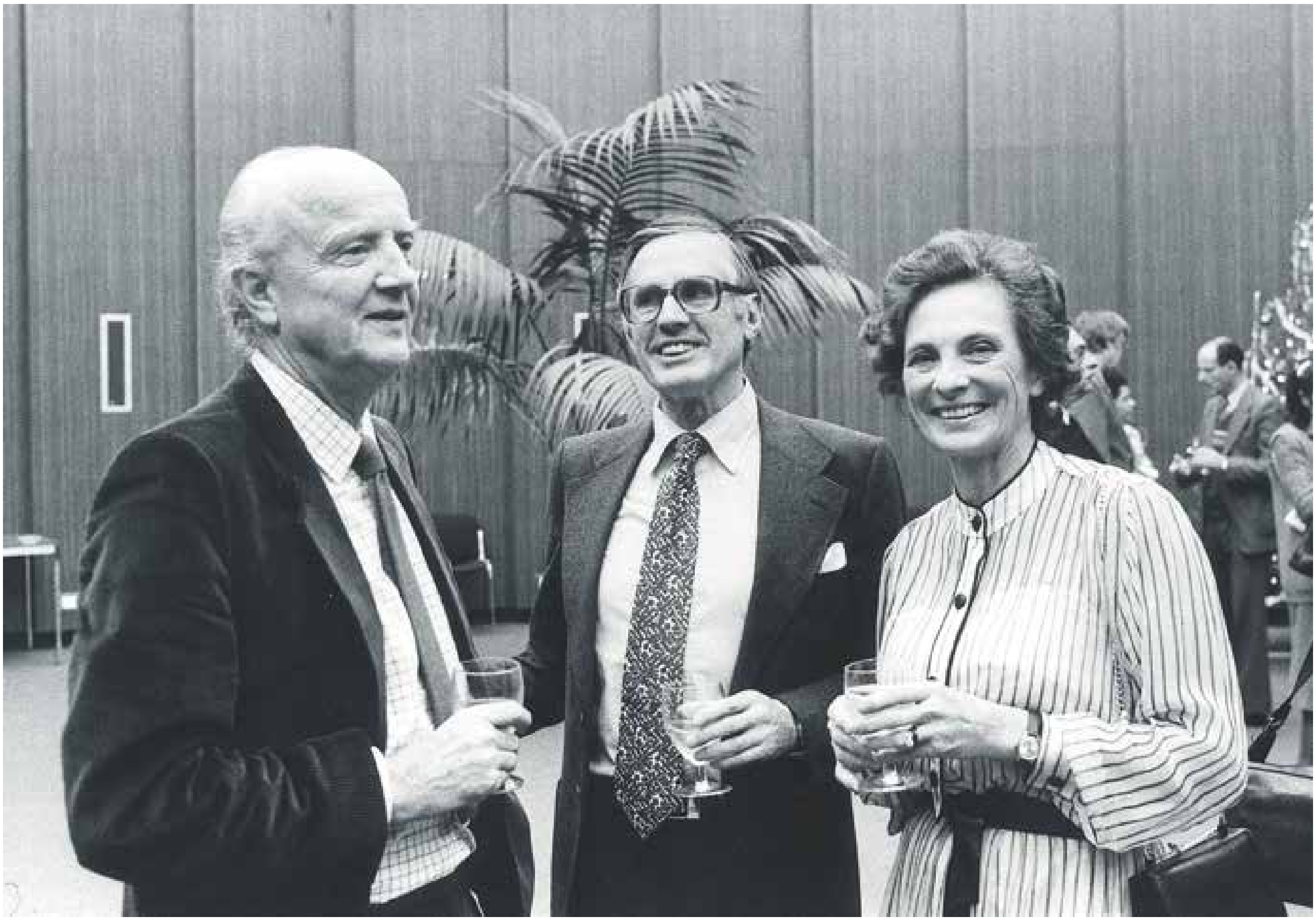
From a population viewpoint, cancers have always been present in humans (and other animals); the first mention dates back to about 3000 BC, in an Egyptian papyrus that reports breast cancers. Two factors have greatly increased the number of cancer cases recorded in contemporary populations: our diagnostic ability to recognize them as separate from other diseases, and the progressive ageing of populations. Cancers of epithelial tissues, such as those arising in the lung, colon, and breast, represent more than four fifths of all cancers and have a frequency that increases sharply with age. The ubiquitous presence of cancer had already made it a major public health issue, nationally and internationally, in the early 1960s, when the proposal for an international centre devoted to catalysing cancer research was formulated.

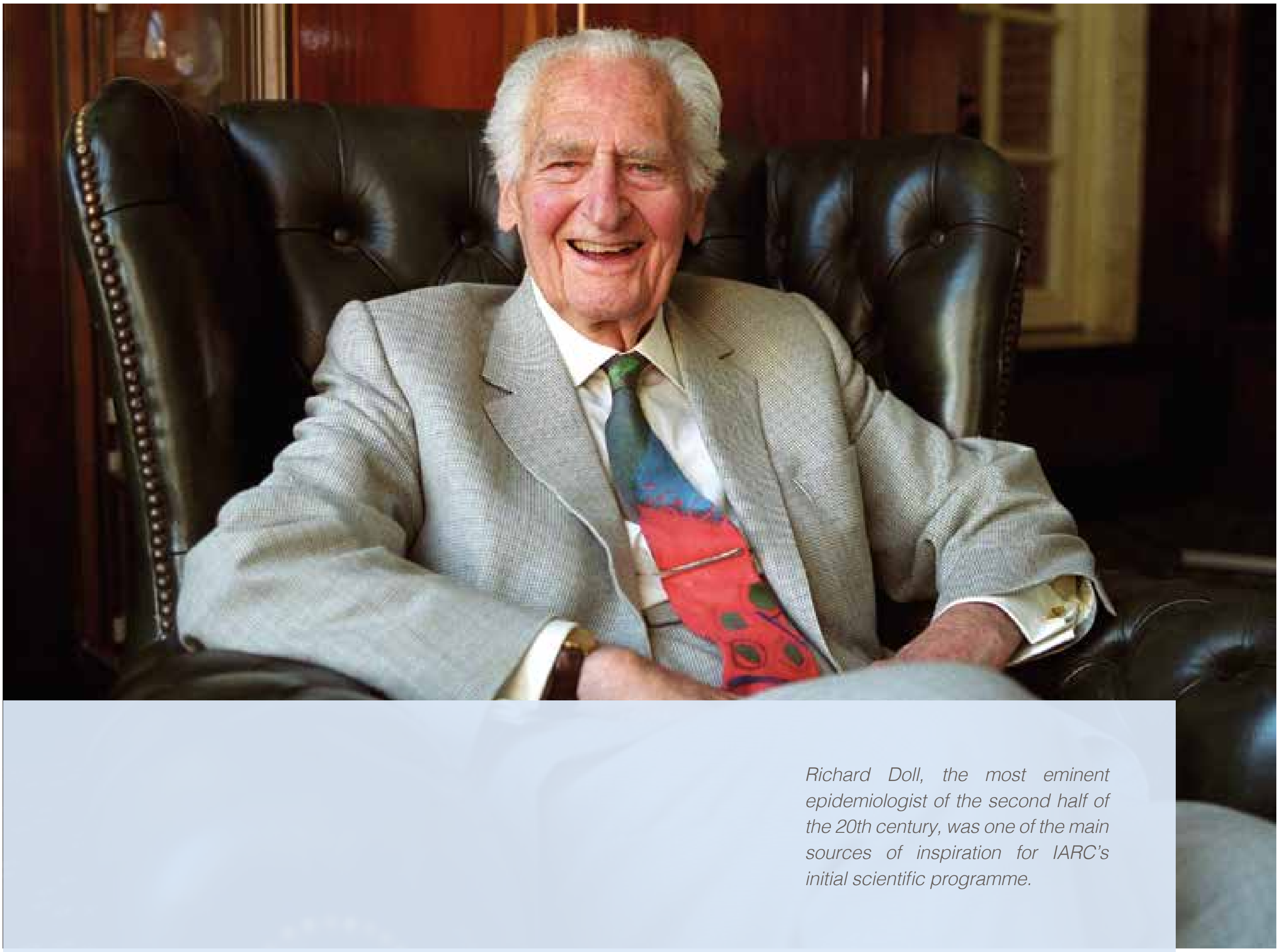
A new outlook on cancer

Cancer research was soon included in these justified hopes (see "Cancer is hundreds of different diseases"). Although there had been some progress in cancer research and in therapeutic interventions – essentially, surgery and radiotherapy – during the first half of the 20th century, the stark reality of cancer in humans was captured by the opening sentence of a 1956 paper: "The most obvious manifestation of cancer is that it kills." However, some attempts had already been made to treat cancer with single drugs synthesized in the 1940s and capable of countering the proliferation of cancer cells in cases of lymphoma and childhood leukaemia.

Transient remissions of disease were obtained, motivating the development of rigorous studies of efficacy in humans. Randomized clinical trials to test various multidrug regimens, including several new molecules, were initiated by such institutions as the United States National Cancer Institute in 1954–1955 and the United Kingdom Medical Research Council in 1957. The idea that cancers are basically not medically treatable faded away, as did, about a decade later, the concept that cancers are not preventable. Richard Doll's 1967 book *Prevention of Cancer: Pointers from Epidemiology* most effectively expresses this changed view, buttressed by sound scientific arguments (see "Preventing cancer").

John Higginson, the first IARC Director (from 1966 to 1981), is seen here at a New Year's reception with his wife Nan and Anton Geser (left). Geser is the epidemiologist who, with Guy de Thé, conducted the IARC studies on Burkitt lymphoma in Uganda and the United Republic of Tanzania (see the chapter "Viruses and vaccines").





Richard Doll, the most eminent epidemiologist of the second half of the 20th century, was one of the main sources of inspiration for IARC's initial scientific programme.

PREVENTING CANCER

The following is an extract from the introduction of Richard Doll's *Prevention of Cancer: Pointers from Epidemiology.*

"When, some fifteen years ago [in about 1950], a professor of surgery told me that it was not only a waste of time but also faintly immoral to try to prevent cancer, he had in mind the idea that the development of cancer was part of the normal process of ageing. Attempts to interfere with it were, at best, doomed to failure. At worst they represented the sort of *lèse-majesté* which Prometheus was guilty of, and were liable to lead to some comparable retribution. This view was not, I hope, widely held; but it represented, in extreme form, a fatalistic attitude that was. So little was known about the nature of malignant cells and of the processes that normally regulate tissue growth that the prevention of cancer, regarded as theoretically possible, was not thought to be a practicable current objective. Medical education and public hopes were, therefore, concentrated on methods of improving treatment and of diagnosing the disease at an early stage, when treatment might be more effective.

"Since then the situation has altered radically. New classes of chemical carcinogens have been discovered, some of which occur naturally in the human environment and are capable of causing experimental cancer in organs that were previously difficult to affect. It is now known, for example, that nitrosamines, given by mouth, will readily produce cancer of the oesophagus, stomach, or large bowel. Fungi, like Aspergillus flavus, have been shown to produce metabolites in foodstuffs stored under hot and humid conditions, minute doses of which will produce cancer of the liver and stomach. ... And overshadowing all this is the discovery that viruses can produce cancer in so many species of animals that it is difficult not to believe that they can also produce some types of cancer in man.

"*Pari passu* with these developments, epidemiological studies have shown that cancer incidence in man is far more dependent on the conditions of his life than had previously been supposed. The few classical examples of cancers that occurred with heavy exposure to a specific occupational hazard, or were associated with such bizarre habits as smoking a cigar with the burning end inside the mouth, have been steadily added to; and in some instances it has been possible to show that the incidence of cancer falls when the method of work or the associated habit is changed. Variation in incidence is, moreover, now known to be the rule rather than the exception. No cancer that occurs with even moderate frequency, occurs everywhere and always to the same extent. A range of ten or twentyfold is common and for some types of cancer it is far wider. Sometimes it has even been possible to recognize an epidemic, similar in scale to an epidemic of infectious disease, but modified by the fact that the induction period may be of the order of thirty years.

"A change in attitude has, therefore, occurred and the prevention of cancer is now coming to be regarded as a practicable alternative to its cure. We are, however, still almost totally ignorant of the mechanism by which cancer is produced at the cellular level and, until we know this, our methods of prevention are liable to be cumbersome and inefficient. Ethical considerations and the time scale of the disease make it impossible to obtain experimental evidence in man, and we have to decide what action to take from observation of Nature's experiments and by analogy from experiments in animals."

One of the most striking features that contributed to this new perspective was the observed variation in the occurrence of specific types of cancers in different geographical areas, as reflected in cancer mortality statistics or directly documented by recorded clinical diagnoses of new cases. Such variations were often very large, suggesting that they could be due to the variability of the conditions prevailing in the various areas. For instance, lung cancer was reported to be 40 times as common in areas of the United Kingdom as in Uganda, oesophageal cancer 100 times as frequent in some districts of the Islamic Republic of Iran as in the Netherlands, and liver cancer 1000 times as common in Mozambique as in Sweden. A hypothetical country in which the lowest observed rates of each cancer occurred would have had about 90% fewer cancers than a hypothetical country with the highest observed rates of each cancer. Therefore, the reasonable hypothesis was put forward that the great majority of cancers, perhaps even 90% of all cancers, could be due to external conditions or "environment", which John Higginson, the first IARC Director, defined as follows: "Environment is what surrounds people and impinges on them. The air you breathe, the culture you live in, the agricultural habits of your community, the social cultural habits, the social pressures, the physical chemicals with which you come in contact, the diet, and so on."

The cancer-causing factors that had been established by 1967	
Type	**Factor**
In the general environment	Ionizing radiation
	Ultraviolet radiation
In the local and occupational environment	Asbestos
	Nickel refining
	Chromate manufacture
	Inorganic arsenic compounds
	Mustard gas manufacture
	Fumes from gasworks
	Isopropylene
	Alpha- and beta- naphthylamine
	Benzidine
	Xenylamine
	Benzene
	Tar and other coal combustion products
	Ointments containing coal tar
Personal behaviours	Chewing of tobacco, betel, and lime
	Tobacco smoking
	Alcohol consumption
Pharmaceutical drugs	Chlornaphazine
Infections	*Clonorchis sinensis* (Chinese liver fluke)
	Virus inducing Burkitt lymphoma
Predisposing conditions	Tropical ulcers
	Ulcerative colitis

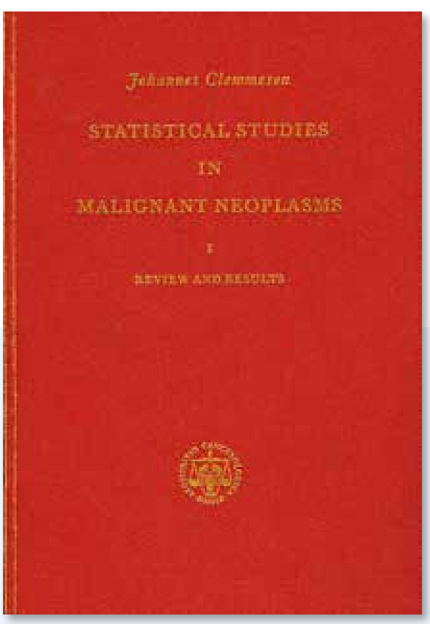
The plausibility of this hypothesis was supported by what was already known about several cancer-causing factors, all belonging to the environment in its broadest sense. The table summarizes the evidence as portrayed in Doll's book. Johannes Clemmesen, who founded the world's first nationwide cancer registry, in Denmark in 1942, reviewed and presented in detail all relevant studies available up to 1965 in his masterly opus *Statistical Studies in the Aetiology of Malignant Neoplasms*. Epidemiological research, by itself and in combination with experimental investigation in animals, was identifying causal factors of cancers within a variety of environments, while observations of variations in cancer occurrence between populations were providing valuable indications of where to look for such factors. Investigating environments and populations at the international level appeared to be the best response to the need for developing these research avenues. Onto this favourable ground fell the French initiative for a new cancer agency (see the chapter "The birth of

IARC"). This proposal was well in tune with the contemporary climate of confidence in biomedical research and clinical medicine, and with the willingness of individuals and governments to promote international collaboration in science via the establishment of new institutions, as had already occurred for CERN and EMBO.

Rounding off the corners

Newborns occupy space, and IARC was no exception. Established in 1965 as a consequence of the proposal by French public figures, IARC first had to identify its specific areas of research, to avoid overlaps (and friction) with other organizations, to fill unmet needs, and to create new opportunities for synergistic collaborations. In broad terms, IARC's areas of research would be cancer etiology, including the study of mechanisms, and cancer prevention. After initially being hosted by WHO in Geneva, IARC moved to temporary premises in its permanent home, Lyon, and finally to the 14-floor tower ordered expressly for IARC by the French authorities. In the design of the new building, the corridors of the square tower joined at right angles, which posed an obstacle to the passage of laboratory carts. This obstacle was removed – as remembered by Higginson's wife – by rounding off the corners of the corridors (see "John Higginson, first IARC Director").

There were corners of a different kind to be rounded off as well, concerning IARC's research strategy. Two such decisions were crucial for IARC's future. During the discussions leading to the establishment of IARC, diverging views had been expressed by representatives of the countries involved about the suitability of having laboratories included within IARC at all. One view was that IARC's activity should be centred on and limited to epidemiology. It is to Higginson's credit that by "rounding off the corners" he eventually carried the case for laboratories to be an integral part of IARC's activity. This had two advantages. First, it favoured



JOHN HIGGINSON, FIRST IARC DIRECTOR

Nan Higginson paints a vivid portrait of her husband John at the time that he was appointed as the first IARC Director: “John viewed the invitation to be the first director of the newly established idea of an international centre for cancer research as a unique opportunity to expand the field of environmental cancer research into an integrated global endeavour.

“Although happily established in his job in Kansas, USA, it became evident to him that his path seemed to lead to such an international position, starting with his medical degree from Trinity College in Dublin, Ireland, then in the pathology department at the Western Infirmary in Glasgow, Scotland, followed by eight years at the South African Institute for Medical Research, in Johannesburg. In South Africa, he was also a pathologist at the 200-bed Baragwanath Hospital. His experiences at this hospital and his visits to the surrounding mission hospitals led to him becoming particularly interested in cancer research.

“Under his leadership, IARC established satellites in over 70 countries around the world. This was a result not only of John’s dedication to the advancement of cancer research as an international pursuit, but also reflected his profound respect for the scientific endeavours of scientists from all over the world, as well as a deep enjoyment and curiosity regarding different cultures.

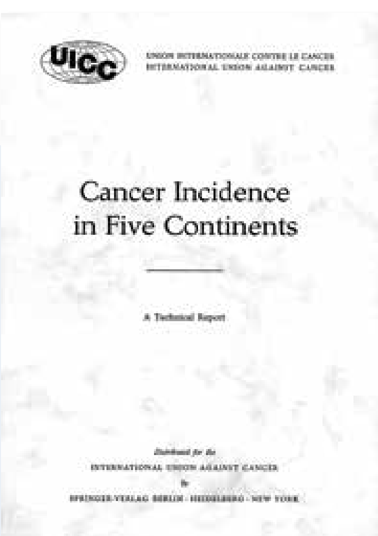
“When John started at IARC, he had to wear many different hats! He took a keen interest in all aspects of the running of the centre, ranging from the layout of the laboratories to the construction of the new building. For example, the numerous architects handling the construction of the building hit a stumbling block when it was pointed out to them that their design was not suitable for the laboratory floors, as the trolleys could not get around the corners of the passages. When they were unable to find a solution, it was John who suggested that they should round off the corners of the corridors, which is what they did!”

The IARC tower building in the eighth district of Lyon, with the waving flags of the World Health Organization and of the 24 IARC Participating States.

the incorporation of laboratory tests into epidemiological studies, a feature of growing importance with the development of biomarkers of exposure, susceptibility, and early lesions that are measurable in humans. Second, placing epidemiologists and scientists carrying out in vivo and in vitro experimental research under the same roof enabled even a moderately sized institution like IARC to stay at the frontiers of cancer research.

> *Richard Doll was one of the first editors of* Cancer Incidence in Five Continents*, and this publication demonstrated that the variation in cancer rates between one country and another was real, which meant that where cancer was common, it didn't have to be.*
>
> – Richard Peto, long-term IARC collaborator

Corners also needed to be rounded off with respect to the development of descriptive epidemiology, a key raison d'être of IARC. Registration of all cancer cases occurring in a defined population had initially taken the form of studies covering a limited period of time. In the 1940s and 1950s, this had been upgraded into permanent systems of case recording or "cancer registries", such as those for the state of Connecticut in the USA or for the whole country in Denmark. Registries became fundamental tools for measuring cancer incidence in defined populations. (Incidence is the expression of the ensemble of carcinogenic factors active in a population, whereas mortality provides a less clear picture since it is also determined by treatment.) To enable the comparison of statistics across different populations, methods of registration and of data analysis needed to be uniform. The International Union Against Cancer (UICC, now called the Union for International Cancer Control), an association of national scientific cancer organizations, had played a key role in promoting cancer registration and had commissioned a team of scientists to produce a first report on data from several registries, which was published in 1966 with the title *Cancer Incidence in Five Continents*.



UICC promoted the collection of cancer incidence data worldwide. The first comprehensive compilation of the most comparable information available at the time was published in 1966 as a volume edited by Richard Doll, Peter Payne, and John Waterhouse (shown here).

The development of the appropriate technical capacity at IARC translated into a collaborative endeavour of UICC and IARC for the second volume of the report, published in 1970. With the rapid increase in the number of cancer registries around the world, the programme became, with the third volume (in 1976), a major ongoing activity of IARC in cooperation with the International Association of Cancer Registries, a nongovernmental organization established in 1966.

2015: IARC'S GOLDEN ANNIVERSARY

Today, IARC is active in a world that has changed even more in the 50 years since its establishment than in the previous half a century. Postdoctoral fellows in their twenties or thirties working at IARC today make continual use of email and smartphones with a wide variety of applications for daily life and work. They can participate in videoconferences when organizing a new project and certainly spend most of their working time in front of a computer screen. In the laboratory, a vast range of operations, from manipulating blood samples, cells, or tissue specimens to performing biological, physical, or chemical procedures, now use automatic and programmable equipment. None of these existed in 1965. Then, the analysis of data – a fundamental daily task for all research – was routinely done using mechanical calculating machines. Writing down the results, entering them into the next step in a calculation, and repeating the whole procedure at least twice to be sure that the results were correct – all this had to be done directly by a human operator. Calculating the dependence of a variable like body weight on several other variables, such as caloric intake, amount of physical exercise, and quantities of different foods, kept an operator busy for hours or days, depending on how many sets of variables were being explored. Today, such a calculation takes a matter of seconds or minutes with a computer performing 10 billion operations per second.

"The arrival of computing was a revolution. What was important was that over the years the revolution was a success: the performances in terms of data management improved considerably, particularly as a result of the computing team that was brought together at that time.
– Jacques Estève, former IARC scientist

Between 1965 and 2015, biology has been transformed as deeply as computer sciences and information technology. It has come all the way from deciphering the basis of the genetic code embodied in DNA to the determination of the sequence of more than 3 billion base pairs in a typical human genome, completed in 2004. It is now possible to determine the genome of a single individual with all its sequence variants at a cost of about US$ 1000 – and falling. Major advances in scientific knowledge may or may not lead to practical applications, but they invariably generate a large spectrum of new questions to be investigated. This is now under way in the ever-expanding "omics" fields like transcriptomics, proteomics, metabolomics, and epigenomics, which in their turn have been embraced by IARC scientists. These approaches allow exploration of how physiological messages are dictated by DNA in its individual variants and interact with non-genetic messages arising from the environment – beginning with influences of the maternal environment on the embryo – to guide the development of the organism and regulate (and deregulate) its functions.

Medicine, too, has come a long way since 1965. In addition to improvements in all fields, several entirely new branches have been developed. Body imaging, then limited to X-ray techniques, now includes a variety of ultrasound methods, computed tomography (CT) scans, magnetic resonance imaging (MRI), and positron emission tomography (PET) scans, and more techniques are constantly being developed. Intensive care medicine, still in its infancy in the 1960s, has transformed the treatment of many acute conditions. Organ transplants, then confined to corneal transplants and very tentative early attempts for other organs, have become routine. Minimally invasive and robotic methods are changing the practice of surgery. Cancer medicine has prominently participated in and contributed to these transformations both in diagnosis and in treatment. A single feature aptly captures how advances in cancer medicine have translated into benefits for the population: survival rates of all cancer patients in defined areas, irrespective of care and treatment. The figures in the table are from the USA, but the time trend (although not necessarily the actual survival percentages) is similar in many developed countries; there has been a remarkable improvement for most sites, with dismal figures persisting for a few sites.

Progress in cancer treatment: percentage survival (relative to normal life expectancy) of patients at 5 years after initial diagnosis, for main cancer sites

Site	Period		
	1947–1951	**1975–1977**	**2003–2009**
Oesophagus	4	5	19
Stomach	7	15	29
Colon	36	51	65
Rectum	32	48	68
Pancreas	2	2	6
Larynx	47	66	63
Lung	5	12	18
Breast (women)	54	75	90
Cervix uteri (women)	62	69	69
Ovary (women)	28	36	44
Prostate (men)	28	68	100
Bladder	38	72	80

Thus, for half a century, a story has unfolded of remarkable scientific and technological advances, spreading to increasingly larger areas of the world. The radical changes, which have contributed to creating challenges in all aspects of life, have never before occurred in such a form or on such a scale.

Global challenges for the new century

Three of these global challenges form the broad background to the present and future activity of IARC: the ageing of populations, environmental change, and the evolving inequities between and within countries. These challenges are crucial both individually and in their interactions.

Global ageing of populations

Cancer is largely a disease of ageing, and as life expectancy continues to increase, notably in the developing countries, the global burden of cancer will rise (see the chapter "IARC: the second 50 years"). As shown in the table, average life expectancy at birth increased worldwide from 51.2 years in 1960–1965 to 67.9 years in 2005–2010, a gain of more than 4 months per year, and a striking 6 months per year in Asia. Combined with sharply decreasing fertility, from 4.9 births per woman in 1960–1965 to 2.5 in 2005–2010, this is revolutionizing the population structure of the human species. While the proportion of young people (below age 15) is diminishing worldwide, the proportion of older people (above age 65) is increasing rapidly; the fastest growing group is those older than 80. A United Nations estimate indicates that by 2050 – when the world's population is likely to have exceeded 9 billion – for the first time in history the number of people older than 60 will exceed the number of people younger than 15; this has already happened in several economically developed countries. Population ageing has profound consequences and implications in all spheres of life. For each person above age 65, there were 12 people of working age (15–64 years) in 1950, and 9 in 2000, and in 2050 there will be only 4. This sharp increase in the elderly dependency burden placed

Average life expectancy at birth (in years)

Region	Period	
	1960–1965	**2005–2010**
World	51.2	67.9
Africa	42.4	55.2
Asia	46.4	69.0
Europe	69.6	75.4
Latin America	56.8	73.4
North America	70.2	78.2
Oceania	64.1	76.6

on people of working age is further aggravated if only a fraction of people of working age are economically active. Health is obviously a prominent aspect of population ageing; 80% of older people have at least one chronic condition and 50% have two or more, and acute diseases and injuries take a disproportionate toll on older people. Population ageing already requires major changes in the organization and functioning of health and social services and poses a challenge to all strategies of cancer control.

Global environmental change

The health effects, acute and chronic, of local, home, and occupational environments have long been known and continue to be described and investigated. Lung cancers caused by air pollutants, like diesel exhaust or asbestos fibres, and skin cancers caused by solar ultraviolet radiation are just two examples among many. In recent years, a potential new threat – of a global nature – has emerged. As the extensive work of the Intergovernmental Panel on Climate Change has documented in its periodic Assessment Reports (the fifth of which was published in 2014), man-made emissions of greenhouse gases, principally carbon dioxide, continued to increase from 1970 to 2010, with larger increases after 2000. Two factors are driving this trend of increasing emissions that outpace the reductions due to improvements in energy efficiency: population growth and expanding economic activities. If unmitigated, the greenhouse effect may cause an increase in the global mean surface temperature of 3.7–4.8 °C by the end of this century, with major effects on sea levels and coastal configurations, land fertility and agricultural production, and animal species (survival, location, migration patterns, and species interactions). Ultimately, human health will be affected – both directly, by environmentally induced diseases, and indirectly, through disruption of agriculture or as a consequence of mass emigration from areas that become inhospitable. There is currently some evidence of increased heat-related mortality and decreased cold-related mortality in some regions as a result of global warming. Heat waves have shown a precipitating lethal effect on subjects vulnerable because of pre-existing serious conditions, including cancers, especially when these are combined with low socioeconomic levels. At present, the worldwide burden of ill health, including cancer, related to global warming is small and is not well quantified. However, to be effective, actions to prevent further warming and more extensive damage to human health cannot be postponed; they must be taken now.

Global inequities

Two distinct and often diverging forces, each with an impact on the health of populations, are at work at the beginning of this century. First, a heightened awareness of the crucial role of social determinants of health and disease is prompting a variety of actions and programmes that aim to improve these determinants. Second, and often discordantly, an increasingly dominant free-market approach in all domains of life, public and private, is tending to treat health as a commodity whose value is signalled by its market price.

HEALTH AND DISEASE ARE SOCIALLY DETERMINED

The Commission on Social Determinants of Health made the following concise statement in its final report.

"The poor health of the poor, the social gradient in health within countries, and the marked health inequities between countries are caused by the unequal distribution of power, income, goods, and services, globally and nationally, the consequent unfairness in the immediate, visible circumstances of people's lives – their access to health care, schools, and education, their conditions of work and leisure, their homes, communities, towns, or cities – and their chances of leading a flourishing life. This unequal distribution of health-damaging experiences is not in any sense a 'natural' phenomenon but is the result of a toxic combination of poor social policies and programmes, unfair economic arrangements, and bad politics (that prize the interests of some over those of others – all too often of a rich and powerful minority over the interests of a disempowered majority). Together, the structural determinants and conditions of daily life constitute the social determinants of health and are responsible for a major part of health inequities between and within countries."

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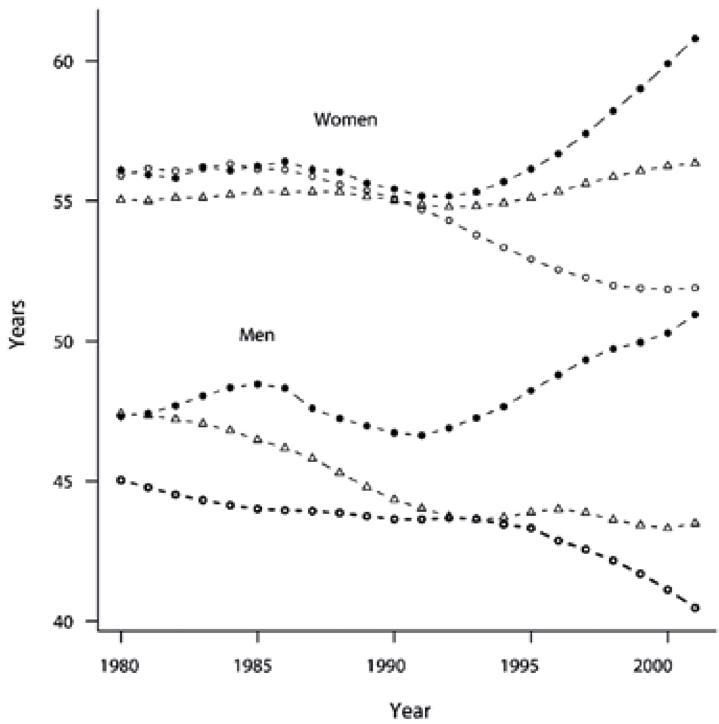
Current male life expectancy at birth (in years) in selected countries and in two selected locations within the United Kingdom (Scotland) and within the USA

Location	Life expectancy at birth
United Kingdom, Scotland, Glasgow (Calton district)	54
India	62
USA, Washington, DC (Black residents)	63
Philippines	64
Lithuania	65
Poland	71
Mexico	72
USA	75
Cuba	75
United Kingdom	77
Japan	79
Iceland	79
USA, Montgomery County (White residents)	80
United Kingdom, Scotland, Glasgow (Lenzie North)	82

The crucial role of social determinants of health has been delineated in a key report of the Commission on Social Determinants of Health (see "Health and disease are socially determined").

The examples in the table tell a story of general importance: health, as measured by life expectancy at birth, is worse in poorer countries, and within richer countries it is worse among more deprived populations. Additional striking confirmation comes from episodes of worsening population health after a rapid deterioration of socioeconomic conditions. For example, during the 1990s, life expectancy (at age 20) declined sharply in the Russian Federation, most notably among less educated men, because of a rise in adult mortality ensuing from the dissolution of the Soviet Union in 1991, accompanied by drastic changes in the political, economic, and social systems. More recently, the economic "austerity" measures imposed in Greece due to the debt crisis are reflected in increased rates of suicides and mental disorders and in a reversal of the long-term trend of decreasing infant mortality.

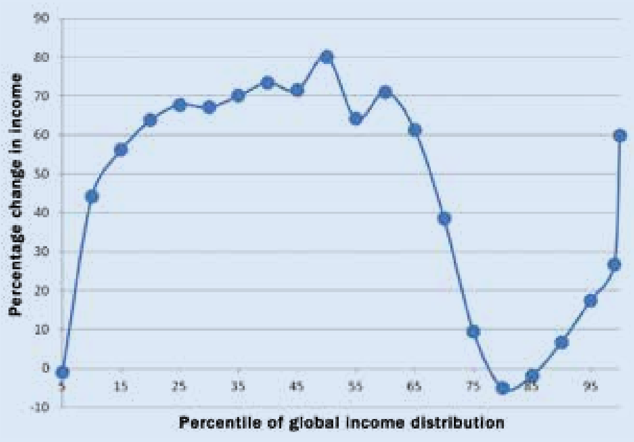


Trends in life expectancy (in years) at age 20 years in the Russian Federation among men and women with different levels of education (open circles, elementary; triangles, intermediate; filled circles, university).

Based on its diagnosis of the overwhelming impact of social determinants on health, the Commission formulated three overarching recommendations to "close the inequity gap" within one generation: improve daily living conditions; tackle the inequitable distribution of power, money, and resources; and measure and understand the problem and assess the impact of action. The recent evolution of the global economy and the distribution of people's incomes, as a result of globalization policies mostly guided by pro-free-market priorities, may hinder rather than help the achievement of this goal.

PEOPLE'S INCOMES ARE UNDERGOING MAJOR CHANGES

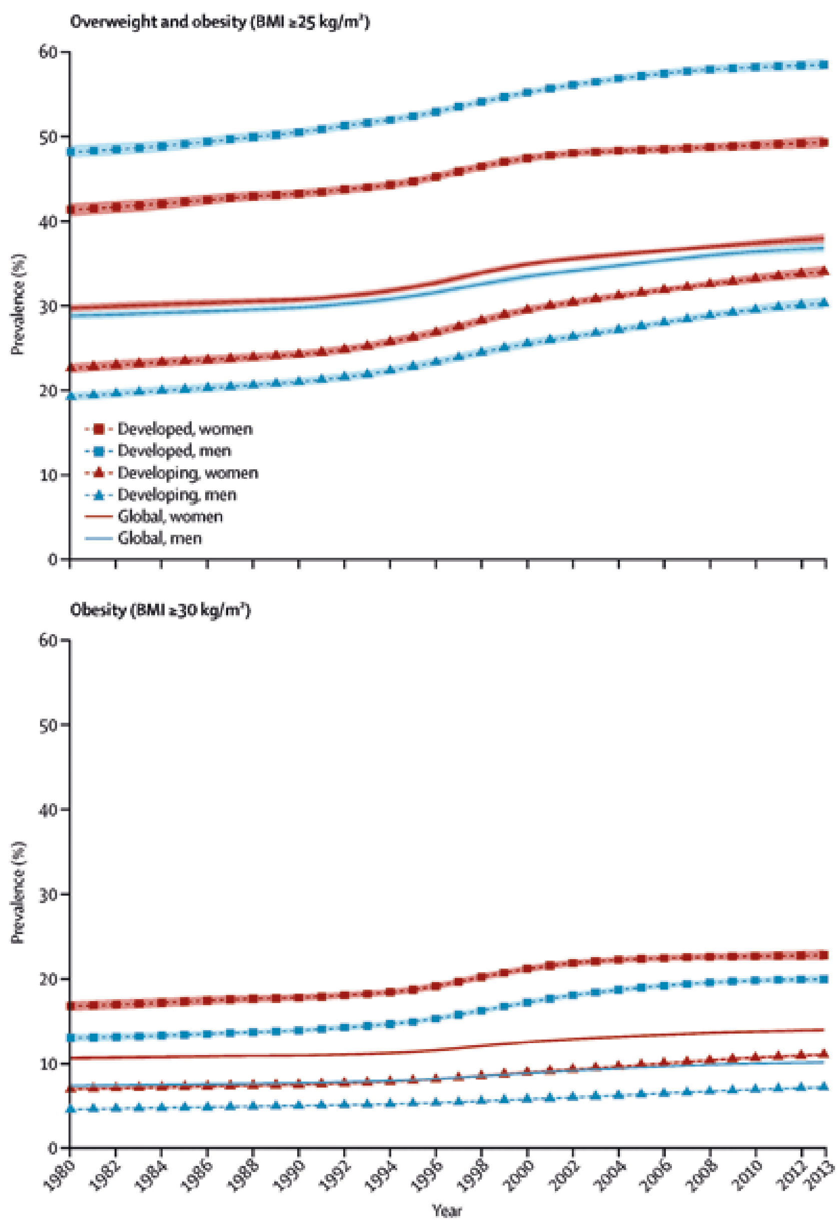
Only recently has the World Bank been able to collate sufficient data to place people from all countries in the world on the same common scale of personal income (gross domestic product per capita). Incomes are expressed in international dollars; an international dollar would buy in the cited country a comparable amount of goods and services as a United States dollar would buy in the USA (say, in 2005). Once estimated in this way, the incomes for all people in the world are ranked from the lowest to the highest and subdivided into groups. In the graph, the horizontal axis shows the relative position in the global income distribution. The percentile positions run from 5 to 95, in increments of 5; for example, 5 indicates the lowest 5% of world incomes, and so on until 95. The top 5% of the distribution is further subdivided into two groups: people between the 95th and 99th percentiles, and those in the top 1%. The vertical axis shows the percentage change (increase or decrease) in the real income for each of the groups.



Percentage change in real income between 1998 and 2008 at various percentiles of the global income distribution (calculated in 2005 international dollars).

The time evolution of incomes over the 20-year period shows a striking pattern. There was no improvement at all for those at the extreme left, i.e. bottom, of the scale: the poorest 5%. A remarkable improvement (up to an 80% increase) occurred for people who in 1988 were in the central 10th to 70th percentiles of the global income distribution. They include the large number of people who form the emerging global middle class: more than 200 million Chinese, 90 million Indians, and 30 million people each from Brazil, Egypt, and Indonesia. There was a minor improvement (of less than 10%), or even a decrease, for people who in 1988 were between the 75th and 90th percentiles of the income distribution; essentially, these are the middle classes of the developed countries. Finally, a sharp increase occurred for those who were already the best-off in 1988, particularly the top 1% (an increase of 60%). In this respect, it should be noted that because the scales of the graph are relative, the same percentage increase corresponds to vastly different absolute increases in income: for a low annual income of 2000 international dollars, falling towards the left end of the graph, a 50% increase means a gain of 1000 international dollars between 1988 and 2008, whereas for people at the right end of the graph with annual incomes of 100 000 international dollars or more, the same 50% increase means a gain of 50 000 international dollars or more.

The dominant policies of the past decades are a mechanism that is capable of raising the income of large populations, but at the cost of generating new inequities (see "People's incomes are undergoing major changes"). In particular, the persistence of extreme poverty and the increasing gap between a tiny minority of people with very high incomes (and wealth) and the rest of the population – a global pattern that is replicated within countries – may stretch to breaking point the ties between all members of a society, the very basis of



Obesity has been on the increase in developed countries as well as in many developing countries, and worldwide the prevalence of obesity has nearly doubled since 1980. In 2008, one third of adults aged 20 years or older (more than 1.4 billion adults) were overweight, and more than 10% were obese. In 2012, more than 40 million children under the age of 5 years were already overweight or obese.

solidarity rightly deemed by the Commission to be essential to remove health inequities. And social solidarity, stemming not only from private initiatives of philanthropists but above all from enlightened governmental actions, was also the foundation on which IARC was built.

IARC, a landmark scientific institution

In 2015, cancer has become a global health problem. The cancer incidence burden is projected to increase from 14.1 million new cases in 2012 to 21.6 million by 2030. It is estimated that by 2030 the worldwide burden of noncommunicable diseases, including cancers, cardiovascular diseases, chronic respiratory diseases, and metabolic diseases like diabetes, will have overtaken the burden of communicable diseases. The main reason for this is the rising burden of noncommunicable diseases, and cancers in particular, in developing countries, due to growing and ageing populations and to the spread of major cancer-causing factors like tobacco use, alcohol consumption, and obesity from unhealthy diets combined with the adoption of sedentary habits at home, at work, and in transportation. As a result, many developing countries are now confronted with the double burden of still-prevalent communicable diseases together with a rising incidence of noncommunicable diseases, including cancers. Whereas in the past attention has often been given to cancer in developing countries because of scientific interest, this new epidemiological situation means that the emphasis must shift towards supporting developing countries in their efforts to tackle what is becoming a major public health issue. Currently, for many cancers survival is markedly lower in developing countries than in developed countries, as exemplified in the table by 5-year survival in children at four locations. Improving the effectiveness of cancer diagnostic and treatment services is an obvious, if economically demanding, priority. Yet in a medium- to long-term perspective, the cancer problem can hardly be solved in this way in any country. In fact, population ageing, already well advanced in developed countries and catching up in developing countries, is bound to increase the number of cancers occurring each year worldwide, particularly among older people, the group for which gains in years of life from effective treatments come at the highest costs.

This perspective provides compelling reasons for prevention, aimed primarily at curtailing the number of cancers by avoiding their occurrence. When IARC was established in 1965, prevention was recognized as the key avenue towards cancer control because cancer treatments had definite but limited scope. Today, and most likely tomorrow, the escalating costs of cancer treatments – effective, or just promising – in ageing populations point again to prevention as the cornerstone of cancer control. IARC, an institution of comparatively modest size (about 300 people), has become an international landmark in the cancer research field because since the very beginning IARC's scientific programme has been designed to produce "knowledge for prevention". As the chapters of this book highlight, the programme has been articulated on two levels. The first level is developing tools and infrastructures for cancer research internationally, ranging from education and training of personnel in various areas of cancer research through

Percentage survival at 5 years after initial diagnosis in children (ages 0–14 years) at four locations in different countries				
Cancer type	**Location (period)**			
	Australia (1997–2006)	**Shanghai, China (2002–2005)**	**Chennai, India (1990–2001)**	**Thailand (2003–2004)**
All cancers	79.6	55.7	40.0	54.9
Leukaemias	80.6	52.2	36.3	57.4
Lymphomas	89.9	58.8	55.3	59.5
Central nervous system tumours	71.0	41.2	26.8	41.7
Neuroblastoma	67.8	—	36.9	33.6
Retinoblastoma	98.4	75.0	48.1	73.1
Renal cancers	88.6	86.7	58.0	70.4
Liver cancers	76.0	33.3	10.5	44.5
Malignant bone tumours	68.9	52.6	30.6	33.7
Soft tissue sarcomas	72.1	54.1	36.3	50.1
Germ cell tumours	89.4	78.4	38.0	70.6
Carcinomas and melanoma	93.3	88.9	35.1	—
Other	72.2	—	—	—

to establishing cancer resources like repositories of biological samples (biobanks) in different geographical settings. The second level spans several research axes, from analysing cancer occurrence data in order to gather hints about potential, not yet identified cancer causes to testing the efficacy and effectiveness of preventive interventions. The pressing need to improve the diagnosis and treatment of cancers in developing countries has fostered the inclusion in the programme of several screening and early diagnosis projects, although primary prevention targeted at removing causes of cancer remains a key objective of IARC's research activity.

IARC was born in 1965 as an initiative of a few economically developed countries in which cancer represented a major public health issue. Significantly, cancer research in developing countries, particularly epidemiology supported by laboratory investigations, was embedded in IARC's programme from the outset and immediately gave rise to several projects. Subsequently, some of IARC's greatest achievements, notably the studies leading to the identification of human papillomaviruses as the cause of cervical cancer and the vaccination trial to prevent chronic hepatitis and liver cancer, have taken place in developing countries. Today, when cancer is also becoming a relevant public health problem in developing countries, IARC is at the forefront of research in these areas of the world and is a prime example of solidarity between developed and developing countries.