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SIR MARTIN ROTH

Ageing and the Aged in  
Contemporary Society

INDIANA  
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Distinguished Lecturer Series 3

## **Ageing and the Aged in Contemporary Society**

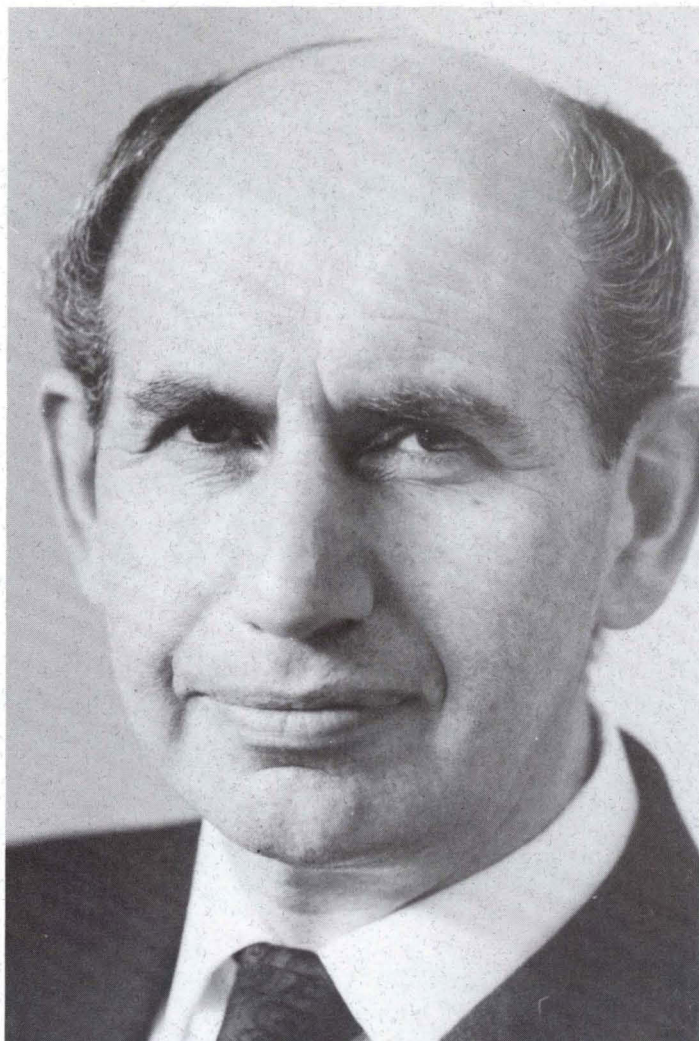
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Fellow  
July 14-25, 1990

Indiana University  
Institute for Advanced Study

Indiana University  
1993





Sir Martin Roth is a Fellow of Trinity College and Professor Emeritus of Psychiatry in the University of Cambridge. His inquiries into depressive and anxiety disorders earned him the First prize of the Anna Monika International Foundation and his research into the classification and origins of mental disorders of the aged the Sandoz Prize of the International Gerontological Association. The Society for Biological Psychiatry has awarded him its Gold Medal and the Max Planck Institute in Munich the Kraepelin Gold Medal. He was elected First President of the Royal College of Psychiatrists and received an Honorary Doctorate of Science from Trinity College, Dublin. In 1972 he was knighted by Queen Elizabeth and in 1979 he was awarded the Gold Florin of the City of Florence.



## SIR MARTIN ROTH

### *Ageing and the Aged in Contemporary Society*<sup>1</sup>

INTRODUCTION: Sir William Osler and his Remedy for the Problems of Ageing

The increase in the number and proportion of aged persons in the population has created mounting concern in the more developed countries in the past few decades and caused their medical and social services to strain at the seams. At the beginning of the century the main factors which contribute to the ageing of populations, namely the declining birth rate and the fall in rates of mortality, were just beginning to exert their effects, to converge and to interact with each other. The problems of ageing were not yet visible on the agenda of social affairs or health services. It was at this time, in 1905, that an eminent physician gave a lecture that aroused widespread indignation. This was William Osler, who was about to leave The Johns Hopkins Medical School and to embark on an illustrious career as Regius Professor of Medicine at Oxford University. He entitled his valedictory lecture after Trollope's novel "The Fixed Period", which had described radical measures widely used among some ancient societies to cope with the problems presented by the aged. They were taken to the rivers at the age of sixty years where they were precipitated into the water and allowed to drown.

Osler confessed to two "harmless obsessions". The first was the "comparative uselessness" of men who had passed the age of 40. He cited the lives of Vesalius, Harvey, Hunter, Virchow, Lister and Koch among others to buttress his view that it was young men who had made every important advance in the science and art of medicine. That the general law implicit in his comments was refuted by the achievement of Michelangelo, Titian, Verdi, Voltaire, Picasso, Freud, Jung, Monet and Bertrand Russell among a multitude of others seems to have escaped his notice.

His second "harmless obsession" concerned the "... uselessness of men above 60 years of age and the incalculable benefit it would be in commercial, political and professional life if, as a matter of course, men stopped work at this age" (see Osler entry in "References" section). He went on to give tentative consideration to another solution for the problems of senescence that faced ageing academics. His view had been shaped by the calamities likely to befall men in the seventh and eighth decades. His scheme entailed retirement from College at the age of 60 for a year of contemplation before a peaceful departure by chloroform.

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<sup>1</sup> Lecture given in the "Distinguished Lecturer Series" under the joint auspices of the Society for Advanced Study and of the Institute for Advanced Study of Indiana University on July 19, 1990.

On reflection, as he was approaching the critical age limit, Osler confessed himself as having grown dubious about the merits of the chloroform solution. He claimed later that he had been joking. But some of his audience took him seriously and the wider public responded with anger and indignation. The verb "to oslerise" (or "to put to death by chloroform") reached the correspondence columns of *The Times*.

For all its exaggeration and onesidedness, Osler's thesis had drawn attention to a process which had at that time hardly begun to unfold. It was to exert a fateful influence upon the structure of societies everywhere. Reductions in birth rates, in infectious diseases and in mortality, improved nutrition, major advances in medical sciences, and ameliorations in health services would in subsequent decades combine to cause rapid expansion in the proportion of the aged in the affluent societies. Similar developments were to follow in the less advanced countries within decades.

It was a process without historical precedent which called for a drastic revision of preconceived ideas about the origins and significance of the ageing of populations. This evolution had not been inflicted on less developed societies by improved living standards and the progress of medical science. The decline in birth rates had been a far more important factor; it provided the only means of averting the imminent crisis created by explosive growth of the world's population. Other measures would make little impression in the absence of an overall diminution in birth rates. And any success achieved would cause populations to age. The increased burden of dependence created by a minority of the aged would be more than offset by the benefits that flowed from the process.

## **Some Demographic Aspects of the Problem of Ageing**

Some figures about the size and range of change in proportions of aged provide a necessary backcloth for an examination of the main biological, social and medical aspects of problems they present, and for their alleviation. In the middle of the nineteenth century average life expectancy in the Western World was around 36 years. In 1985 it was almost 75 years in the United States, nearly 77 in Sweden and between 74 and 75 years in the majority of other European countries (US Department of Commerce, Bureau of the Census 1987). The life expectancy of more than 77 years among the Japanese is the highest in the world.

In every developed society women on the average live longer than men. The disparity exceeds seven years in North America and several European countries but is lower by two to four years in a number of other developed nations. As the single and the widowed are more likely to become institutionalized in old age, a



narrowing of the disparity in life expectation between the sexes would relieve the strain on health and social services.

The proportion of those aged 65 and over is approximately 12% of the entire population in the United States, 15% in the United Kingdom and 1-3% less in other European countries. There will be only modest increases in these proportions in the West in the next twenty years. But there will be large gains in the Soviet Union of between 9 and 13 percentage points.

There has been an increase in the duration of life of some two to four years among those in their eighth decade in developed countries during the period 1960-1980, slightly greater among women (US Bureau of Census 1987). This extension in life span stems from advances in medical science and has brought a whole range of problems in its wake. Where heart attack, stroke or malignant disease usually meant death within a short time, an increasing proportion of individuals in the developed countries survive such events but in a state of chronic ill health or with residual disabilities. Longer survival also means that a higher proportion become candidates for the development of Alzheimer's disease and other forms of progressive mental decline in late life. These disabilities and mental decay in particular, which create a state of total dependence on others in their advanced stages, constitute the heart of the social and medical problems posed by aged persons in our time. The attempts to mitigate them have comprised efforts aimed at defining the biological basis of ageing, at discovering the social factors that aggravate its effects, and at identifying and treating conditions due to specific diseases rather than to the ageing process.

## **Some Biological Theories of Ageing**

Biological theories have their starting point in the fact that many organs and functional systems show an increasing tendency to become impaired and fail with advancing age. There must therefore be some fundamental biological change underlying the simultaneous development of these manifold deficits and disabilities.

Certain rare diseases which give rise to a premature form of ageing appear to provide a strong line of evidence for this view. Werner's syndrome is an example. It is an inherited disease determined by a single autosomal recessive gene. Growth is retarded and there is an elderly appearance of early greying of the hair, cataracts, peripheral vascular disease, often with arterial calcification, and thin atrophic skin. Hypogonadism is common in the male and in women, periods are scanty, irregular, and the menopause occurs early. There is premature osteoporosis. The penis is small and there is testicular atrophy, decreased pubic hair, diminished libido, and sterility. Half of the patients with Werner's syndrome develop maturity-onset diabetes which is "insulin resistant".

For all their interest these models fail to explain the existence of some of the most characteristic disabilities of senescence. The Alzheimer syndrome has some association with the ageing process in that the great majority of cases appear after the age of 65. It gives rise to progressive impairment of higher mental functioning which ultimately reduces the individual to a purely vegetative life. It also causes a marked shortening of the life-span. However, the distinctive form of pathological change associated with this disease is confined to the neuronal cells of the brain. The other tissues are entirely normal. Moreover, even at an advanced stage of the disease the outward appearance of the affected person may be strikingly youthful. That this condition is associated with the ageing process is further illustrated by the fact that after the age of 65-70 years an increasing proportion of individuals whose mental functions remain in most cases intact until the end of life develop changes of Alzheimer-type in their brains. It is only in that minority of individuals in whom the changes accumulate beyond a certain measurable threshold point that progressive decline in mental functioning is initiated (Roth et al 1967, Blessed et al 1968, Roth 1986).

There are other diseases of the Central Nervous System, such as Parkinsonism and specific maladies confined to isolated organs, which are similar to Alzheimer's disease in leaving the greater part of the body intact with the approach of the terminal stages. All such phenomena are difficult to reconcile with general theories of ageing. A general theory of ageing is demanded by the fact that we are increasingly liable as we grow old to succumb to and to die from diseases that we can surmount in the earlier years.

Ageing is due, according to another theory, to errors in cell division owing to the instability of the machinery for protein synthesis (Orgel 1970). The imperfections generated are broadly similar to those that appear when we try to make successive copies of a photograph through a negative. Orgel has suggested that the feedback of protein errors into the process of information transfer from DNA to protein might ultimately give rise to an error catastrophe bringing the function of cells to a halt. There is evidence both in favor and against this theory.

A full review of biological theories of ageing cannot be undertaken here. But one that leans upon evolutionary theory and has a particular relevance for the diseases associated with human ageing will be summarized.

The process of natural selection will ensure that metabolic resources will be preferentially invested to ensure maintenance of the germinal cells. From this point of view the maintenance of the cells of the body beyond the reproductive phases of life would be wasteful. Ageing may therefore be viewed as the process which eliminates the body after it has ceased to be able to contribute through its fertility to the maintenance of the species. This disposal will be assisted by the manner in which selection deals with harmful genes which exert their effects in the form of some disease in early life when they first appear as mutations. As



these early effects threaten the integrity of the organism the age of manifestation of such genes will tend to be postponed to later and later stages of the life span until they are manifest after reproductive life has ceased. Those in whom the defect or disease appears later will have more offspring than those afflicted at an earlier age. Genes that no longer interfere with reproductive efficiency are beyond the reach of natural selection. Such postponement into the post-reproductive period is just as good in evolutionary terms as complete elimination of the genes (Medowar 1957). However, individual members of the species are rendered vulnerable by such postponement to the manifestation of a multitude of harmful genes whose deleterious effects have been postponed down the generations to the evolutionary backwater of later life.

Now if this theory is correct and heredity is the only factor at work it would be expected that the rates of morbidity, mortality and the life expectation of women would be more unfavorable than that of men. For their reproductive life is shorter. However, the sex-specific mortality rates prove to be just the reverse of what would be expected on the basis of the genetic hypothesis outlined. The mortality of males for ischemic heart disease, cerebro-vascular disease and many forms of malignant disease tend to be markedly higher than that of women. Women outlive men in virtually all countries by 5-7 years in North America and a number of European countries. In West Germany and the United States there are twice as many women aged 65 and over than men and the proportion of those among 80 and over is closer to 70% (US Department of Commerce 1987).

These differences may therefore reflect a significant contribution by endogenous and environmental factors. There is indeed a large body of evidence from a number of developed countries that habits such as cigarette smoking, excessive consumption of alcohol, dangerous drugs of addiction, and serious traffic accidents occur at far higher prevalence among men than women. These all have a well established relationship with the commonest causes of mortality in late life. The hopeful inference that emerges is that a number of the commonest causes of premature death often, after years of chronic disablement, may arise from potentially reversible causes open to change through social action, the application and advance of medical science, or both lines of approach.

## **The Social Aspects**

In her remarkable book *On Ageing* Simone de Beauvoir has made the point that the worst deprivation of old age arises from the inhumanity and injustice of the economic order of the most affluent societies. The majority of individuals receive a measure of sustenance and respect only as they are able to contribute through their work to the economic prosperity of the existing order. When no longer useful to this end they are devalued and jettisoned. They lose self-respect and become impoverished. The affluent are protected by nurture and education

and immunized against the worst deprivations of old age through the cultural satisfactions of literature, art, music, contemplation and civilized discourse as well as their wealth. Such satisfactions are denied to the most under-privileged who stand naked and exposed in old age, unable even to contribute with the labor that was the sole source of their dignity. Hence, says de Beauvoir, in order to solve the problem of old age we have to eliminate the existing social and economic order, the grinder and destroyer of men, and strive to enrich the lives of all. No-one who has been involved in works with the aged will fail to acknowledge that the picture drawn by de Beauvoir is in certain respects true to life. But the sufferings and deprivations of old age cannot be attributed entirely to economic causes. The worst maladies of old age, Alzheimer's disease and other forms of dementia are no respecters of class or social station. The princess and peasant woman are equally at risk.

Although economic factors are clearly important it is the strength and character of the familial and social relationships that determine the quality of life of most aged persons in the community. For a long time it had been assumed that the three-generation family had disappeared in the heart of the large cities of the modern industrial world.

But investigations undertaken in the U.S.A., Denmark and Great Britain (Shanas et al 1968) showed that most aged people were in frequent and close contact with children and/or other members of the family. Some enquiries into three generation families brought to life evidence of "objective solidarity" in terms of joint activities, reunions and mutual assistance across the generations (Bengtson and Black 1973). The findings of Townsend in London (1968) demonstrated with particular clarity the reciprocal flow of services between the generations. The young cared for the aged in sickness and in vicissitude, and in return the elderly rendered a whole range of services to their children releasing them for work and social activities in the community by looking after grandchildren. There were all sorts of imponderable contributions the aged made to the life of the family such as the transmission of the skills in home care and child rearing and the fruits of a lifetime of experience in general.

One statistic serves to bring the situation clearly into focus. Townsend calculated that, but for the contribution by families to the care of their elderly and sick, the demand on the Social Welfare and Health Services might have been four to five times as great as it has. This is a daunting statistic. For if only one quarter of this care provided by families to the sick and disabled were to be suddenly transferred to the health and welfare services they would be in dire straits.

These investigations had therefore uncovered networks of social support that probably represent the manner in which the aged had been cared for by families over many generations. Recent investigations have provided an encouraging



picture of sustained intergenerational solidarity in terms of emotional relationships and mutual services (Bengtson 1986). It is clearly of crucial importance that such networks, precious and irreplaceable, should be sustained. Increasing social and geographical mobility may endanger the symbiotic relationships between the aged and the younger members of their families unless appropriate political measures and social action are directed towards conserving them. For it is difficult to conceive of means of support at the disposal of existing Health and Social Welfare services that could provide anything like an adequate substitute for the family.

Observations by Alexander Leaf, a distinguished medical scientist and formerly Professor of Medicine at the Harvard Medical School, of some of the world's oldest people in the foothills of the Caucasus, the mountains of the Hindu Kush and an Andean village in Southern Ecuador merit close attention. One striking figure in all these cultures was the high social status of the aged and their close integration with their families and the community. Each elderly person lived within the family and occupied a privileged and respected position. Diets were largely vegetarian and fat intake was low even in the affluent Caucasus community. Even those in their 90's and over continued to participate in the work of the community, tending sheep, cleaning house, making tea, caring for grandchildren and giving counsel born of their long experience to members of the family and to society as a whole. An important feature was that of the fifteen thousand persons above the age of 80 studied more than 70% remained very active. They died quickly once they lost their useful roles in their societies. The manner and causes of these deaths were unclear but would be of great interest. As Leaf comments in relation to the active roles and respected status of the aged in these cultures: "These are not conditions likely to endure in our mobile 'educated' industrial cultures", in which only a small minority of the elderly have any employment or role.

### **Influences on Quality of Life in Old Age: The Interaction of Psychosocial and Biological Factors**

In communities with a simple agrarian economy such as in those studied by Leaf the mortality rate would have been high prior to senescence. The vigorously active and masterful aged may have been selected for survival into advanced age by their exceptionally robust, strong and stable physical and mental make-up. But in affluent societies where mortality rates have declined steeply in the last fifty years many of those who would have died prematurely a half century ago now enjoy a longer span of life albeit with disabilities and diseases in a substantial proportion. There is therefore a much wider variation in quality and expectation of life among the aged than is the case in economically less developed societies. Little is known about the factors underlying these

differences. But a number of long-term investigations have begun to shed light on the subject. The evidence from such studies may in time make it possible to decrease the striking disparity that exists between those who remain vigorous, active, productive and in full possession of their faculties until they die and those who suffer deterioration and have to endure chronic physical and mental ill health in old age.

One of the most interesting of the long-term enquiries, the Bonn Study of Ageing (BALSA), began in 1965 (Thomae 1976, 1983, Lehr and Thomae 1987). It originally included 220 men and women born in 1890-1895 and 1900-1905. Over a period of fifteen years the sample was assessed at seven measuring points on a set of demographic, social, psychological and medical variables. A thousand items were measured per person and the data was obtained from a weekly testing program, including interviews, intelligence and personality tests and about 200 items from a medical screening program, which included a general health rating expressed as a global score for 'objective health status'.

At the time of the original measurement point in 1965 significant differences were already manifest between those who were to die in the fifteen year period that followed and those who survived until the final examination of the survey. It is of interest that health status as subjectively perceived by the individual showed a highly significant difference between the two groups. However, objective health rating as measured in this relatively healthy sample did not have any predictive value. At this first measurement point those who proved to be non-survivors had slightly lower acuity of hearing but there was no difference in respect of physicians' rating of general health, cardio-vascular insufficiency or of vision and mobility. But during interviews regarding the life situation and the daily activities and experiences of the persons in the survey, survivors had expressed more concern about their health, namely "more actively coping styles". In contrast the non-survivors reacted in a more depressive or aggressive, resentful manner to their health problems. Although the survivors showed more concern about their health their feelings about it were more positive and they obtained significantly higher scores for subjective health. It is noteworthy that it was subjective health status and not the global score for 'objective health' that best predicted longevity. This feeling of subjective well-being was not correlated to mental test scores in contrast to the objective health status assessed by the physician, which did correlate with these scores. Those who perceived themselves as more healthy were rated in 1965 as more active, as having a more positive and better mood, as being more secure and more responsive and having a better future perspective.

The group of survivors had higher verbal scores of intelligence tests and better psycho-motor performance. Although the two groups did not differ significantly in terms of social participation at the outset in 1965, the survivors had more





Alexej von Jawlensky, *The Old Man*, 1912

By courtesy of the Indiana University Art Museum

extra-familial social role activities and showed an increase in these scores during the period of observation.

The interpretation of the findings has to be undertaken with caution. As Ursula Lehr (1989) has pointed out there is a well established contribution by genetic and biological factors to longevity. Personality development and experiences in the formative years, education, familial and social background had also very likely contributed substantially to shape the outlook, behavior patterns and life-long attitudes of individuals in their study.

It is worthwhile setting such constitutional elements aside, however, in attempts to define more sharply potentially remediable factors that might have operated to determine disparities in quality and duration of life in this inquiry. The factors worthy of particularly close attention were affective or emotional characteristics that discriminated the long-lived from the short-lived persons in the cohort. Those who were pursuing satisfying patterns of life might also have differed from those set in inactive and inflexible life styles in respect of similar emotional factors.

The possibility that survivors just happened to be more physically healthy than non-survivors is difficult to reconcile with the finding that objective health status as assessed by physicians failed to differentiate between the groups. On the other hand measures of subjective well-being (into which mood must enter) had significant correlations with longevity as well as quality of life. A similar finding that subjective feelings of health or illness were better predictors of mortality than assessments of physical health emerged in the Newcastle epidemiological investigation of the aged (*Kay and Bergmann 1966*).

The results of the Bonn study showed that the 'short-lived' persons differed from 'long-lived' ones in terms of lower degree of satisfaction with life situation, weaker feeling of being 'needed', more 'negative mood.' The short-lived were also more markedly affected by 'reduction in range of social contacts.' This underscored the significance of emotional factors that were not correlated with biological indices of physical health. As we will see in a later section there is evidence from other sources that emotional state and depression of mood in particular may be capable of making an independent contribution not only to quality of life but to life expectation.

## **Medicine in Old Age With Special Reference to Depressive Illness**

The manner in which old age is manifest in individuals can be powerfully influenced, as outlined in the previous section, by psychosocial factors, some of them of a potentially remediable kind. The history of geriatric medicine and psychiatry provides even more striking examples of conditions in old age previously regarded as expressions of biological ageing which have been proved



in recent years to stem from specific illnesses that could be effectively treated. One reason for the failure to identify medical conditions in old age in the past has been that the symptoms and signs may be "silent". Heart attacks or myocardial infarction which usually cause intense pain in the chest may be present with little or no pain. Pneumonia may be associated with little rise in temperature. Over-activity of the thyroid gland or hyperthyroidism may develop without such characteristic signs as protrusion of the eyes and enlargement of the thyroid gland. A combination of depression, apathy and an irregularity of the pulse may be the main features. Illnesses may also go unnoticed because certain conditions such as pulmonary tuberculosis and sub-acute bacterial endocarditis, which in the past were largely confined to young persons, are liable to develop insidiously in old age. Though potentially lethal they respond well to treatment if diagnosed in time.

In the field of mental health, progress has been made along similar lines in identifying conditions that had formerly been attributed to age-related degeneration in the brain. A severe form of schizophrenic illness which appears in senescence was attributed to senile cerebral degeneration partly because it proved incurable. It is now known to respond to treatment more favorably than the corresponding disorder of earlier life.

Depressive illness is the most common of the conditions that have come in the last few decades to be recognized as illnesses rather than among the characteristic features of the mental state of old people. They are the commonest form of mental suffering found among aged persons in the community. Depression, often with a blend of anxiety, sufficiently severe to incapacitate old persons in pursuit of their every day lives was found in 14% of those aged 65 and over in a community sample (Kay et al 1970). Similar figures have emerged from other studies. The lower figures reported in some studies probably resulted from different methods of assessment.

The features of the commonest forms of depression in the aged bear some resemblance to milder and less disabling mood changes common among normal old people. Those with depressive illness are preoccupied with feelings of regret or ideas of guilt or remorse about the past: a sense of emptiness, of futility about the present and a helpless pessimism about what is to come in the years that remain. Sleep is impaired and waking in the early morning is common. Appetite and energy decline and so does mental and physical activity. Nothing in life arouses pleasure or satisfaction and the blunting of feelings of love and affection causes distress. Sexual desire and satisfaction have waned or vanished. Memory and cognition may be impaired in a patchy and inconsistent way and lead to an erroneous diagnosis of dementia, a disorder which is untreatable at present. By the seventies many women are widowed and feel desolate and some cry out for the support of others. Physical pain and discomfort are anxiously over-

interpreted even by those without concomitant physical illness as signaling the beginning of the end. The depressions are often non-severe but suicidal ideas may be present and there is a considerable risk of consummated suicide in such cases.

In studies of community samples in Newcastle (*Kay et al 1964a and 1964b*) women predominated among those judged to have a depressive illness. A history of previous psychiatric disorder, evidence of longstanding maladjustment and difficulties in interpersonal relationships were usually elicited. Other features were low economic status, few friendships or social contacts, a history of physical ill health and a range of long-established and well-ingrained attitudes comprising feelings of chronic dissatisfaction, loneliness and tendencies toward self-commiseration. They complained a great deal in importunate ways of being alone and neglected. But investigations with objective indices showed them not to be isolated in terms of the number of visits from relatives and friends. In contrast those who were found to be truly isolated complained of loneliness much less often; the isolation had been a self-chosen and self-imposed style of life in a high proportion. Despite the long history of maladjustment and psychiatric disorder, pharmacological and psychological treatment will often alleviate the distress of these elderly patients and transform the quality of their lives. We have learned that while there is depression there is hope.

## **The Association with Chronic Physical Illness**

I should like to take up the important association first defined more than two decades ago between depressive illness and somatic disease. Depressed patients both in hospital and in community samples were found to exhibit a significant excess of chronic physical illness when compared with control subjects. This excess was confined to men. Although women in the samples investigated were often physically ill the prevalence of such illness was not greater than found in women without psychiatric disorder. There was a significant increase in mortality rate as compared with normal controls but this was also confined to male depressives.

This excess of deaths could have been due to the associated physical illness. But standardized assessment of their physical health status showed them not to differ in this respect from aged men without mental disorder. It was interesting, however, that depressed persons felt more ill subjectively than control subjects without depression in the same community sample. This finding was reminiscent of that reported by Ursula Lehr on the strength of her comparison of "short-lived" and "long-lived" subjects in the Bonn study. Also, in her sample the subject feeling of ill health was a better predictor of subsequent duration of



life than the findings that had been recorded in the course of medical examination. Hence the possibility arises that depression makes an independent contribution to diminished life expectation among the aged and in men in particular.

That the complication of chronic physical disease by depressive illness adversely affects the duration of life is suggested by a number of studies (Petty & Noyes 1981, Roth 1984). Depression has been shown to exert an adverse influence on the prognosis of ischemic heart disease (Lown 1980) and on duration of life in malignant disease. These facts are of considerable importance for every branch of the practice of medicine

The association between depression, chronic physical disease and increased mortality is illustrated with particular clarity by studies of consummated suicide. In an early study Sainsbury (1955) found 14 cases of cancer among 390 consummated suicides drawn from all age groups. As in the majority of inquiries into suicide in every part of the world there was a predominance of males and of persons in middle and late life. The incidence of cancer was twenty times greater than that found in the general population. Similar findings were recorded in an Australian study. Barraclough (1971) has reported a significantly greater number of malignant growths at post-mortem examination in elderly patients who had committed suicide than closely matched control subjects.

The typical features of these patients were well exemplified by a 93-year old widower who had lived alone for fifteen years following the death of his wife. He enjoyed his independence and had many friends by whom he was liked and respected. Some weeks before he suffocated himself by placing his head in a plastic bag, he began to complain of anxiety and said he was "going out of his mind". He thought about poverty — became increasingly miserable, solitary and agitated. At post-mortem a gastric carcinoma with extensive spread was found. It had gone undetected in life: another case of "silent" but fatal physical disease.

### **What is the Significance of the Association?**

In the association between male sex, depressive illness with an excessive prevalence of chronic illness or disability, and suicide, the direction of causality is difficult to determine. Biological factors may be the main causal agents but there is evidence that psychodynamic factors also make a significant contribution. There is a definable group of men without a previous history of emotional illness who are successful in their careers and emotionally stable until middle or late life. They then suffer the first physical illness which carries some threat of chronic aftermath. This is trivial in some cases, more serious in others. In either case it appears to overwhelm emotional equilibrium. The coping mechanism will be found to have been equal in the past to dealing with other forms of stress and challenge. But exploration of the past history usually

provides some insight into the reasons for the menacing significance of physical disablement. Some will have had a limited physical disability such as a slight limp or a residual defect since an illness in childhood. Or more subtle causes may have created the Achilles heel in the personality. Overcompensation in the form of heavy investment of effort and time in the cultivation of physical strength and fitness frequently follows.

A parody of this kind of disorder is provided by the phenomenon of "Athlete's Neurosis" investigated by Little (1969). In more than a third of his 72 neurotic male patients, self-esteem had been heavily invested in health, physical prowess, stamina, and fitness. An excellent health record was a source of pride and the bedrock of feelings of security. The resulting syndrome was predominantly depressive with a coloring anxiety or hypochondriacal self-scrutiny with frequent counts of the pulse or measurements of blood pressure. In their premorbid state these patients had often been cheerful and outgoing and shown a non-neurotic profile.

In such men even a non-severe chronic illness (often the first illness) augurs loss of strength and virility, and of prestige and mastery. Women's experience of physical pain and discomfort is different from that of men. Menstruation, childbirth and their physical and emotional concomitants familiarize them early in life with the fragility and imperfection of the physical constitution. Physical strength and endurance, athletic fitness and dominance have in the past rarely figured prominently in the self image of women; minor illnesses or defects that do not disfigure were less of a threat to self esteem. Such psychological dimensions have to be explored and handled with sensitivity in the management of the depressions of elderly persons.

### **An Illustrative Case**

During the greater part of his adult life Ernest Hemingway was to be powerfully attracted to scenes of violence and combat. Hunting, bullfighting and other blood sports excited him and he was swift to rush to the scene of wars in progress. The courage of the warrior, hunter and bull-fighter constituted for him the essence of the manly virtues, and the scenes of carnage in which he had been involved were incorporated into his novels. He was proud to the point of vainglory of his sexual conquests saying that he had slept with all the numerous women who had attracted him, as well as others who failed to attain that special standard of excellence. However, the emotional relationships between men and women in his novels reflect more complexity and conflict in his sexual nature than he openly conveyed. Women dominate and emasculate their lovers like the female mantis who is sometimes said to devour her partner in the act of mating.

In *For Whom the Bell Tolls* the hero begs his mistress to have an abortion lest the child born should prove a rival and compete for her love. It is the fear and



hatred rather than the love of women that predominates. In middle life hypertension, liver disease and chronic alcoholism compounded Hemingway's personal problems, and emotional decompensation followed. For some years he suffered from a depressive illness with a strong coloring of delusions, of persecution and harassment. Early one morning he killed himself with a double-barreled shotgun. The great writer who had extolled courage above all other manly virtues had lost the courage to continue living. But it is clear that his depression had prominent endogenous and psychotic features. His father (also called "Papa" Hemingway) had committed suicide in similar fashion. Mental illness had probably evolved from an interaction between psychodynamic and biologically determined endogenous factors. The depression that complicates a substantial proportion of patients' suffering from carcinoma has been shown to respond favorably to treatment (Costa *et al* 1985) and similar findings have been recorded in patients with other chronic forms of physical illness. There are also observations to suggest that treatment of the concomitant depression in such cases prolongs life expectation. It is known that Hemingway was under the care of psychiatrists towards the end of his life. But too little information has come to light about the treatment he received and the response he made to permit a judgement as to whether, as in other cases, depressive and other symptoms could have been regarded as a sign of hope at an early stage in their development.

### **Progressive Mental Deterioration in Later Life**

A slow and circumscribed decline in the intellectual faculties occurs in the course of chronological ageing. By the sixties or earlier the ability to acquire new knowledge is somewhat impaired and recently acquired information has become more difficult to retain, recall and retrieve with precision. Intellectual functions are liable to grow more inflexible and the capacity for original creative thinking becomes blunted. It is important to stress that a substantial number of persons appear to be exempt from such age-related deterioration. And the great majority is not seriously incapacitated by it. Most old persons retain sufficient mental skill and agility to conduct their every day lives. A substantial proportion are capable of remaining in some form of occupation and the ability to derive satisfaction and stimulus from hobbies, from reading, music and the visual arts, and emotional fulfillment from human relationships usually survives intact.

However, in a minority of some 10-12% of those aged 75 years and over progressive decline is manifest. The capacity to remember remote as well as recent happenings is impaired. Even simple tasks cannot be learned, the skills required for independent life are lost, speech loses its cohesion and ultimately becomes an incoherent jumble of words and sounds. The emotions are coarsened and blunted and the distinctive features of the individual's personality are

obliterated. Towards the end he is incontinent, helpless, and capable only of a vegetative existence. At this stage he is oblivious of the change that has occurred in him, cannot recognize his relatives and may even be bewildered by the apparition that confronts him when he stares into the mirror. These dementias of which the commonest forms are Alzheimer's disease and the dementia due to multiple strokes (multi-infarct dementia) are the most dreaded and terrible afflictions of late life.

The fact that the great majority of persons who survive into advanced age with their intellects and personalities intact, while a minority are wholly bereft of their faculties fifteen to twenty years earlier, deserves our closest attention. Perhaps the most powerful stimulus to research in relation to the dementias of late life is provided by the vast disparity between a Michelangelo, Verdi, Bertrand Russell, Freud, Casals and the multitude of the less celebrated who remain mentally vigorous and creative into their eighties or later, and the presenile cases of Alzheimer's disease reduced to a vegetative existence in their sixties. There must be some specific causes underlying such different states. And scientific research should enable us to narrow the gap between them.

The mild impairments which characterize normal ageing have been shown to have some relationship to and some continuity with gravely incapacitating forms of pathological mental ageing. But there are also discontinuities, qualitative differences between mental disorders such as Alzheimer's disease and the slow and limited impairment of the intellect which we find in most elderly people. This situation is analogous to that which obtains in relation to emotional life in old age. Feelings of sadness and grief are common in bereavement, in response to physical illness and as concomitants of the loss of role and common desolation of old age. But there are also extreme forms of such emotional states in which a state of inconsolable sadness afflicts the person for long periods for reasons difficult to define. A minority are determined to end their lives and succeed in doing so. Qualitative differences of a biological nature separate these persons from those with ordinary sadness in late life. And we have fortunately learned ways of controlling these morbid depressions with the aid of medical and psychological treatments.

A similar relationship is found between ordinary forgetfulness in the senescence at one extreme and the condition that is Alzheimer's disease (AD) at the other, except for our failure to discover any effective treatment for AD. Investigations of the changes to be found in the brain of patients with Alzheimer's disease and brains of subjects whose mental functioning is relatively intact have shown AD to be a gross exaggeration or caricature of the changes to be observed in normal aged persons. But the extremity of the deviation from normal ageing of the brain manifest in AD has introduced some differences in brain structure and chemistry that are qualitative:



1. Each of the three main forms of structural change which characterize the brains of patients with AD: the neurofibrillary tangles (NFT), plaques and granulo-vacuolo degeneration are found in the brains of well preserved normal elderly subjects in a lesser degree of severity and more limited distribution.
2. There are highly significant correlations between the scores on tests of intellectual impairment and personality deterioration recorded during life, and the quantitative amount of pathological change as estimated in the cerebral cortex or mantle after death. In other words, the greater the severity of the intellectual impairment and personality deterioration during life the larger the number, the more dense the concentration of the Alzheimer changes in different parts of the cortex.
3. There is a clearly defined threshold effect. Until the accumulation of plaques and tangles is found to have reached a certain level of density in the brain, mental functioning remains within relatively normal limits during life. Those in whom this threshold (as defined by the presence of an average of more than twelve plaques or an excessive number of tangles in a certain region per microscopic field) is exceeded have been found during life to have been indubitably demented (*Roth et al 1967, Blessed et al 1968, Tomlinson et al 1970, Roth 1971*).
4. The structural changes prominent in the brains of patients with Alzheimer's disease cannot be insignificant by-products of the main causal agents in the condition as has been suggested by some observers. For it has been established that the greater the number of tangles and plaques in a certain area of cortex, the smaller the number of neurons in identical regions of the opposite hemisphere of the brain.

Neuronal damage as reflected by the Alzheimer changes may proceed up to a certain point without resulting in dementia, probably because they do not exceed the brain's reserve capacity. Beyond this threshold the accumulation of Alzheimer changes is associated with progressive intellectual and personality deterioration. The structural changes have also been shown to be correlated with the concentration of the enzyme concerned with the synthesis manufacture of the neuro-transmitter acetylcholine. This enzyme (choline acetyl transferase) is the most consistent and widespread neuro-chemical deficit found in the brains of patients suffering from Alzheimer's disease. However, for the present, all attempts to remedy this deficit by pharmacological treatments have failed to alleviate the symptoms of the condition.

Comparison and contrast of the clinical picture and the pathological changes in the brain of patients with the late-onset, benign form of Alzheimer's disease, the more fulminant early version, and normal mentally intact elderly persons, have defined the neurofibrillary tangle (NFT) as being probably the most specific

pathological characteristic of the process of degeneration in AD (*Roth & Wischik 1985, Roth 1986*). Attempts have therefore been made in recent years to define molecular structure of the paired helical filaments (PHF). Both the NFT's and the swollen and deformed nerve terminals, which are located in the dense coronal network that surrounds the cores of the senile plaque, are filled with these filaments.

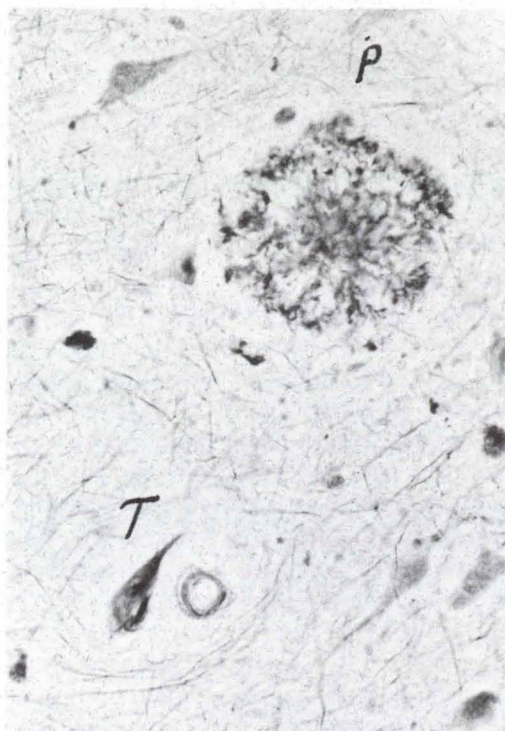
The research which we have undertaken in collaboration with the Laboratory of Molecular Biology in Cambridge has also been directed towards discovering the molecular structure of the proteins of which the paired helical filament was constituted. The structural and immunological methods of molecular biology have been utilized in attempts to shed light on the PHF role in the destruction of neurons in the brain. Recent results have provided us with some insight into some of the steps in the process that causes progressive depletion of the brain's neuronal population.

I am limited here to giving an outline of one group of inquiries among a multitude of studies in different parts of the world. A number of these may well prove to have been more fruitful than our own. But an overview would be impossible in a lecture such as this and I am therefore attempting to sketch in outline the one with which I am most familiar: that in which my colleagues and I are engaged in Cambridge.

Structurally the PHF proved to be constituted of a double helical stack of sub-units formed into a ribbon and twisted into a left-handed double helix (*Wischik et al 1985, Crowther & Wischik 1985*). Recent investigations have shown that the central portion of the amino acid sequence of a protein called the Tau protein forms an integral part of the paired helical filament (*Wischik et al. 1988b*). The remaining portions of the Tau molecule are located in the fuzzy coat that surrounds the inner core of the PHF with its double helical structure. One complete molecule of Tau protein appears to be present in each sub-unit of the paired helical filament and constitutes about 26% of its total mass.

One important function of the Tau protein is to promote the assembly of an important component of the cytoskeleton, the microtubule, which is also made of a specific protein. Microtubules are involved in the transport within nerve cells of various substances indispensable for maintaining the structural integrity and function of these cells. The effect of immobilization of a large proportion of a total pool of this protein in the nerve cells that contain tangles means that there may be insufficient amounts of Tau protein available for maintaining microtubules in their normal state, thus resulting in interference with transport and ultimately in the destruction of neurons. Abnormalities to the structure of microtubules may be observed in cells that do not contain tangles. Hence the events in tangle-containing cells have repercussions for the functioning of those





Paired helical filament

neurons in the brains of patients with the Alzheimer syndrome, which appear to be superficially intact when examined by light microscopy.

These investigations have traced the course of events associated with the degeneration of tangles, the changes they bring about in the shape and appearance of neurons, and the extrusion of tangles from brain cells to the space outside them. A range of antibodies prepared against different parts of the amino acid sequence of the Tau protein and of the beta amyloid protein (which has been prominent in some theories of causation) has helped to trace the course of events in the degenerative process underlying Alzheimer's disease. Neurons which have tangles within their cell bodies have intact membranes and often a visible nucleus. They constitute a quite distinct population from those neurons in which the tangles are in the process of becoming extracellular.

The former neurons have an elegant elliptical shape while the latter neurons are wider with irregular, bulging outlines and a fragmenting appearance. Portions of tangle can be seen to be protruding through the ruptured cell membrane into extracellular space in some cases. The differences between the

two types of neuron in respect of interactions with antibodies show the extracellular tangles to be undergoing dissolution by protein solvents. In the neurons with intact boundaries containing intracellular tangles this proteolysis appears to be in its earliest stages as judged by interactions with different portions of the amino-acid sequence of tau and beta amyloid proteins. In these changes we appear to be witnessing successive steps in the process by which neurons undergo destruction in Alzheimer's disease (Bondareff et al. 1990). This disruption of tangle-bearing neurons is probably the fundamental change in the causation of Alzheimer's disease.

But some investigators believe that it is the protein which is to be found in the core of the senile plaque and in the form of amorphous deposits in the cerebral cortex in patients with Alzheimer's disease that constitutes the first step towards the final common part that culminates in the destruction of neurons. This protein is known as the beta amyloid protein. The gene that codes for the precursor molecule of this protein has been mapped to chromosome 21. Located on the same chromosome there is another gene which is responsible for the hereditary transmission of certain early onset forms of Alzheimer's disease from one generation to the next. But this has proved to be at some distance from the gene that codes for the amyloid protein precursor so that there is no necessary functional relationship between the two. Moreover, deposits of amyloid are common among well preserved non-demented persons aged 70 and over. And only a very small minority of such persons proceed to develop Alzheimer's disease. The remainder remain mentally intact to the end of their lives. Amyloid deposits also occur in certain regions of the brain where there is no evidence of neuronal damage nor any neurological deficits that can have arisen from these deposits of amyloid. It appears doubtful whether amyloid or any sub-fractions of the protein are damaging or destructive to neuronal cells.

Quite recently several groups of investigators have adduced evidence that has mapped a gene for familial Alzheimer's disease to a locus on chromosome 14. The gene appears to be responsible for the commonest forms of early onset of Alzheimer's disease in which heredity plays a major role (Schellenberg et al 1992). When the product of this gene has been discovered it may provide some clue to the nature of the relationship between the deposition of amyloid in the brain and the process whereby paired helical filaments are caused to accumulate and to cause destruction of pyramidal neurons in the cerebral cortex. Further successes in defining and understanding the steps in the process that leads to fall-out of the cells of the brain's highest centres may enable us to develop treatments that slow down or arrest the degeneration of the brain. We will then come within sight of alleviating the worst and most widely feared scourge of the later years.



## Concluding Remarks

Despite the relentless advance of the degenerative process no two cases of AD are exactly alike. Care has to be tailored to the needs of each patient. In those previously gifted musically, the capacity to play an instrument or to derive pleasure from music survives mysteriously in certain patients until an advanced stage. In others quite different residual talents persist for a time. Efforts have therefore to be made to stimulate and conserve such remnants of the personality, for they help to keep emotions alive.

The well-being of the carers of AD patients must not be forgotten. They are often entering old age themselves and endure onerous stress. Their health requires sensitive and vigilant attention.

A more general question condenses the purpose and meaning with which the later years of life should be endowed. Is old age to be an empty interregnum between retirement and death or has it a positive function? I believe the latter is the case.

There is much to be learned from the models of the families delineated by a number of enquiries in which a reciprocal flow of services continues between the aged and their second and third generation relatives. The communities in the foothills of Kashmir and the Caucasus studied by Leaf, with the active involvement, dignity and service of the aged as grandparents, counsellors and transmitters of the tradition and of the accumulated wisdom of past generations, are relevant for the culture of industrialized societies. The dementias represent the darkest chapter in the medicine and sociology of old age. But the advances of recent years suggest that, provided adequate effort and resources are invested, methods of alleviating these conditions may be discovered.

Some observers have discussed the ageing of the population as if it were certain to prove an unmitigated disaster. I do not accept this verdict. Older societies move more slowly, are more influenced by the experience of the past and less given to innovation than younger ones. The enterprises of the imagination do not come so easily to them. But the ageing societies of the modern world need not repeat the errors of the ancient gerontocracies.

The healthy aged tend to be more dispassionate and longsighted, less doctrinaire, steadier in nerve and more generous in spirit. Our societies need a period of respite and consolidation. They have to take stock of the enormous problems which rapid industrialization and the concomitant social changes have bequeathed to us. Less rapid change would doubtless carry disadvantages but might on balance prove a blessing in disguise. We require a moratorium, a breathing space, in which to deal with the threat posed by overpopulation, environmental pollution, racial conflict, dwindling energy resources and the dire threat posed to the very existence of the human race by nuclear weapons. In a population with a high proportion of the old, there would be less

unemployment, less crime, violence and alcoholism, less drug dependence, sexual turmoil and social unrest. A respite from the high fever of youth-dominated cultures might enable us to clear our vision of the world of those wishful fantasies backed by threats of violence without discarding our ideals or values. It might enable us to extract some of the lessons taught by the most calamitous and bloody years in the history of the human race with two major wars, three revolutions that have radically changed the political complexion of the world, and others too numerous to be counted.

A society with a higher proportion of the old would have less predatory violence and crime and more altruism. Violent crimes are a phenomenon of youth, altruism is a feature of old age and the suicides which show peak prevalence in late life, in virtually every country in the world, are merely parodies of it. The world could do with more of the wisdom and the selflessness of old age.

I will end with a quotation from an ageing philosopher and mathematician: "An individual human existence should be like a river - small at first, narrowly contained within its banks, and rushing passionately past boulders and waterfalls. Gradually the river grows wider, the banks recede, the waters flow more quietly and in the end without any visible breadth, they become merged in the sea and painlessly lose their individual being. A man who in old age sees his life in this way will not suffer from the fear of death since the things he cares for will continue." The author of these words was Bertrand Russell.





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Corrigendum for caption to illustration on page 19:

Tangle (T) within a neuron and a plaque (P) in the brain of a patient with AD. The T is made up of phf and isolated phf are also found around the plaque core.