Nutritional Pathogenesis and Prevention of Stroke

Y. Yamori\textsuperscript{a}, K. Ikeda\textsuperscript{a,b}, M. Tagami\textsuperscript{a,c}, K. Yamagata\textsuperscript{a,d} and Y. Nara\textsuperscript{a,d}

\textsuperscript{a}WHO Collaborating Center for Research on Primary Prevention of Cardiovascular Diseases, and \textsuperscript{b}Otsuka Department of International Preventive Nutritional Medicine, Kyoto; \textsuperscript{c}Graduate School of Human and Environmental Studies, Kyoto University, Kyoto, and Sanraku Hospital, Tokyo, \textsuperscript{d}Division of Life Science, Graduate School of Integrale Science and Art, University of East Asia, Shimonoseki, Japan

Introduction

The importance of nutrition in the pathogenesis and prevention of stroke was first experimentally proven by our works on stroke-prone spontaneously hypertensive rats (SHIRSP) [1–3]. These experimental studies clearly demonstrated that stroke caused by nutritional disturbance was preventable by nutritional improvement. Further, our worldwide epidemiological studies confirmed the applicability of our experimental findings to humans. Lastly, our recent studies demonstrated oxidative stress caused neuronal death in cultured neurons \textit{in vitro} and our animal model of stroke \textit{in vivo} and therefore, antioxidants could prevent stroke and hopefully also cerebrovascular dementia.

The Japanese are now enjoying the longest average life expectancy in the world and the longevity was achieved during the latter half of the 20th century. The most rapid increase of the elderly populations was observed in Japan among developed countries for the last five decades.

The prolongation of the average life span now reaching 77 and 84 in males and females respectively, is partly ascribed to the rapid reduction of age-adjusted stroke mortality rate observed in both genders in Japan since 1950. This rapid reduction appears to be related with the improvement of nutritional conditions in the past; protein and fat intakes have increased from very low levels to a moderately high level, while salt consumption used to be very high gradually decreased down to 12–13 g/day on average.
Nutritional Pathogenesis and Prevention of Stroke

The rapidly increased average life expectancy is statistically closely related to increases in protein intake and also in the height of school children, that is, general nutritional improvement in Japan.

**Experimental Studies on the Nutritional Pathogenesis of Stroke**

The importance of nutrition for preventing stroke was first confirmed in our experimental model for stroke. Spontaneously hypertensive rats (SHR) and SHRSP were established at our laboratory in 1963 and 1974 respectively, and have been useful for studies on hypertension and its major complication, stroke in the world. Particularly, SHRSP maintained by us quickly develop severe hypertension and hemorrhagic and/or thrombotic stroke without exception at latest at the age of 24 weeks.

Our pathological studies on stroke in SHRSP and also in human autopsy cases of stroke in Japan have facilitated the understanding of the pathological process of stroke caused by so-called small-vessel diseases.

Typical basic hypertensive vascular changes in both hemorrhagic and ischemic strokes in SHRSP and also in men are arterionecrosis or fibrinoid necrosis of small perforating arteries in the brain [4]. There are predilection sites of stroke such as basal ganglia and subcortical regions in hypertensive patients as well as in SHRSP [5]. These predilection sites were confirmed to have common angioarchitectural characteristics.

These perforating arteries branch off from the cortical artery rectangularly or recurrently, and blood flow into these perforating arteries is decreased rheologically in hypertension, and the proportion of erythrocytes carrying oxygen in the blood stream into perforating arteries is reduced as well. We first demonstrated the reduction of regional cerebral blood flow before the development of stroke in SHRSP [6]. Moreover, these perforating arteries have no _vasa vasorum_, that is, capillaries surrounding vasculature to feed arterial wall from outside.

Nutritional supply to vascular smooth muscle cells (VSMC) through endothelial cell layers is severely limited because of the blood-brain barrier. Mainly glucose is permeable but amino acid supply through the blood-brain barrier is limited and may not be enough for feeding VSMC when blood flow is reduced in hypertension.

Electron microscopically, focal necrosis of VSMC starts always at the outer layer of the media, the farthest part from the arterial lumen in the intracerebral arteries, and then degeneration and necrosis spread over the whole layer of the media. This morphological observation indicates that the basic process in cerebrovascular damage in hypertension is due to local nutritional disturbance.

A similar process was proven to occur in humans. In autopsy cases of cerebral hemorrhage, the intracerebral arterial wall appeared thickened.
However, monoclonal antibody against VSMC actin successfully demonstrated that intact VSMC with actin remained only at the inner layer and the outer layer was totally replaced with collagen [7]. We further demonstrated macrophages were actively involved in the process of arterionecrosis by using monoclonal antibody against human alveolar macrophages [7].

Therefore, the importance of nutrition in the mechanism of stroke can be summarized as follows, based on our experimental findings in SHRSP and also on our immunohistochemical findings on autopsied stroke cases in Japan. Hypertension induces reduction of cerebral blood flow which aggravates local nutritional disturbance in the VSMC of small intracerebral arteries and accelerates degeneration or necrosis at the outer layer of the media. When macrophages invade into necrotized vascular wall from outside as scavenger cells, their fibroblast-stimulating factor accelerates collagen synthesis and process of arteriosclerosis.

When macrophages invade through the endothelial cell layer and destroy the blood brain-barrier, fibrin deposits in arterial walls and results in cerebral hemorrhage when the wall is ruptured, or in cerebral infarction when the vascular lumen is occluded with thrombosis. Therefore, the basic process of vascular lesions in stroke is regarded as VSMC degeneration and necrosis of intracerebral arteries caused by local nutritional disturbance.

This concept of the importance of nutrition in the pathogenesis of stroke is strongly supported by our previous observation of the preventive effect of nutrition on stroke in SHRSP.

**Experimental Studies on the Nutritional Prevention of Stroke**

SHRSP given low protein-excess salt diet quickly develop severe hypertension and died of stroke within a shorter period. However, in SHRSP given high protein-excess salt diet the development of hypertension was attenuated and the incidence of stroke was remarkably reduced [8]. Without excess salt, high protein diet feeding delayed the development of severe hypertension and prevented stroke more effectively than low protein diet. The results indicate high protein diet prepared from fish meat counteracts the adverse effect of salt and the hypertension mechanism of SHRSP.

On the other hand, hypertension and stroke are also genetically controlled in SHRSP. We obtained F1 and F2 offspring from crosses between SHRSP and WKY and have been analyzing gene loci related to hypertension, salt-sensitive hypertension and stroke by linkage analysis [9, 10]. So far, we detected loci on rat chromosomes 1, 3, 4 and 10, which were linked with blood pressure (BP) elevation, and a locus on chromosome 4, which is linked with stroke but this region has no influence on BP [10].

We further analyzed the contribution of each gene locus to the BP elevation in the F2 offspring from 5 weeks of age to 1 year, and the effect of excess
Salt intake, 1% salt in drinking water was observed from 5 to 12 months. The locus on chromosome 1 appears to contribute to the early development of hypertension and the locus on chromosome 10 is involved in the BP rise due to the gene-environmental interaction after salt-loading [11].

Salt-induced rise in BP is not only genetically determined but also greatly affected by other nutritional factors such as protein, K, Ca, Mg and dietary fiber intakes. The supplementation of dietary fibers, psyllium which absorbs Na in the intestine, for example, clearly attenuated the development of severe hypertension in SHRSP fed on high salt diet [12].

The survival rates of SHRSP were greatly influenced by psyllium supplementation, which was proven to prolong the life span by the prevention of stroke [12], indicating diets would overcome the influence of salt-sensitive hypertensive genes closely related to stroke.

The remarkable dietary preventive effects of protein, Ca, and Mg supplementation on stroke in SHRSP were confirmed by observing their survival curves [4]. SHRSP developed severe hypertension and all died of stroke before the age of 100 days when they were given a normal diet and 1% salt water for drinking. Their life spans were twice as long when they were fed on a soy protein diet or Mg- or Ca-added diets even with salt water for drinking.

And their life spans were further prolonged to over 300 and 400 days on average when they were fed on soy protein with Ca or soy protein with Ca and Mg, respectively. The mechanisms of stroke prevention by these dietary components are various; protein, Ca and Mg counteract the adverse effect of sodium to reduce BP, some amino acids or oligopeptides from protein may contribute to the attenuation of hypertension and the improvement of the nutritional supply to vascular wall.

Worldwide Epidemiological Survey on Nutrition and Cardiovascular Diseases

We can now conclude dietary components are important and effective for preventing stroke in SHRSP.

In order to test the applicability of such effective dietary prevention to humans, we proposed an international cooperative epidemiological study, WHO-coordinated Cardiovascular Diseases (CVD) and Alimentary Comparison (CARDIAC) Study to WHO in 1983 [13–18]. Sixty populations in 25 countries were so far examined for the last 15 years by the CARDIAC Study (Fig. 1) [13–18].

The characteristic of the CARDIAC Study is first the application of biological markers of 24-hour urine and blood samples to the objective nutritional estimation. For collecting 24-hour urine easily, we developed a new so-called ‘aliquot cup’ [19, 20]. By simply pushing a button, exactly 1/40th of the urine can be collected into a small undercompartment after each voiding.
Fig. 1. The WHO CARDIAC Study.
With the introduction of such a simple procedure, 24-hour urine samples were successfully collected even in developing countries like Tibet and Tanzania. This study demonstrated that Tibetans drinking salted tea were taking excess salt, 18 g daily, and suffering frequently from severe hypertension.

Biological markers of the urine such as Na, K and amino acids were examined as indices of dietary intakes of Na, K and animal or vegetable protein. Blood samples were analyzed not only for serum cholesterol but also for fatty acids of serum phospholipids to examine what kinds of fat were taken from diets, and we also examined glycohemoglobin in erythrocytes as an index of population tendency to diabetes.

Another characteristic is the standardized measurement of BP by an automated BP measurement system. This study demonstrated Masai people who used no salt at all, had almost no hypertension at the age of 50–54 in 1987.

However, when we examined Masai people again in 1998, 11 years after the first survey, they had started to salt their meat and food in some villages where cheap salt was available from the market and their prevalence of hypertension was increased 3 times higher (12%) than the traditional Masai using no salt at all (4%) [unpubl. data].

The situation of people living in Dar es Salaam, the capital of Tanzania, was the worst and the prevalences of hypertension and obesity were over 50% in both genders aged between 47 and 57 [21].

Our CARDIAC Study clearly demonstrated that both systolic and diastolic BPs were significantly positively related with body mass index in both genders, indicating obesity as the major risk factor of hypertension.

Our worldwide study on 24-hour urinary Na excretion in relation to BP showed both systolic and diastolic BPs were positively related to Na excretion, thus Na intake in males but the relation was not significant in females because our study population in females included both menopausal and postmenopausal women, and the relation was proven to be significant in menopausal women in the world [22]. The lowest NaCl excretion was 2.5 g/day in Masai who were taking Na mainly from milk and more K, Mg and Ca from milk.

The CARDIAC Study confirmed the beneficial effect of macro nutrients such as Mg for lowering BP in various populations as it was demonstrated, by a significant inverse relationship between urinary Mg excretion and diastolic BP [23].

Another beneficial dietary factor is protein [24] or amino acids such as taurine [25], and urea nitrogen was measured as a biological marker of protein intake in the CARDIAC Study [18]. The adjusted regression coefficient of 24-hour urinary urea nitrogen to BP in each population, weighted by the inverse of each variance, was pooled to yield an overall effect in the whole CARDIAC Study population. Pooled regression coefficients were $-0.223$ for systolic BP and $-0.196$ for diastolic BP, both were statistically significant. These figures
Nutritional Pathogenesis and Prevention of Stroke

**Fig. 2.** Urinary salt excretion and stroke mortality.

indicate 1 g higher UN excretion would decrease both systolic and diastolic BP by about 0.2 mm Hg in the average population.

Since hypertension is influenced by Na intake, our CARDIAC Study indicates also 24-hour urinary Na excretion is positively related with the age-adjusted mortality rates of stroke in 25 populations, indicating excess salt intake is the major risk factor of stroke [18]. High stroke mortality rates in some Chinese and Japanese populations are ascribed to their high salt intakes. Low stroke mortality in Okinawa is related to their lowest salt intake among Japanese populations (Fig. 2).

The regression equation indicates salt intake should be reduced down to 6 g/day for preventing stroke and the data supports the WHO recommendation, daily salt intake should be 6 g or less.

As a significantly positive regression equation was also obtained between stroke and 24-hour urinary ratios of Na/K, the reduction of Na/K ratios in the diets appear to be important for preventing stroke. Our experiment in SHRSP K intake accelerates urinary Na excretion to counteract the adverse effect of Na. A lower Na/K ratio due to higher intake of K may explain the lowest stroke mortality in France.

Moreover, stroke mortalities were inversely related with serum cholesterol levels [18] (Fig. 3) which might be the reflection of the dietary animal protein intake, the beneficial nutrient for stroke prevention as proven experimentally in our animal models. Other epidemiological studies in Japan and USA also confined the similar inverse relationship between serum cholesterol and stroke, especially hemorrhagic stroke mortalities indicating risk factor for
stroke is different from those for coronary heart diseases as first experimentally shown by our animal experiments in the early 1970s [8].

In contrast to stroke mortality rates, age-adjusted coronary heart disease mortality rates were strongly positively related with serum total cholesterol (Fig. 4). These results of the CARDIAC Study indicate there should be ‘happy
medium in serum cholesterol level which can keep both major cardiovascular disease mortalities lower, that is, around 180–200 mg/100 ml. This happy medium actually corresponds to the population average of Okinawan people who are now enjoying the longest average life expectancy in Japan, thus in the world, with the lowest mortalities of both stroke and coronary heart diseases in Japan.

Correlation coefficients of log stroke mortality rates and selected nutritional factors are summarized in Figure 5. Nutritional risk factors are salt intake and Na/K ratio obtained by 24-hour urinary Na and K excretions. These nutritional factors affect BP and also stroke mortality. Other than minerals, arachidonic acid (Arc) ratio in the serum phospholipids was positively related to stroke mortality rates. Since Arc is not statistically positively related to BP itself, increased Arc due to the excessive intake of n-6 polyunsaturated fatty acids may be a risk related to cerebrovascular thrombosis.

On the other hand, the serum total cholesterol level which may reflect the better nutritional condition is the one significant correlation coefficient negatively related to stroke mortality. Urinary 3-methylhistidine [24] and taurine [17], markers of animal and fish protein intakes were detected as possible beneficial factors for reducing stroke mortality rates. Serum albumin, also a marker of protein intake, is associated with the reduction of stroke mortality. Twenty-four hour urinary K reflects K intake which counteracts the adverse effect of Na to reduce stroke mortality. These findings are consistent with our previous findings in SHRSP.

**Fig. 5.** Correlation coefficients of log stroke mortality rates and selected nutritional factors.
**Oxidative Stress and Antioxidants in the Cause and Prevention of Stroke**

Our recent experimental findings indicated oxidative stress was important in the pathogenesis of hypertension and stroke in SHRSP [26]. Hypoxia and reperfusion of oxygen are known to cause neuronal death. We could successfully demonstrate hypoxia and reperfusion caused apoptosis of cortical and hippocampal neurons under tissue culture conditions more severely in the cells from SHRSP than in those from WKY [27, 28] indicating genes might be involved in this augmented process of apoptosis in SHRSP [29]. Moreover, the addition of vitamin E, a typical antioxidant to the culture medium, completely prevented apoptosis in both neurons from SHRSP and WKY.

These animals underwent 30 min of cerebral ischemia and 9 days of reperfusion. In the hippocampal CA-1 regions of SHRSP, the neurons were damaged. Most cells lost cell organelles, diminished in size and become electron dense. Cells lost cell and nuclear membranes, the chromatin made clusters and they were abnormally distributed within the nuclei. The astroglial cells became swollen.

In contrast, in the hippocampal CA-1 regions in SHRSP fed on high vitamin E diet, all neurons remained intact.

We counted the number of apoptotic cells per 1,000 neurons. Thirty minutes of cerebral ischemia and 6 or 9 days' reperfusion greatly increased apoptotic cell numbers only in SHRSP, but no increase was observed in WKY, and in SHRSP fed on vitamin E-supplemented diet.

These results also confirmed hippocampal neurons in SHRSP were vulnerable to oxidative stress caused by ischemia and reperfusion, and vitamin E is an effective agent against the radical-mediated damage to the brain.

In order to investigate further the mechanisms involved in neuronal vulnerability in SHRSP, we compared the expression of Bcl-2, thioredoxin (TRX) and cytochrome c oxidase III mRNA in the cultured cortical neurons isolated from SHRSP and WKY at 15 days of gestation by quantitative reverse transcription polymerase chain reaction [29].

In short, the mRNA expression of Bcl-2, apoptosis-inhibiting molecule was significantly attenuated in SHRSP compared with WKY, indicating apoptosis more readily occurred in SHRSP neurons after hypoxia and reoxygenation.

We also demonstrated the mRNA expressions of TRX 1 and 2, redox regulatory proteins localized in cytosol and mitochondria, respectively, were significantly low in SHRSP after reoxygenation, while the expression became remarkably strong in WKY particularly 30 min after reoxygenation, suggesting that the defense system against oxidative stress should be weak in SHRSP.

Moreover, the expression of cytochrome c oxidase III, an energy metabolism indicator, was significantly higher in SHRSP neurons before and after hypoxia but the increase in response to reoxygenation was significantly attenuated, indicating energy production was easily damaged in SHRSP.
Nutritional Pathogenesis and Prevention of Stroke

We can now conclude from our experimental, pathological and epidemiological studies, that two major mechanisms are involved in the nutritional pathogenesis of stroke. One is vascular mechanism based on gene-nutritional interaction in hypertension and hypercholesterolemia, two main CVD risk factors which cause arterionecrosis and atherosclerosis, and result in hemorrhage stroke or in ischemic stroke or cerebrovascular dementia when accompanied with thrombosis (Fig. 6).

The other is neuronal vulnerability to oxidative stress induced by hypoxia and reoxygenation which often occur in the brain with pathological vascular changes due to arterionecrosis, thrombosis and atherosclerosis.

The weak expression of apoptosis inhibiting molecule, Bcl-2 and redox regulatory proteins, thioredoxins 1 and 2, may be involved in the genetic neuronal vulnerability resulting in neuronal death causing ischemic stroke and cerebrovascular dementia.

**Conclusion**

Since nutrition is involved in the basic pathogenesis of stroke, nutrition is most important in the prevention of stroke as demonstrated experimentally and epidemiologically by our worldwide cooperative studies (Fig. 7).

Some minerals, dietary fibers, protein, amino acids, soy isoflavones and fatty acids counteract two major CVD risk factors, hypertension and...
hypercholesterolemia, as well as prevent directly or indirectly the pathological processes of arterionecrosis, atherosclerosis and thrombosis. Antioxidants counteract the development of atherosclerosis and thrombosis, and are effective for modifying genetic vulnerability causing neuronal death due to oxidative stress.

Although many more studies are needed to understand the gene-nutritional interaction in stroke, particularly in man, we could conclude nutrition should contribute greatly to the prevention of stroke by controlling the phenotype expression of genes related to stroke and other CVD risk factors.

References


Nutritional Pathogenesis and Prevention of Stroke


Discussion

*Dr. Fernstrom:* Could you comment on whether there are any metabolic studies or transport studies showing how the blood-brain barrier changes in stroke-prone rats?

*Dr. Yamori:* We did some experiments culturing endothelial cells with astrocytes, and showed that astrocytes normally produce a factor that keeps the blood-brain barrier tight, but astrocytes from stroke-prone rats produce less of this substance. This explains why the blood-brain barrier is permeable in these genetic stroke models.

*Dr. Uauy:* I was fascinated to see the beneficial effect of animal protein. Have you explored specific amino acids? For example, nitric oxide may be linked to arginine.

*Dr. Yamori:* We did a lot of experiments to investigate the effect of each amino acid, and found that arginine actually prolonged the lifespan of stroke-prone rats somewhat. Some amino acids such as lysine did not affect blood pressure but still had a preventive effect on stroke. Taurine, which is obtained from fish, decreases blood pressure and attenuates the activity of the sympathetic nervous system. We did intervention studies giving taurine to people who do not eat fish and thus normally have very low taurine levels. We measured taurine in 24-hour urine samples from populations all over the world, and found that Tibetan people were always taurine-depleted. We then gave a group of borderline hypertensive Tibetans 3 g of taurine a day for 2 months and showed a clear decrease in blood pressure – significant evidence that taurine is an effective agent in populations with low fish intake. We have also been interested in amino acids from meat protein after I showed that 3-methylhistidine, a metabolite of animal meat, was inversely related to stroke mortality. We were unable to show a significant correlation between 3-methylhistidine and stroke mortality in our combined multinational data, but in 12 Chinese populations we could show a beautiful inverse relation between 24-hour 3-methylhistidine excretion and blood pressure and stroke mortality. It seems likely that proteins in pork meat may be involved, as Chinese people eat a great deal of pork, and some data suggest that peptides from pork may have converting enzyme inhibitor activity. It is possible that pork protein may reduce blood pressure sufficiently to decrease stroke mortality. Populations in both China and Japan, particularly Okinawans with the longest life expectancy are consuming pork regularly.

*Dr. Arroyo:* Could you comment on the effect of a reduction in salt intake? Is it associated with a reduction in stroke mortality and also of high blood pressure? How did you get your population to reduce their salt intake?
Dr. Yamori: Our worldwide study clearly indicated that a reduction of salt is effective in reducing stroke mortality and also in reducing blood pressure, particularly in men. In women, we did not see such a significant relation; in fact there was an inverse relation. The reason for the lack of effect in women seemed to be that our female populations were mixed premenopausal and postmenopausal. When we analyzed postmenopausal women separately there was the same significant positive relation between 24-hour urinary sodium excretion and blood pressure levels as in the men, so estrogen appears to affect salt sensitivity, with postmenopausal women becoming more salt-sensitive. We also observed ethnic differences in salt sensitivity. I told you that the Masai people had almost no hypertension on our first survey, but 11 years later there were starting to be cases of hypertension, even though their salt intake was still low at 6 or 7 g/day. The lowest Japanese salt intake (in Okinawans) is only 8 g/day, so it appears that the Masai and also Africans in Tanzania seem to be salt-sensitive. We therefore carried out a kind of clinical experiment. We recruited groups of black Tanzanian, Japanese, and white Brazilian medical students and gave them a very low salt diet (3 g/day) for a week, while during the following week we gave them a high salt diet (21 g/day). In the white Brazilians and also in the Japanese, there was no increase in blood pressure after 1 week on the high salt diet, but there was a significant increase in the Tanzanian blacks. Stroke-prone SHR have salt-sensitive hypertension, but salt-resistant SHR develop hypertension without stroke. The latter strain of rats seems not to be salt-sensitive. There is a genetic difference between stroke-prone SHR and stroke-resistant SHR. So when we discuss salt and hypertension we need to consider such genetic differences and ethnicity.

Dr. Rosenberg: We've learned so much about physiology and pathophysiology from your SHR studies. Now you are suggesting a mechanism which may teach us something about cognitive function. I was fascinated by the observation that in SHR you are able to show decreased blood flow, particularly in the penetrating arterioles, long before you actually get stroke. It seems to me that in this continuum that Dr. Vellas was referring to, and that I think I was trying to point out – of underperfusion, microvascular lesions, maybe macrovascular lesions, and changes in cognitive function – perhaps a very early effect would have to do with early perfusion, or nutrient perfusion, phenomena. I wonder if it would be possible to see whether there are brain functional changes in the SHR associated with those very early underperfusion observations that you made.

Dr. Yamori: Yes, I think that's a very interesting point, and particularly as our recent studies indicate that neurons from stroke-prone SHR are more vulnerable to oxidative stress induced by underperfusion and reoxygenation in various regions in the brain, so they seem to be very good models for studying cerebrovascular dementia. However, they quickly develop severe hypertension, so it's rather difficult to keep them alive long enough. We need to control their severe hypertension pressure so they can live longer, then they would be good models for cerebrovascular dementia.

Dr. Haschke: Could you tell us more about dietary fiber? I think you said the major fiber component you studied was psyllium.

Dr. Yamori: We have studied the effects of various types of dietary fiber on the development of hypertension and stroke in these animal models. One interesting kind of fiber is obtained from brown seaweed. It absorbs sodium and decreases stroke mortality rate in our animal model. In fact it absorbs sodium so efficiently that even when stroke-prone SHR are given 1% salt in their drinking water, their blood pressure elevation was attenuated and stroke mortality reduced. Thus, dietary fiber that effectively absorbs sodium in intestine is likely to be helpful for the prevention of stroke.
Dr. Abdul Rabbo: In relation to ethnic susceptibility to salt loading and hypertension, is the problem related to sodium retention? That is to say, did the Tanzanian blacks fail to clear the sodium load to the same degree as the Brazilian whites?

Dr. Yamori: We are very much interested in sodium sensitivity but we don’t yet know the mechanism. We are planning to study these ethnic differences in salt sensitivity by analysis of salt-sensitive genes. The problem seems to be particularly serious in people who have traditionally survived on a very low salt intake. When their lifestyle changes they develop problems dealing with surplus salt in the diet. In Tanzania, more than half the black people in the age range 50–54 are now hypertensive.