Epidemiology of chronic non-infectious disease: current status and future perspective*

Epidemiologia de doenças crônicas não-infecciosas: situação atual e perspectivas futuras

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Introduction

Epidemiology is one of the oldest branches of medical science and was for many years among the most important, for the good reason that its practice required only the use of records, simple arithmetic, and some clinical acumen. Its history and evolution were described by Mervyn Susser in a keynote paper given at the Pan American Epidemiology Congress in Salvador in April 1995, which was published in an expanded version a year later (Susser & Susser[1], 1996). In that account Susser & Susser[1] describe how quantitative epidemiology originated in concern for public health in the mid-17th century and how its application progressed from the study of mass statistics of mortality and morbidity at the beginning of the nineteenth century, through the study of the spread of disease caused by specific infectious organisms, to the study of the behavioural and environmental causes of chronic non-infectious disease, which has tended to be its principal focus over the last few decades. In my paper, I consider only this last group of diseases, the role that epidemiology has come to play in their investigation, and how it may develop in the future.

That the epidemiology of chronic non-infectious disease is characteristically a science of the second half of the twentieth century is indisputable, but it has a history extending back at least a century earlier. I do not count as epidemiological the observations that Ramazzini made, when he recognized the syndrome of lead poisoning and the importance of reproductive factors in the aetiology of breast cancer, nor those made by Pott, when he related scrotal cancer to employment as a chimney sweep in childhood, as these were essentially clinical in character. I count rather the observations that went under the head of geographical and historical pathology and were so clearly described by Hirsch[2] in his handbook on that subject, the first volume of which was published in 1864, although the distinction is admittedly arbitrary. Non-infectious disease played only a mi-

nor role in his three volumes, but he had short sections on cancer and hypertension and longer ones on chronic diseases that, in the spirit of the times, he classed as infective, but which we now know not to be; such as the avitaminoses, gout, and late onset diabetes. His accounts were purely epidemiological in character, but limited to incidence and mortality, and their variation over place and time. The modern subject of the epidemiology of chronic non-infectious disease, with its use of case-control and cohort studies, emerged only after the first world war and then only gradually, and it gathered pace with the addition of randomised controlled trials only after the second world war had ended.

Current status

In the 50 years since then, epidemiology has been responsible in one way or another for establishing nearly all the known causes of human cancer – now totalling over 50 - for determining the main causes of ischaemic heart disease and chronic obstructive airways disease and the dietary causes of stroke. It has also demonstrated the extraordinary range of effects of smoking tobacco and the high proportion of deaths attributable to it, amounting to over 20 per cent of all deaths from all causes, when cigarette smoking has been prevalent in a country for many years, as it has been in the UK. Epidemiology has also determined the balance of benefit and risk from the widespread use of alcohol and of steroid and other contraceptives, quantified the effects of ionizing radiation and many occupational hazards, and discovered the causes of the occasional outbreaks of unusual diseases, such as the toxic oil syndrome in Spain, Minimata disease in Japan, and eosinophilic myalgia in the United States. That is only a partial list; but it is, I suggest, more than enough to justify the claim that epidemiology has achieved the status of being one of the principal tools – perhaps even the principal tool –for determining the causes of chronic non-infectious disease.

It is certainly also too long a list for me to attempt to summarize the detailed evidence that has enabled this claim to be made and I shall limit this review to some aspects of the subject that have seemed to me the most important and support the belief that it still has much to offer the science of preventive medicine in future.

Proof of causation

That epidemiology could produce hypotheses about the cause of disease was soon accepted, but that it could establish that a factor was indeed a cause was disputed for many years. I say **a** cause rather than **the** cause, because one of the characteristics of most non-infectious diseases is that many different factors contribute to their development and can be said to be causes in the sense that, in their absence, the incidence of the disease is reduced and that, in their presence, the incidence is increased. That this was accepted only slowly was, I suspect largely because pathologists, who were the arbiters of aetiology at the beginning of this century, were accustomed to test ideas about causation by the application of Koch's postulates. These had been elaborated to test whether a specific organism could be regarded as the cause of an infectious disease and they stated that:

1. The organism should be found in all cases of the disease in question and its distribution in the body should correspond to the lesions observed.
2. The organism should be cultivated outside the body of the host, in pure culture, for several generations.
3. The organisms so isolated should reproduce the disease in other susceptible animals.

Even these criteria, it may be noted, fall short of satisfying the philosophical definition of cause that is still occasionally raised as an objection to the idea that epidemiology can prove causation: namely, something that is both necessary **and sufficient** to produce the specific effect. As criteria for defining causes of disease, Koch's postulates, however, served the

medical profession well at the time when microbiology was developing and the causes of infectious diseases were being defined; but they were quite inappropriate for non-infectious diseases. The first and third of them, nevertheless, tended to be applied in the modified form that the factor being studied should be present in all cases of the disease and that it should reproduce the disease in animals. Extraordinary as it seems now, some physicians dismissed the idea that smoking could cause Buerger's disease (Doll[3], 1998) and, as I learnt from personal experience, that it could also cause cancer of the lung, because they had seen cases of both diseases in non-smokers. For the idea that something could be **a** cause without being **the** cause had not been duly appreciated.

In 1950, when Professor Bradford Hill and I published the preliminary report of our case-control study of lung cancer (Doll & Hill[4], 1950), we were able to exclude bias as a cause of the observed association, by showing that the relationship with smoking held only for patients who were proved to have cancer of the lung after they had been interviewed and not at all for patients who were thought to have the disease when interviewed but proved not to have it. We were also able to exclude all the factors for which there was any evidence that they might confound the results and we found support for causation from a variety of different types of evidence that subsequently became codified in Hill's[5] (1965) guidelines for establishing a causal relationship. We consequently concluded from the totality of the evidence that "cigarette smoking was a cause, and an important cause, of carcinoma of the bronchus"

Hill's guidelines, which are now widely used by epidemiologists, are summarized in Table 1. They are not criteria, as Hill stressed, but aids to thought. Only one is obligatory; namely, that exposure to the factor should occur before the onset of the disease, and, if that is satisfied, one other may, in exceptional circumstances, alone be sufficient to establish causality: namely, the existence of an association that is so strong that the incidence of the disease is increased more than (say) 10-fold by the exposure. In most circumstances, however, most of the conditions need to be satisfied and even then, if the association is weak, the conclusion about causality may still be hard to reach. These guidelines have, however, been found to be of practical value and they have not been improved on – except, perhaps by making the explicit statement that the coherence of the evidence should be examined separately for both internal coherence within the findings of the study and external coherence with ecological evidence for the distribution of the disease by sex, community, and time.

Table 1 - Guides to causality of observed associations

Strength of the association	
Consistency	Specificity
Dose-response relationship	Coherence of evidence
Temporal relationship	Experience
Biological plausibility	Analogy

Source: Hill[5], 1965

To prove causality, in the sense that it is established beyond reasonable doubt and that the findings justify action to reduce risk, it certainly helps to have laboratory evidence that the agent can produce similar disease in animals; but such evidence is certainly not essential. Leaving aside the question of whether the production of cancer on, say, the skin of experimental animals is sufficient evidence to justify the classification of the agent as a human carcinogen, if exposure in humans is associated with an increased risk of cancer in some other organ, the International Agency for Research on Cancer[6-8] (1980, 1988, 1995) has classed at least three agents as human carcinogens without their having been shown to produce cancer in **any** organ in animals at the time of its review: namely, arsenic, alcohol, and wood dust.

Controlled trials

The strongest evidence is, of course, that obtained experimentally by means of a randomised controlled trial. Experiments to produce disease in humans are, however,

anathema; but there is no reason why they should not be carried out to **prevent** disease and the first randomised trial ever to have been used in medicine was not the test of the efficacy of streptomycin in the treatment of pulmonary tuberculosis, which is usually cited because it was the first to be publicly reported, but an experiment in prevention, a test of the efficacy of a vaccine to prevent whooping cough. Both trials were sponsored by the British Medical Research Council under the guidance of Professor Bradford Hill and both were begun in 1946, the trial of whooping cough vaccine being the first to be started but the second to be completed (Medical Research Council Streptomycin in Tuberculosis Trials Committee[9], 1948; Medical Research Council Whooping Cough Immunization Committee[10], 1951). Controlled trials to test hypotheses about the causes of disease by seeking to remove them followed only slowly, but they are now an integral part of modern epidemiology.

One is a trial of periodic doses of vitamin D, which is being carried out by Professor Khaw* in Cambridge, to see if it will reduce the risk of osteoporosis, and hence of fractures, in the elderly.

Others have been undertaken to elucidate the role of several vitamins and other micronutrients in the prevention of cancer. None, as yet, has revealed an important cause and two have even suggested that the addition of β-carotene, which case-control and cohort studies had suggested might be a panacea against many types of cancer (Peto et al.[11], 1981) might even be harmful (The Alpha-tocopherol Beta-carotene Cancer Prevention Study Group[12], 1994; Omen[13] et al. 1996). This, however, was found not to be so in the largest study carried out for the longest time, in which some 20,000 US doctors took tablets containing either β-carotene or a placebo for some 12 years, without knowing which they were taking (Hennekens et al.[14], 1996). More encouraging results have, fortunately, been obtained in the trials of HMG CoA reductase inhibitors, which have shown that the reduction of high levels of blood cholesterol (high by North American and European standards) will reduce the risk of myocardial infarct without increasing the risk of other diseases (The Long Term Intervention With Pravastatin in Ischaemic Disease (Lipid) Study Group[15], 1998; Downs et al.[16], 1998) and a current trial is now testing whether the reduction of blood levels that are within what has, mistakenly, been considered to be a "normal" range in economically developed countries will also be generally beneficial (Peto**).

The best must not, however, be allowed to be the enemy of the good and the evidence provided by less well-controlled experiments may sometimes be almost equally compelling. Fletcher and his colleagues, for example followed some 800 men for 8 years measuring their respiratory function every few months (Fletcher et al[17], 1976; Fletcher & Peto[18], 1977). When they found that the rate of decrease of forced expiratory volume decreased with age more rapidly in smokers than in nonsmokers, was not influenced by intercurrent infections, and reverted to the rate in non-smokers when smoking was stopped, there was no real alternative to the conclusion that smoking was the principal cause of chronic obstructive airways disease.

Strong Associations

The associations that have been observed in the past and have been shown to reflect causes of non-infectious disease have, for the most part, been strong, even very strong; but they are in many cases much stronger than has generally been appreciated, because of the phenomenon of regression to the mean.

Regression to the mean

When any measurement is made of a biological characteristic it is always liable to two sorts of error: technical error in the actual measurement and biological error in

* Khaw KT. Cambridge. Personal communication.
** Peto R. Personal communication.

that the values will vary to a greater or lesser extent from hour to hour and day to day. Consequently, if these variables are measured in a population survey, classified in ordered groups, and then remeasured in all or in random samples of each group, the mean value of the lowest group will be found to have risen and that of the highest group to have fallen. The effect of this "regression to the mean" has been demonstrated many times and particularly clearly on cohorts of people whose blood pressure and blood cholesterol have been measured at the start of a study. It was shown by the measurements of blood pressure over the first four years of the Framingham cohort study (Dawber[19], 1980) which were examined by MacMahon et al.[20] (1990) and are summarized in Table 2. The range of the mean diastolic blood pressures from the lowest to the highest group when the men were first examined was 53 mm Hg, two years later it was reduced to 30 mm Hg, and as expected, was much the same after a further two years, regression to the mean having been largely eliminated by the second set of measurements. The true relationships between **usual** blood pressure level and the subsequent mortality from stroke is consequently much stronger than would have been predicted from only the initial observations the increase in risk per unit rise in usual diastolic blood being about 60 per cent greater (MacMahon et al.[20], 1990) - and the same is also true of the relationship with the risk of ischaemic heart disease.

This effect of the regression to the mean is of quite general application, although the size of the effect will naturally vary from one measurement to another. It also explains what has otherwise often been thought to constitute a difference between epidemiological and clinical findings, the clinical effects of treatment for high blood pressure having been apparently greater than those predicted by epidemiological observation, while they are actually very similar when the regression to the mean is taken into account (Collins et al.[21], 1990). Similarly, in the case of blood cholesterol, recognition of the effect of regression to the mean eliminates the difference that has been thought to exist between the findings in cohort studies and the ecological studies of the incidence of ischaemic heart disease in different communities reported by Ancel Keys (Keys et al.[22], 1957) and Richard Peto*.

Weak Associations

The discovery of strong associations, or their demonstration after they have been suggested by clinical observations, has been the most obvious contribution of epidemiology in the last 50 years; but such associations are not necessarily the most important for public health. The demonstration that nasal sinus cancer was several hundred times more common in men employed in the refining of nickel than in the general population (Hill, 1939 cited by Morgan[23], 1958) was immensely important for the

Table 2 - Change in distribution of blood pressures over 4 years: Framingham cohort

Diastolic blood pressure at baseline (mm Hg)	Mean diastolic blood pressure (mm Hg)		
	at baseline	after 2 years	after 4 years
less than 70	63.6	72.7	73.1
70-79	73.8	77.0	77.6
80-89	83.6	83.0	83.9
90-99	93.5	91.2	91.3
100-109	103.4	99.2	98.5
1 10 or more	116.4	102.3	104.7
Range	52.8	29.6	31.6

Source: Dawber[19], 1980; MacMahon et al.[20], 1990.

* Peto R. Personal communication

nickel industry and its employees, but not much ill-health was consequently prevented as the number of employees was small and even this immensely high relative risk did not cause a high absolute risk as the disease was normally so rare. A weak association producing an elevated risk of (say) 10-50 per cent may be much more important, if the agent is prevalent and the disease produced is common. It is also much more difficult to establish and, when established, to show that it reflects causality. Unfortunately, too, what are apparently weak associations are easily produced by chance, when the numbers studied are relatively small, and the report of weak associations that are subsequently shown not to exist has been used to give epidemiology a bad name - though in fact such misleading reports are just as likely to be made by laboratory scientists as by epidemiologists.

Our response as epidemiologists should not be to abandon interest in weak associations. Rather, I suggest, we should learn from the experience of therapeutic medicine, which has found that small improvements in the treatment of common diseases with a substantial fatality, such as myocardial infarction and breast cancer, can save thousands of premature deaths a year and that they can be demonstrated by very large controlled trials or by well conducted meta-analyses of small trials. Very large studies of the size required to give conclusive results are possible in epidemiology, but they require the cooperation of many individual scientists as, for example, has now been obtained in the European Prospective Investigation of Cancer (EPIC), which has been designed primarily to obtain information about the effects of nutrition. Information is being obtained from some 400,000 middle-aged men and women by 22 collaborating teams in 9 European countries (Riboli & Kaaks[24], 1997). Questions are asked about physical activity, sexual maturation and reproductive history, and the consumption of alcohol and tobacco, and country-specific dietary assessment methods are used that are capable of measuring habitual food intake at the individual level in great detail from the responses to standardized questionnaires, which have been calibrated to enable measurements between countries to be compared. The subjects will be followed for at least 10 years, by which time some 23,000 cancers are expected to have occurred.

Another example is the UK study of childhood cancer, which will, I hope, determine whether or not electromagnetic fields in the vicinity of high power electricity cables cause a small risk of childhood leukaemia, something that may not be very important from the point of view of public health, but is very important from the point of view of public concern - at least in Europe and North America. In this study, Great Britain has been divided into ten regions and a leading epidemiologist has organized the investigation of every case of childhood cancer over a four or five year period in conjunction with the local paediatric oncologists, under the guidance of a national steering committee. Altogether some 4500 children with cancer, including nearly 1500 with acute lymphatic leukaemia, and some 9000 matched controls, selected at random from the National Health Service lists, have been studied and measurements made of the magnetic field, radon, and terrestrial gamma ray exposures in a high percentage of their homes. The results will, I hope, be available in a few months.

Collaborative reanalysis

If a sufficiently large study is not practicable – and it may need to be very large we can undertake what I prefer to call a collaborative reanalysis rather than a meta-analysis of small studies, because epidemiological studies, unlike ran-domised controlled trials, are seldom sufficiently similar in detail to permit the common analysis that meta-analysis requires. Two such reanalyses have recently been carried out to assess the risks of breast cancer attributable to the use of steroid contraceptives (Collaborative Group on Hormonal Factors in Breast Cancer[25], 1996) and to the use of hormone replacement therapy (Col-

laborative Group on Hormonal Factors in Breast Cancer[26], 1997).

In the first reanalysis, 66 studies were identified which involved at least 100 women with breast cancer. One investigator declined to cooperate and the raw data for 11 studies could not be recovered. The investigators responsible for the remaining 54 studies met to prepare a common form in which the data could be recorded and subsequently submitted the data in the agreed form to a central group for common analysis. For this purpose, cohort studies were converted into nested case-control studies with four control subjects randomly selected for each woman with breast cancer, after matching for age and survival to the date when the breast cancer was diagnosed. Altogether the reanalysis included 53,000 women with breast cancer and a little over 100,000 controls. The results, which were standardized for study, for centre within each study, parity, age, age at first birth, and age at which risk of conception ceased showed that the use of the drugs did increase the risk of the disease, but only by 7 per cent and, as is shown in Table 3, principally whilst they were being used, when the risk was increased by 24 per cent. After use stopped, the relative risk decreased and had virtually disappeared after 10 years. For discussion of the reasons for concluding that the associations are causal, I must refer you to the original publications. Unexpectedly the results also showed that the breast cancers associated with the use of steroid contraceptives tended to be localised to the breast, as is shown in Table 4, and it is possible that the mortality from the disease was not increased at all. Whether it was or not is now the subject of further enquiry.

In the second study, concerning the use of hormonal replacement therapy, the method of enquiry was similar. Over 52,000 women with breast cancer and 108,000 controls were included and the results were standardized similarly, apart from age at which risk of conception ceased. Since menopausal status, time since menopause, and obesity after the menopause all have major effects on the risk of breast cancer, the main analyses were limited to postmenopausal women and were standardized also for time since menopause and body mass index. The results showed an increased risk of 14 per cent and, for current and recent users, a highly significant trend for increasing risk with increasing duration of use (2p<.0002) as is shown in Table 5. When, however, use had been stopped for 5 years or more the increase almost, if not entirely, disappeared (relative risk 1.07, SE 0.05). As with the use of oral contraceptives, the breast cancers associa-

Table 3 – Risk of breast cancer in users of oral contraceptives

Use of oral combined steroid contraceptives		Risk relative to that 2p in non-users (95% confidence interval)	
Continuing		1.24 (1.15-1.33)	<0.00001
Stopped	1-4 years	1.16 (1.08-1.23)	<0.00001
	5-9 years	1.07 (1.02-1.13)	0.009
	10 or more years	1.01 (0.96-1.05)	-

Source: Collaborative Group on Hormonal Factors in Breast Cancer[25], 1996

Table 4 - Type of breast cancer associated with the use of combined steroid oral contraceptives

Time since last use (years)	Relative risk of breast cancer by time since last use of contraceptives: localised to breast	spread beyond breast	
Never used	1.00 (0.025)-	1.00	(0.028)
Less than 5	1.21 (0.043)	1.09	(0.046)
5-9	1.07 (0.036)	0.96	(0.039)
10 or more	1.04 (0.026)	0.93	(0.028)

*Standard deviation

ted with the therapy tended to be localized to the breast and it remains to be seen whether or not the mortality from breast cancer was also raised.

Balance of Benefit and Risk

The fact that a risk has been demonstrated does not, however, necessarily mean that exposure to the agent causing the risk should always be avoided, for the agent may have compensatory benefits either for the exposed individual or for society as a whole. In either case some quantitative estimates of both the risk and benefit are highly desirable, if not essential, and only epidemiology can provide them. Ideally the answers should be provided by randomised controlled trials and one such trial to assess the overall effects of hormonal replacement therapy, to which I have just referred in relation to the specific risk of breast cancer, has been sponsored by the British Medical Research Council and begun by Professor Meade and his colleagues in London. It will, however, be many years before a useful result is obtained. More usually we have to make do with the results of large cohort studies of people in whom the exposure has not been allocated by the investigator and try to assess the extent to which the participants' selection of exposure may have modified the generalisation of the results, as has been done with exposure to ionizing radiation (United Nations Scientific Committee on the Effects of Atomic Radiation[27], 1994), the risks of which have to be assessed against the benefit of, for example, the use of mammography to detect small breast cancers.

Another, more recent, example relates to the consumption of alcohol. This is particularly notable as, on clinical grounds, the effects of alcohol were long thought to be only detrimental, apart, that is, from the pleasure that many people obtained from drinking it. Gradually, however, over the last few decades, it has come to be recognized that a modicum of alcohol reduces the risk of vascular disease by such a substantial amount that in many countries, where ischaemic heart disease is common, the benefit in middle-aged and elderly people more than compensates for the harmful effect of the increased risks of several different types of cancer, haemorrhagic stroke, cirrhosis of the liver, alcoholic psychosis, and accidents and other trauma. The evidence of overall benefit from amounts of the order of 10 to 20 g ethanol a day is now overwhelming. It cannot be accounted for by bias or confounding and it is biologically plausible, now that we know that ethanol experimentally increases the concentration of high density lipoproteins in the blood, reduces the concentration of fibrinogen, and reduces the aggregability of the platelets (Doll[28], 1997). The findings in the American Cancer Society's study of nearly 500,000 middle-aged and elderly men and women are typical (Thun et al.[29], 1997). A similar beneficial effect from one or two standard drinks a day is also observed in women, despite the fact that alcohol slightly increases the risk of breast cancer (Smith-Warner et al.[30], 1998) because they have (or have had) a lower risk of alcohol induced trauma. In formulating public policy, other social effects have, of course, also to be taken into account; but the balance in regard to its direct medical effects on the individual in countries in which vascular disease is common is clear and could have been demonstrated only by epidemiological research.

Future perspective

In this review of the epidemiology of chronic non-infectious disease, I have emphasized the developments which I suggest point the way to its future contribution, noting particularly the role of controlled trials of prevention and the collaborative reanalysis of the data obtained in many small studies of weak associations. I did not mention, except by implication, the need to collaborate with laboratory workers to measure and record biological markers of exposure to environmental agents or to determine the extent of individual variation in response to the exposure. Such collaboration has become an integral part of modern epidemiology in both case-control and cohort studies, often in the latter

Table 5 – Relative risk of breast cancer associated with use of hormone replacement therapy by duration of use and time since last use

Duration of use (years)	Relative risk: last less than 5 years	Use before diagnosis 5 or more years
0	1.00 (0.021)*	1.00 (0.021)
Less than 1	0.99 (0.085)	0.12 (0.079)
1-4	1.08 (0.060)	1.12 (0.068)
5-9	1.31 (0.079)	0.90 (0.115)
10-14	1.24 (0.108)	0.95 (0.145)
15 or more	1.55 (0.128)	0.95 (0.145)

*Floating standard error.

in the form of establishing blood banks that can serve to provide material for nested case-control studies when members of the cohort develop specific diseases. It was an essential feature of the cohort study that established the relationship of oestradiol to the risk of breast cancer (Thomas et al.[31], 1997) and plays a central part in the European Prospective Investigation of Cancer to which I referred earlier and must become increasingly important, as medical science adjusts to the revolutionary discoveries of molecular biology.

Some proportion of most, if not all, chronic non-infectious diseases will be found to be genetic in origin, in the sense that the disease will occur because of the structure of an individual's DNA at birth and largely irrespective of the conditions of life an individual may normally be expected to encounter, but for all common diseases the proportion is likely to be small. What, I suspect, will be more important from the point of view of public health is the identification of the range of polymorphic enzymes, some 100,000 variants of which have already been discovered, which interact with environmental and behavioural factors to produce greater or lesser degrees of risk. Past experience has, admittedly, not been encouraging. We have known about the variation in risk of gastric cancer, peptic ulcer, and myocardial infarction with variation in the ABO blood group antigens for 40 years without having learnt much from that knowledge about the way these diseases are produced, and we have had innumerable reports of differences in susceptibility to the effect of different carcinogens depending on variation in the efficacy of different enzymes, many of which have not subsequently been borne out. An example of the latter will, I suspect, be the recent claim that smoking helps to protect against breast cancer if the woman is unfortunate enough to have the Br Ca 1 gene (Brunet et al.[32], 1998). It would, however, be pessimistic in the extreme to think that experience with the ABO blood group antigen would be typical, while the unreliability of the reports of differences in susceptibility to different carcinogens is attributable to the overeagerness of investigators to make discoveries based on sub-group analyses of small numbers of cases. When, as has now become possible, reports can be based on the replication of findings in thousands of cases, the situation is changed and epidemiological findings can be expected to provide important clues to the mechanisms by which non-infectious diseases are caused, by demonstrating the importance of different metabolic processes in determining the risk of the disease.

Conclusion

I conclude, as I began, that epidemiology has been the principal tool for unravelling the avoidable causes of chronic non-infectious disease and I see no reason why, in collaboration with laboratory scientists, it should not continue to be so in the future; not only in relation to vascular disease and cancer, to which it has contributed so much to in the past, but also in relation to the chronic diseases of old age – those affecting bone loss, sight, hearing, and memory – which are becoming progressively more important as advances in preventive and curative medicine enable an increasing proportion of the population to live into their 80s and 90s.

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