REVIEW PAPER

Chemical ecology in coupled human and natural systems: people, manioc, multitrophic interactions and global change

Doyle McKey · Timothy R. Cavagnaro ·
Julie Cliff · Roslyn Gleadow

Abstract Chemical ecology provides unique perspectives for managing plant/human interactions to achieve food security. Allelochemicals function as chemical defences of crop plants, enhancing yields. While ingested allelochemicals can confer health benefits to humans, at higher concentrations they are often toxic. The delicate balance between their positive and negative effects in crop plants is influenced by many factors. Some of these—how environment affects optimal levels of defence, how metabolic interactions with nutrients affect toxicity of ingested allelochemicals—are the province of chemical ecology. These biological factors, however, interact with social factors, and neither can be studied independently. Chemical ecologists must work together with social scientists to understand the overall system. Here, we illustrate such an integrative approach, analysing the interactions between people and the major tropical crop manioc, which contains cyanogenic glucosides. Polymorphism for cyanogen levels in manioc facilitates analysis of how costs and benefits of crop defences vary among social systems. We first show how people/manioc interactions diversified in this crop's Amazonian homeland, then turn to the remarkable cultural adaptations of African farmers since manioc's introduction 400 years ago. Finally, we evaluate new coevolutionary challenges in parts of Africa where people are still unfamiliar with a potentially dangerous crop. Current environmental and social catastrophes have restricted farmers' options, resulting in acute problems in health of humans and ecosystems. We show that high cyanogen levels confer important agronomic advantages, but also impose costs and constraints that can only be understood when biology is coupled with analysis of social, cultural and economic factors. Detoxifying manioc technologically requires know-how, time, water and other resources. Detoxifying residual dietary cyanogens metabolically depends on being able to grow, or to buy, the nutrients required for detoxification, primarily sulphur-rich proteins. Solutions that appear adaptive today may not be in the future, as changing climate, rising atmospheric CO_2 levels and decreased access to fertilizers affect productivity of crops and the nutrient and allelochemical composition of the foods they are used to produce.

D. McKey (✉)
Université Montpellier II, Centre d'Ecologie Fonctionnelle et
Evolutive (CNRS UMR 5175), 1919 route de Mende, 34293
Montpellier Cedex 5, France
e-mail: d_mckey@hotmail.com

T. R. Cavagnaro · R. Gleadow
School of Biological Sciences, Monash University,
Victoria 3800, Australia

R. Gleadow
e-mail: ros.gleadow@sci.monash.edu.au

T. R. Cavagnaro
The Australian Centre for Biodiversity, Monash University,
Victoria 3800, Australia
e-mail: tim.cavagnaro@sci.monash.edu.au

J. Cliff
Department of Community Health, Faculdade de Medicina,
Universidade Eduardo Mondlane, CP 257, Maputo, Mozambique
e-mail: julie.cliff@gmail.com

Introduction

Manioc, or cassava [*Manihot esculenta* Crantz (Euphorbiaceae); see Gade (2002) for a defence of 'manioc' as the

best term to refer to this plant in English], is a staple crop for over 750 million people, including 45% of the population of sub-Saharan Africa (FAO 2009), yet contains high concentrations of cyanogenic glucosides, principally linamarin, which break down to release toxic cyanide when crushed or chewed (Cardoso et al. 2005; McMahon et al. 1995; Nhassico et al. 2008). Cyanide in the diet may result in individual cases of acute cyanide poisoning, a frequent complaint in some manioc-dependent parts of Africa. Epidemics also occur, especially in regions where manioc is newly introduced (Cliff 1994; Mlingi et al. 1992). Various processing methods reduce the amount of cyanide eaten in manioc flour, or other preparations, but do not completely eliminate it (Cock 1982; Dufour 2007; Ernesto et al. 2002; Montagnac et al. 2009; Onabolu et al. 2002). Residual cyanogens in the diet over time can lead to chronic disorders such as tropical ataxic neuropathy (TAN) (Oluwole et al. 2000), endemic goitre and cretinism (when associated with selenium deficiency) (Ermans et al. 1980; Vanderpas 2006). The combination of too much cyanide and low protein intake has led to epidemics of the neuropathic disorder known as konzo, an irreversible paralysis of the lower legs, with children and women of childbearing age being particularly at risk (Tylleskär et al. 1992).

While manioc toxicity poses significant public health problems in Africa, where the plant was introduced over 400 years ago (Jones 1959), it is striking that these problems are virtually unknown in Amazonia, where manioc was domesticated probably over 8,000 years ago (Piperno et al. 2000) and where high-cyanogen varieties frequently predominate (Dufour 2007). How can this be explained? We believe that the key to understanding this paradox lies in understanding the dynamics of the chemically mediated biocultural coevolution between humans and manioc, a crop with such well-developed chemical defences that it is the only staple food crop that can be lethally toxic unless it is correctly prepared (Cardoso et al. 2005; McKey and Beckerman 1993).

Two significant problems facing the world today are global climate change and population growth. The link between these is food quality and quantity. How will our crop plants respond to rapid global change? Will they produce enough food to feed a growing population? In chemically defended crop plants such as manioc, will the food they produce still be edible (Gleadow et al. 2009b, c)? While the chemical-defence content of manioc is extreme among crop plants, many other crop plants also contain allelochemicals, and these continue to play significant roles both in agroecosystems and public health (Johns 1990; Nabhan 2004). The sometimes delicate balance between the benefits they confer and the costs they impose may be tipped by global change (Gleadow et al. 1998, 2009a, b).

Chemical ecology lies at the crux of a significant issue in human health and environmental sustainability. But the contribution of chemical ecologists to resolving this issue depends on our ability to see the problem in its entirety. The objective of this review is to illustrate such an integrative approach to human/plant chemical ecology, using the case of manioc. After a brief overview of the complexity of human/plant chemical ecology, we examine in detail the biocultural coevolution between humans and manioc. We first trace the plant's chemical ecology in its region of origin, the Neotropics, and then in areas into which it was introduced from the 1600s onwards. We then discuss the new coevolutionary challenges to the mutualism between manioc and humans that are posed by rapid change, not only in global and regional environments, but also in the social, cultural, economic and political factors that affect agroecosystems and human food choices and health. Two final sections examine the broader implications of our findings.

The coevolutionary challenges posed by manioc and other chemically defended crops are also challenges for management: upon their outcome hang both human health and the sustainability of agriculture in a large part of the tropical developing world. Therein lies also a challenge to chemical ecology: to join forces with other disciplines in a common endeavour to manage and mitigate global change. By the very definition of the field, practitioners of chemical ecology have crossed traditional disciplinary boundaries from the beginning. Building upon a solid framework for human chemical ecology (Johns 1990, 1999), chemical ecologists should be able to, and indeed must, rise to these new challenges.

An integrative view of human/plant chemical ecology

Connecting ecosystems and the human organism

The chemical ecology of interactions among plants, their herbivores and pathogens, and the natural enemies of these plant pests has a long history of fruitful applications in ecosystems managed by people for food production (Schoonhoven et al. 2005; Wink 1988). More recently, studies of the chemical ecology of vertebrate herbivores and omnivores have inspired approaches to understanding the ingestive behaviour of humans (Johns 1990, 1999; Krebs 2009), the most omnivorous vertebrate of all in terms of diversity of foods eaten (Procheş et al. 2008). Discoveries in this realm have begun to outline fascinating applications, realized or potential, in human nutrition and health, in domains as diverse as nutrigenetics (Verginelli et al. 2009), exploitation of plant chemical defences by humans to fight their own parasites and pathogens (Forbey

et al. 2009; Johns 1990) and drug addiction (Sullivan et al. 2008). These two facets of human chemical ecology—interactions in the agroecosystems that have become the major providers of our food over the last 10,000 years, and interactions between humans and the plants they ingest—are inextricably linked. We have fashioned highly edible plant foods by selecting against allelochemicals in many crop plants (Johns 1990; Johns and Alonso 1990; Wink 1988), but the durability of this solution depends on our ability to fashion sustainable agroecosystems, in which, for example, direct chemical defences are replaced by indirect defences, i.e. protection by farmers (Glass and Thurston 1978; Ruelle and Bruggers 1982). In other cases, allelochemicals are still present in the crops we grow and continue to play roles in plant defence (Jones 1998; Osbourn et al. 2003; Wink 1988). Despite detoxification during food preparation, these same compounds, or their derivatives, may also be present in the foods we eat and have diverse significant roles, positive or negative, in human health and nutrition (Dillard and German 2000; Friedman 2006; Gerber et al. 1999; Raubenheimer and Simpson 2009). In yet other cases, exploitation of biologically active allelochemicals is precisely the reason why humans ingest some plants (Billing and Sherman 1998; Sherman and Billing 1999). Such positively selected allelochemicals probably also play unappreciated roles in chemical defence in agroecosystems. The links between chemically mediated interactions in agroecosystems and in human bodies go very far indeed, reflecting an even deeper interdependency: in the long term, human health fundamentally depends on sustainable agroecosystems (Johns 2003).

Despite such links, these two facets of human/plant chemical ecology are still too often treated separately. There is an urgent need for studies that examine these linkages. Why is such integration important? Today, both agroecosystems and human nutritional ecology are facing rapid change, and change at each level is affecting the other. Unless we understand these complex feedbacks, we will not be able to mitigate change or adapt to it. Management recommendations driven solely by considerations from nutritional ecology or public health may have hidden costs at the ecosystem level (Crohn and Bianchi 2008). To cite an example involving chemical ecology, solving food-toxicity problems by developing allelochemical-free crop plants could increase their susceptibility to pests and pathogens and increase our dependence on synthetic pesticides (Katz 1990; Kliebenstein 2009; McKey and Beckerman 1993; Nhassico et al. 2008; Riis et al. 2003a, b). Despite such concerns, a recent comprehensive review article focusing on producing genetically engineered toxin-free food crops does not even mention the potential consequences for pathogens and herbivores (Gallo and Sayre 2009).

The chemical ecology of human/plant interactions is faced with the challenge confronting all of ecology in a world increasingly dominated by humans: analysing the reciprocal interactions between ecological and social processes (Liu et al. 2007). Processes and phenomena we once analysed from purely natural science perspectives must increasingly be studied as coupled human and natural systems, integrating a wide range of disciplines (Carpenter et al. 2009; Liu et al. 2007). Chemical ecology has an essential role to play, but it must be coupled with analyses of social, cultural, economic and political factors affecting what crops farmers grow, what foods people eat, the ways in which they are prepared, and the diverse roles and fates of allelochemicals from ecosystems to human diets and back again.

The complex chemical ecology of people–plant interactions

The chemical ecology of humans encompasses an enormous range of interactions with plants (Johns 1990, 1999). Omnivorous mammals endowed with extreme behavioural flexibility, humans exploit a great range of wild plants as food and medicine (Proches et al. 2008). Adaptations in nutritional ecology are closely tied to other specifically human adaptations. According to the "expensive-brain" hypothesis, the extraordinary development of this organ, metabolically expensive to construct and to maintain (Aiello and Wheeler 1995), was incompatible with investment in a specialized (and costly) digestive system with great capability for digesting plant fibres and detoxifying allelochemicals. Nourishing the brain thus required an abundant supply of high-quality energy-rich food, with low contents of toxic and anti-nutritional allelochemicals (Ragir 2000). Great interest has focused on underground storage organs of plants as a reliable source of calories in the savanna environments in which early hominins lived (Laden and Wrangham 2005). The quality of underground storage organisms as food for hominins would have been greatly enhanced by cooking (Dominy et al. 2008), another specifically human biological (or biocultural) trait (Wrangham and Conklin-Brittain 2003). Cooking has many effects on chemical and physical properties of plant-derived foods (Dominy et al. 2008), among them the detoxification of thermolabile allelochemicals (Johns 1990; Stahl 1984). Detoxification is important because plant underground storage organs tend to be chemically defended, in contrast to other less abundant and more seasonally restricted alternative plant foods such as mature fleshy fruits, where defences may function as "filters" but not as general deterrents (Cipollini and Levey 1997). Biological considerations suggest a much earlier origin and spread of cooking than has commonly been thought (Wrangham and Conklin-Brittain 2003), but this inference awaits

archaeological evidence (Brace 2000). On the other hand, cooking can sometimes make the situation worse, for example, by denaturing the degradative enzymes required for detoxification (Morant et al. 2008). This is the case, for example, for cyanogens in manioc and other plants (Dufour 2007). Foraging peoples thus developed a great diversity of other technologies for detoxifying plants (Johns and Duquette 1991; Johns and Kubo 1988).

Like other vertebrates, humans possess a diversity of bitter-taste receptors, belonging to the *TAS2R* gene family, that function to detect (mostly plant-derived) toxins, enabling their avoidance (Fischer et al. 2005; Mueller et al. 2005). Although high sensitivity to potentially toxic compounds is usually adaptive, there may sometimes be an advantage not to be too sensitive to them, because ingestion of biologically active allelochemicals can confer positive benefits. For example, humans, like many phytophagous insects (Opitz and Müller 2009), exploit the chemical defences of plants they ingest to combat their own enemies. Human use of medicinal plants extends the self-medicative behaviour that is part of our primate heritage (Huffman 2001), but many foods also have preventive or therapeutic properties (Billing and Sherman 1998; Gerber et al. 1999; Raubenheimer and Simpson 2009; Sherman and Billing 1999). Individuals with lower sensitivity to allelochemicals that have positive effects might ingest more of them and thereby obtain greater benefits (Bufe et al. 2005; Soranzo et al. 2005).

An intriguing example directly pertinent to interactions between humans and manioc illustrates the selective forces acting on bitter-taste receptor genes. Receptors coded for by the human bitter-taste receptor gene *TAS2R16* detect a large family of bitter-tasting plant secondary metabolites, β-glucopyranosides. These include a diversity of allelochemicals from salicin to cyanogenic glycosides. Patterns of genetic variation at and near this locus indicate that a derived allele conferring twofold higher sensitivity to these compounds rose to high frequency in most populations, even fixation in many, during the middle Pleistocene (Soranzo et al. 2005). This could be interpreted as an adaptation conferring greater ability to detect, and avoid, potentially toxic bitter substances. Such a sensory adaptation could have facilitated and synergized efforts of humans to choose non-toxic plants, to process toxins out of their food and, much later, to breed some toxins out of their crops. Intriguingly, Soranzo et al. (2005) found that Central African populations were characterized by much higher frequency of the less sensitive ancestral allele than other populations. Noting that ingestion of some secondary metabolites, notably cyanogens, has been implicated in resistance to *Plasmodium falciparum* malaria (Jackson 1991, 1996; Katz 1990; see also Nabhan 2004), and noting similarities in the distribution of genetic polymorphisms

conferring partial malaria resistance and that of the ancestral *TAS2R16* allele, they postulated that selection in this region favoured individuals with lower sensitivity to β-glucopyranosides, who would thus ingest more of these and benefit from the protection conferred. If this hypothesis holds, it would imply, as noted by Harris and Meyer (2006), that this allele rose to high frequency in the region about 6,000 years ago (i.e. much later than the spread of the more sensitive allele), when the expansion of agriculture led to conditions favourable for *P. falciparum* malaria.

Allelochemicals help shape human preferences in foraging for wild plants. Domestication opened opportunities for farmers to change plant defence phenotypes to their own benefit. What have been the fates of chemical defences during plant domestication? The most frequently cited pattern is that they have tended to be bred out (Kliebenstein 2009; Wink 1988). However, because allelochemicals not only impose costs but can also confer benefits, both to crops in fields and in the foods humans eat, selection pressures acting on them under plant domestication are complex (Johns 1990). Selection should act to favour defence phenotypes that produce the greatest net benefit for farmers. Costs and benefits thus depend on what kinds of plants farmers prefer, and on how the plant's intrinsic traits interact with the cultural practices of farmers, the environment they provide and the plant's role in the overall subsistence strategy. Crop plants and the culture of farmers thus coevolve.

What are the costs and benefits of allelochemicals in crop plants, and how can these be managed for sustainability and resilience? In wild plants, some of the earliest clear evidence identifying and quantifying costs and benefits of chemical defences came from studies of polymorphisms in wild plants (Dirzo and Harper 1982; Goodger et al. 2006; Jones 1962; Kakes 1989). Crops that are polymorphic for important chemical defences can provide similar insights into costs and benefits of defence in systems where plants and farmers coevolve. Manioc is an instructive example for exploring this intriguing phenomenon. Its different varieties show extreme polymorphism in the content of cyanogenic glucosides, particularly in the part most frequently consumed by humans, the tuberous root.

Biocultural coevolution between people and manioc

Among the numerous cyanogenic plants that have been domesticated as food crops (Jones 1998), manioc is the most important, and the only staple crop that possesses potentially lethal levels of toxic secondary metabolites (McKey and Beckerman 1993). Manioc contains two cyanogenic glucosides, linamarin (by far the more abundant) and lotaustralin. All varieties of domesticated manioc contain cyanogens in all parts (except seeds), but two

groups, "bitter" and "sweet", are distinguished on the basis of their high or low content of cyanogens in the part eaten by humans, the starchy tuberous root. This binary distinction masks a more continuous distribution (from <10 mg kg^{-1} as HCN fresh weight basis to >500 mg kg^{-1}; O'Brien et al. 1994), but generally varieties whose roots contain >100 mg kg^{-1} cyanogenic potential (CNP) are considered bitter and unsafe for eating without processing. As reviewed by McKey and Beckerman (1993), cyanogens cannot be eliminated by simple roasting or boiling, which denature the plant's native β-glucosidase and leave the glucosides intact. These can then release HCN when they contact β-glucosidases produced by bacteria in human guts. Roots of bitter manioc must be subjected to more complicated detoxification procedures, which will be described below. Sweet varieties (whose roots contain <100 mg kg^{-1} CNP) are considered safe. While roots of sweet manioc can be processed in the same ways as those of bitter manioc, they can also be safely eaten simply roasted or boiled.

Almost 20 years ago, McKey and Beckerman (1993) argued that chemical defence underlies the principal agronomic advantages of manioc, and that these advantages were more pronounced in bitter than in sweet varieties. These include the ability to produce economically viable yields even in poor soils, under drought conditions and in environments rich in potential herbivores and pathogens, and the capacity for "live storage" of roots for long periods in the soil relatively free from attacks of herbivore and pathogens, enabling plants to be harvested as needed. They also postulated that the balance between the benefits conferred to farmers by defence of the plant's tuberous roots and the costs these defences impose determines whether farmers in a given situation will plant mostly toxic or mostly non-toxic manioc varieties. Coevolutionary analysis of this chemical-defence polymorphism gives insights into the costs and benefits to farmers of having a highly cyanogenic staple crop, and into the adjustments that farmers of sweet and of bitter manioc have made to exploit the respective advantages of their crops to the fullest. In contrast to this picture, in some parts of Africa, manioc varieties and the practices of farmers and consumers with respect to them are still maladaptive and mismatched. Understanding how people and manioc in Amazonia co-evolved in the 8,000 or more years since the crop was domesticated (Piperno et al. 2000) can give insights on how this crop can be better managed for food security in other regions.

The defensive role of cyanogens in plants

Manioc is one of over 2,500 plant species worldwide, including ferns, gymnosperms and angiosperms, which contain ecologically significant concentrations of cyanogenic compounds (Jones 1998; Zagrobelny et al. 2004). The phylogenetic distribution of cyanogenic compounds indicates that they have evolved repeatedly and have played roles in defence for a long span of evolutionary time (Bak et al. 2006; Miller et al. 2006).

Although mechanisms countering cyanogens as defences appear to be ubiquitous—the cyanide-detoxifying enzyme rhodanese is present in many bacteria, fungi and animals, and even many plants (Beesley et al. 1985) and other mechanisms also exist (Zagrobelny et al. 2004)—ecological evidence shows that cyanogenic compounds appear largely to have retained their effectiveness over evolutionary time, and continue to be effective defences of many plants against both generalist (Gleadow and Woodrow 2002a) and at least some specialist (Ballhorn et al. 2007) arthropod pests, against nematodes (Chitwood 2002) and against fungal pathogens of plants (Lieberei 2007). One likely explanation for the evolutionary persistence of cyanogens as plant defences is that their detoxification often imposes a high cost. First, the rhodanese-catalysed detoxification of cyanide to thiocyanate, less toxic and more easily excretable, requires sulphur, donated by one of the sulphur-containing amino acids, methionine or cysteine. The capacity of herbivores to detoxify cyanide thus depends on the availability of sulphur-rich proteins (Gleadow and Woodrow 2002a; Westley 1988). Interestingly, methionine and cysteine are among the essential amino acids most often limiting for mammalian herbivores (Fox and Tedeschi 2003). They occur in particularly low concentrations in manioc leaves (McKey and Beckerman 1993; Montagnac et al. 2009). The suggestion that cyanogenic plants could increase the effectiveness of defence by making proteins with even lower contents of these amino acids than most plants (McKey and Beckerman 1993) appears to be still untested. Second, although thiocyanate is less toxic than HCN, it still has serious negative effects as a goitrogen (Ermans et al. 1980) and is a possible pathogenetic agent in konzo (Tshala-Katumbay 2009). Third, if the diet is deficient in sulphur, HCN is "detoxified" to cyanate (–OCN), a neurotoxin that is a likely candidate in the pathogenesis of konzo (Tor-Agbidye et al. 1999; Tshala-Katumbay 2009).

As for all types of herbivore defence, there are limits to the effectiveness of cyanogenic compounds (Gleadow and Woodrow 2002a). The mode of feeding of most phloem-sucking insects, for example, does little damage to cell walls, thereby limiting the mixing of cyanogenic glucoside (in cell vacuoles) with the degradative β-glucosidases (in plastids and in intercellular spaces) (Morant et al. 2008; Zagrobelny et al. 2008). Also, specialists have often evolved more effective mechanisms to cope with cyanogens. Cyanide-tolerant bacteria, for example, possess a

diversity of pathways for degrading cyanogenic compounds, not all of them relying on sulphur (Dubey and Holmes 1995). Like many plants (Miller and Conn 1980), some insect specialists on cyanogenic plants detoxify HCN using β-cyanoalanine synthase and cysteine synthase in a set of reactions involving no net consumption of sulphur-containing amino acids (Ogunlabi and Agboola 2007; Zagrobelny et al. 2004). The increasing importance of adapted specialist herbivores can lead to phylogenetic patterns of decline in effectiveness of resistance traits (Agrawal and Fishbein 2008). Bak et al. (2006) speculate that the evolution of counter-adaptations to cyanogens by specialists could explain why a few plant lineages appear to have evolved non-cyanogenic secondary metabolites (including glucosinolates; Halkier and Gershenzon 2006) using ancestral pathways to biosynthesis of cyanogenic glucosides. However, some arthropod specialists on cyanogenic plants continue to be deterred, suffering strong fitness reduction when they ingest high levels of cyanogens (Ballhorn et al. 2007). Similarly, despite its possession of the efficient and sulphur-sparing β-cyanoalanine synthase detoxification pathway (Ogunlabi and Agboola 2007), the polyphagous African grasshopper *Zonocerus variegatus* is deterred by high levels of cyanogens in manioc (Bernays et al. 1977).

Cyanogenesis in manioc and its role in defence

Manioc has numerous chemical defences, including tannins, phytates and saponins (Montagnac et al. 2009). The plant's system of laticifers confers mechanical (and probably chemical) defence against herbivores and pathogens, although this has been surprisingly little studied. However, cyanogenesis is by far the plant's best-studied defence. The process of cyanogenesis in manioc has been summarized by several authors (Dufour 2007; McMahon et al. 1995; White et al. 1998). It is initiated when plant tissue is damaged and then proceeds in two steps. First, linamarin in the vacuolar spaces is converted to acetone cyanohydrin, when brought into contact with the plant's β-glucosidase, linamarase, which is stored in the plant cell walls. Second, acetone cyanohydrin is decomposed to yield hydrogen cyanide (HCN) and acetone, either spontaneously or catalysed by a specific α-hydroxynitrile lyase. Cyanogenic glucosides, acetone cyanohydrin and HCN are referred to collectively as cyanogens. The degradation of lotaustralin, the other cyanogenic glucoside in manioc, follows a similar pattern (Morant et al. 2008). The combined concentrations of cyanogens (usually expressed as mg HCN kg^{-1} fresh weight) yield an estimate of the CNP of manioc or of foods prepared from it (Dufour 2007).

Since the review by McKey and Beckerman (1993), more evidence has accumulated that manioc cyanogens have an important role in defence and that roots of bitter manioc are more resistant to pests than are those of sweet manioc. Interviews with farmers document their preference for bitter varieties, and attribute that to the perceptions that they are better protected against insect and mammalian pests (Bellotti et al. 1999; Kapinga et al. 1997; Thro et al. 1994), and more productive than sweet varieties (Wilson and Dufour 2002). Structured interview methods (e.g. Wilson 2003, 2006; Wilson and Dufour 2002, who used pile-sorting methods), however, confirm earlier observations (Boster 1984) that farmers usually pay more attention to overall yield than to individual factors such as pest resistance. Organoleptic qualities of the foods prepared from different varieties often have greater salience for preferences than do either yield or pest resistance.

Despite calls for experimental studies (Kakes 1994; McKey and Beckerman 1993), it appears that in the period since those calls only two insect species have been tested in well-replicated laboratory and field experiments that adequately addressed the role of manioc cyanogens in herbivore defence. Studies by Riis and colleagues (Riis et al. 2003a, b; Cortes et al. 2003) showed that high CNP levels are toxic to the burrowing bug *Cyrtomenus bergi* (Hemiptera: Cydnidae), preventing its development. They also showed that bug attack induced higher production of cyanogens (Riis et al. 2003a). By protecting against these insects, high CNP thus also confers at least indirect defence against the numerous pathogens that gain entry into manioc roots via the wounds it makes (Bellotti and Riis 1994). In contrast, cyanogens play no role in defence against a manioc specialist, the mealybug *Phenacoccus manihoti*, which ingests high concentrations of cyanogenic glucosides in phloem sap (Calatayud et al. 1994a, b). Linamarin is largely absent from its honeydew (Calatayud et al. 1994a, b). However, the linamarase activity is not due to the insect itself or its intracellular symbionts, but possibly to its gut microflora (Calatayud 2000).

Arthropod pests of manioc are today most studied in Africa, where introduced specialists from South America and sucking-insect vectors of viral diseases such as cassava mosaic virus are important pests. It is thus perhaps not surprising that in an overview of manioc pest management in Africa, Herren (1994) does not even mention cyanogens.

Nevertheless, the diffuse community of generalists, deterred by cyanogens, cannot be ignored, and recommendations about changing the CNP of manioc must take into account all costs and benefits (Kakes 1994). Another factor must be considered in the cost–benefit equation. Like many other "secondary" metabolites (Rhodes 1994; Seigler 1977), cyanogenic glucosides seem also to play fundamental physiological roles, for example in metabolism and transport of nitrogen (Jenrich et al. 2007; Selmar et al. 1988). The fact that there are no naturally occurring

acyanogenic manioc plants, and the higher requirement for N in the early stages of tissue culture of RNAi-induced acyanogenic manioc (Jørgensen et al. 2005; Morant et al. 2007; Siritunga and Sayre 2003), support this view.

Technology of manioc detoxification

As noted previously, simple cooking of high-cyanogen manioc does not decrease the risk of intoxication; multi-step procedures are required to reduce cyanogens to levels safe for humans. What is "safe" depends on intake of sulphur-rich proteins (Gleadow and Woodrow 2002a) and other nutrients. Diverse techniques are used, but those effective in detoxification all share two steps. First, destruction of the plant's cellular compartmentation (e.g. by mechanically rasping harvested roots, or by soaking them in water to be macerated by bacteria and fungi) puts cyanogenic glucosides in contact with the plant's β-glucosidases, hydrolysing the glucosides. The HCN thereby generated, water soluble and volatile, can then be leached out by dewatering (e.g. through use of the manioc sleeve press or tipiti), or driven off by toasting or boiling. Processing methods employed by Amazonian Amerindians appear to be highly effective in detoxifying manioc, typically removing 97–99% of cyanogens (Dufour 1989), and this in part explains why chronic toxicity and neuropathic diseases such as konzo have never been observed in South America (Dorea 2003, 2004; Dufour 1989). However, many methods (although not all) employed in Africa are of comparable effectiveness, and the manioc products examined from both continents contained residual cyanogens (Dufour 2007). This suggests that differences in the metabolism of residual cyanogens may explain the virtual absence of chronic toxicity in South America. Relying on fish (rich in sulphur-containing amino acids) as the principal protein source may facilitate the use of manioc as a staple by inhabitants of Amazonia (Dorea 2003; Spath 1981). In the large 1981 konzo epidemic in Mozambique, the coast was relatively spared, probably because fish provided the sulphur-containing amino acids needed to facilitate elimination of residual cyanide (Ministry of Health, Mozambique 1984b). Fish also supply iodine, counteracting the potential goitrogenic effects of a manioc-based diet (Cliff et al. 1986; Dorea 2003; Dufour 2007; Ermans et al. 1980). However, we have found no studies in South America that examine levels of serum or urinary cyanogens, thiocyanate or cyanate. Until comparative data are available on these parameters and on intake of protein and sulphur-containing amino acids, we cannot claim to fully understand the conspicuous absence of chronic toxicity problems in Amazonia.

Techniques for processing bitter manioc have other effects on the nutritional quality of the product. Bak et al.

(2006) state that dewatering results in loss of proteins, vitamins and minerals, but provide no data. Techniques that include fermentation can enhance food quality in many ways, including detoxification of phytates and other anti-nutritional compounds (Montagnac et al. 2009), reducing contamination of foods by pathogenic bacteria (Mensah 1997) and enhancing the bioavailability of nutrients (Hotz and Gibson 2007).

Understanding how detoxification technology, diet and possibly other factors contribute to the good health of Amazonian consumers of manioc is important, because each of these could be subject to change. Mercury pollution of rivers, due both to land-use changes that affect natural mercury cycles and to gold-mining activities, is causing increasing concern about the safety of fish as a protein source in Amazonia (Harada et al. 2001). However, any dietary change in response to this perceived hazard that results in lower consumption of proteins, sulphur-containing amino acids or iodine, is likely to increase risks of manioc toxicity (Dorea 2003, 2004). In addition to such indirect interactions between mercury (also a neurotoxin) and cyanogens, the potential exists for physiological interactions between them, possibly mediated by the diverse and incompletely understood roles of cysteine and methionine in mercury toxicology (Chapman and Chan 2000).

Explaining a chemical defence polymorphism in a crop plant

McKey and Beckerman (1993) proposed a model of disruptive selection to explain the existence of both non-toxic and highly toxic varieties of manioc. According to this model, the optimal level of toxicity of roots is the outcome of interaction between natural and artificial selection. As for plants in general, the strength of natural selection for chemical defence should be greatest when herbivores and pathogens are abundant and when limited resource availability favours resource-conservation over resource-acquisition strategies (Coley et al. 1985). The direction and strength of artificial selection depend primarily on how roots are prepared for food. Where manioc is eaten simply boiled or roasted and is thus not detoxified, strong human selection counters natural selection and maintains low cyanogen levels. Where manioc is processed in ways that detoxify it, human selection against toxicity is relaxed. Natural selection, amplified by human selection for higher-yielding well-defended genotypes, can lead to evolution of high cyanogen levels. Growers of bitter manioc sometimes also express a cultural preference for the taste or other organoleptic qualities of products made from their favoured varieties (Dufour 1993), but whether these qualities are in some way due to their high cyanogen levels (e.g.

higher glucose concentrations resulting from hydrolysis of cyanogenic glucosides) appears unclear.

Based on this model, McKey and Beckerman (1993) then proposed an explanation for the observed geographical and cultural patterns in the distribution of sweet and bitter varieties. In general, bitter manioc cultivation is associated with the courses of the major Amazonian rivers, as well as the coastal areas of South America, where population densities were the highest before conquest. Where bitter manioc is grown, it is always the staple. On the other hand, sweet manioc is the main crop throughout the headwaters of these same rivers in western Amazonia, including the whole length of the Ucayali and Marañon Rivers in Peru, the southern periphery and up into Meso-america. It is also commonly grown on a minor scale where bitter manioc is the major crop.

The coevolutionary model of McKey and Beckerman (1993) offered explanations for these patterns. First, use of bitter manioc entails specialization on this crop, because the demands its processing makes on women's time—several hours each day for each woman (Heckler 2004)—precludes much investment in other crops, or in alternative activities such as gathering. This is the principal "cost" of detoxification. McKey and Beckerman (1993) emphasized that an important function of manioc processing is to make a storable product, because while manioc roots can be "stored live" and harvested as needed, they deteriorate very rapidly after harvest. They argued that modes of food production centred on time-consuming processing of manioc would be most favoured in large sedentary villages along floodplains of major rivers, where local depletion of wild plant resources around large settlements may have lowered the profitability of gathering, and where storage of surplus food could help buffer seasonal variations in food supply. Large, semi-permanent fields in herbivore- and pathogen-rich environments near floodplains would also have favoured bitter varieties. Finally, reliance on fish as a protein source would have supplied the sulphur-containing amino acids and iodine needed to deal with residual cyanogens in the diet.

Detoxification imposes no "cost" additional to the cost of making storable products (McKey and Beckerman 1993), such as manioc flour (farinha) or bread (casabe). In fact, sweet manioc can also be processed to make flour or bread. According to one hypothesis about evolutionary relationships among manioc varieties, sweet varieties came first (Arroyo-Kalin 2010). The initial function of processing was to prepare a storable product from sweet manioc roots by grating or soaking, then dewatering them. Because such processing also resulted in detoxification, human selection against toxicity was relaxed, and natural selection, coupled with human selection for higher-yielding chemically defended genotypes, could have led to the

evolution of bitter varieties (Arroyo-Kalin 2010; McKey and Beckerman 1993).

In contrast, non-toxic varieties would have been favoured in smaller, more mobile societies where processing would conflict with competing women's activities such as gathering, and where it would have been impractical to transport graters, griddles and other equipment for processing, or to construct them anew in each new residential site (cf. Balée 1994). Because there is no need to specialize on a crop whose roots are eaten simply boiled or roasted, sweet manioc could occupy a diversity of roles, from minor crop to staple. Within the framework of the coevolutionary model, it is interesting that bitter-manioc specialists often grow smaller quantities of sweet manioc, but tend to plant them in home gardens, where they are better protected (by greater human presence) from mammalian herbivores than in long-fallow fields far from villages (McKey and Beckerman 1993) and where they tend to be planted on more fertile soils (Wilson 2002). This same pattern has been observed in Africa, where farmers plant bitter varieties in their fields and sweet manioc close to their houses, where they can defend the plants against monkeys (Cock 1982; J. Cliff, personal observation). It is also interesting that the only region where sweet manioc was grown as the staple crop in pre-Conquest America is western Amazonia (Peru, Ecuador), where younger soils, enriched by the Andean orogeny, are more fertile than the old, highly weathered soils of central and eastern Amazonia (ter Steege et al. 2006). McKey and Beckerman (1993) postulated that this region's more fertile soils could have permitted high yields of sweet manioc even under high herbivore and pathogen pressure, and noted that some sweet-manioc specialists use their gardens as "bait", the mammals attracted to this eminently edible crop being important protein sources.

Much of this story about pre-conquest patterns in sweet and bitter manioc cultivation and the ecological pressures that drove them can perhaps never be reconstructed, owing to the profound disruption occasioned by European colonization and the changes in landscapes and modes of life since then (Clement 1999a, b; Clement et al. 2010). However, new data from archaeology, combined with studies of contemporary manioc farmers, have greatly enriched some parts of the story. Fraser and Clement (2008) examined bitter manioc cultivation by *caboclo* farmers, "formed through the encounter between Amerindian peoples and successive waves of migrants from Europe and Brazil's Northeast" (Fraser and Clement 2008), in floodplains and in anthropogenic dark-earth soils, the kinds of fertile soils that were associated with sedentism in valleys of major rivers in pre-conquest Amazonia. Ecologically, these situations are very different from the long-fallow cultivation of bitter manioc on poor soils, the

context in which bitter manioc farming is usually studied today (e.g. Elias et al. 2000), and are representative of a type of intensive agriculture that may have been much more widespread before the Conquest. This work has shown that within the bitter manioc pool, farmers have selected varieties locally adapted to soils of different quality and to growing seasons of different length, conditioned by seasonal flooding regimes (Fraser and Clement 2008; C. R. Clement, personal communication). 'Fraca' ("weak") varieties are often grown on richer soils (Amazonian dark earths, ADE), mature rapidly, and do not 'store' well if left in the field. 'Forte' ("strong") varieties are grown on less fertile Oxisols or Ultisols in longer-fallow systems where burning supplies sufficient nutrients for a cycle of cultivation. Whether 'fraca' and 'forte' varieties differ in resistance to herbivores and pathogens, or in traits such as cyanogen level that might contribute to resistance, is not yet known (C. R. Clement, personal communication). It would be very interesting to study genetically based differences in cyanogen level among these varieties, environmental effects on this trait and the interactions of genotype and environment.

Manioc is a clonally propagated crop; each stem cutting gives a plant genetically identical to that used to prepare it. What is the source of the genetic diversity necessary to generate such locally adapted varieties? Where does this clonally propagated crop get genetic variation, the raw material of evolution? Drawing upon observations by anthropologists, McKey and Beckerman (1993) proposed that cultivators regularly incorporate volunteer seedlings, the products of sexual reproduction, into their stocks of clones. Since then, extensive work has documented the importance of volunteer seedlings as sources of diversity. Manioc's mixed reproductive system combines the advantages of both clonal propagation and sexual reproduction, minimizing their respective disadvantages (for reviews, see Rival and McKey 2008; McKey et al. 2010a, b). Fraser and Clement (2008) document the role of volunteer seedlings in providing the genetic variation from which farmers select genotypes locally adapted to soils of different quality. Genetic diversity also contributes to pest resistance of crop populations (Clement 1999a; McKey and Beckerman 1993).

A major gap in our understanding of the coevolutionary dynamics of manioc in Amazonia is our ignorance of the evolutionary relationships between sweet and bitter manioc varieties. Studies so far have shown that the two groups of varieties are to some extent genetically differentiated for neutral markers (Elias et al. 2004; Mkumbira et al. 2003; Peroni et al. 2007), but owing to the limited geographical scope of these studies this result could have two competing explanations. It could represent an ancient split followed by separate diffusion of sweet and bitter pools, as postulated

by Elias et al. (2004). However, a proper test of this hypothesis would require analysing manioc varieties from a much larger set of localities throughout Amazonia for the same set of markers, to examine whether all bitter and all sweet varieties form two separate clusters. To our knowledge, such a study has not yet been done. The alternative hypothesis is that in different times and places, local-scale differentiation between more toxic and less toxic pools has repeatedly evolved, driven and maintained by disruptive selection and by spatial isolation of the two pools (in large fields and in home gardens, respectively), limiting gene flow between them (Elias et al. 2004; McKey and Beckerman 1993; Peroni et al. 2007). Level of toxicity could be a dynamic trait, evolving rapidly in response to local selective pressures. We also lack information on cyanogen levels in tuberous roots of manioc's wild ancestor, *Manihot esculenta* subsp. *flabellifolia* (Olsen and Schaal 1999). Data on the evolutionary relationships of cultivars varying in cyanogen level and on the ancestral state of this trait before domestication are required to test an intriguing hypothesis inspired by data from archaeology, anthropology and ecology (Arroyo-Kalin 2010). According to this hypothesis, low-cyanogen varieties were the first to be cultivated, in "dump-heap" environments. Increasing sedentism led to the development of processing of low-cyanogen manioc roots to produce storable food. Because processing resulted in detoxification, artificial selection against toxicity was relaxed, so that natural selection and yield-driven human selection could have led to the evolution of bitter varieties, as already proposed by McKey and Beckerman (1993).

Despite exciting advances in genetics, ecology and archaeology, a fundamental question in the coevolution of people and manioc in Amazonia is thus still unresolved. Knowing the evolutionary relationships between sweet and bitter manioc and understanding better the selection pressures that have led to their divergence would supply a large missing piece of the puzzle of the history of this crop—and of its cultivators—in Amazonia.

When plants are introduced, farmer knowledge may not move with them: biocultural coevolution of people and manioc in Africa

The preceding sections show that coevolutionary interactions between people and manioc in Amazonia led to great variation in cyanogen levels in cultivars, reflecting adaptation of this and other traits to local ecological and cultural environments. Processes of local adaptation were fuelled by farmers' use of volunteer seedlings as a source of genetic variation. Local adaptation in cyanogen levels of manioc varieties went hand in hand with cultural adaptations, such as the invention of technologies that effectively detoxified manioc and the fashioning of dietary

combinations that compensated for the effects of residual cyanogens.

When manioc was first introduced into Africa and began to diffuse within the continent, the specialized knowledge and practices needed to use this unusual crop to its full potential were probably not transferred intact along with the crop. It appears likely that problems with manioc toxicity similar to those observed in some parts of Africa today also occurred then, and may well have been widespread. With time, however, African farmers achieved remarkable cultural adaptations to this new crop, developing a range of detoxification technologies sometimes quite different from those commonly employed in Amazonia (Lancaster et al. 1982) but often just as effective in removing cyanogens (Dufour 2007). African farmers also invented new ways to fit the advantages and constraints of sweet and bitter manioc, evident from studies in Amazonia, to new ecological situations. For example, Bateke farmers living in forest/savanna mosaic habitats in Gabon fashioned a system in which bitter and sweet varieties occupy forest and savanna niches, respectively (Delêtre 2010).

African farmers have also put the chemical defences of bitter manioc to novel uses to assure food security. Proponents who argue for development of cyanogen-free transgenic manioc varieties often cite the demands on women's time of the tedious procedures of manioc detoxification (see the preceding section) as a further disadvantage of high-cyanogen varieties. Rivière (1987) similarly emphasized what he saw as the tedium and triviality of manioc processing, in arguing that in Amazonia complex processing technologies functioned principally to control women, by limiting their freedom of action, in male-dominated societies (but see Heckler 2004). As in Amazonia, processing of bitter manioc is often women's work in Africa as well. Chiwona-Karltun et al. (1998, 2002) asked how African women manioc farmers themselves feel about this activity that consumes so much of their time: "Interestingly enough, the women that are the custodians of this crop do not perceive the processing or the toxin to be a problem" (Chiwona-Karltun et al. 2002). They found that farmers, particularly women, preferred bitter manioc, because it conferred greater food security than sweet manioc in three ways. First, it is protected against rodents and other pests. Second, the need to process tuberous roots immediately after harvest deters thieving, principally carried out by children and young single men (Chiwona-Karltun et al. 1998). Third, processing adds value in terms of time invested, reducing the social obligation to share manioc with neighbours. Thus in Africa, as in Amazonia (Heckler 2004), processing bitter manioc is viewed as a useful and valorizing activity.

One realm of knowledge where cultural adaptation in Africa may be lagging behind is in the extent to which farmers exploit volunteer seedlings as a source of potentially useful genetic variation. Our observations in Cameroon (DM) and in Mozambique (TC) indicate that manioc farmers have little interest in manioc volunteer seedlings. Gibson et al. (2000) showed that farmers in Africa often lacked knowledge about volunteer seedlings of another clonally propagated root crop introduced from the Neotropics, sweet potato, and noted that failure to exploit them could endanger the sustainability of sweet potato production in Africa. Use of volunteer seedlings by manioc farmers in Gabon has been studied in detail by Delêtre (2010). He found great variation among villages of different ethnic groups, and even among individual farmers within villages, in attitudes towards and use of volunteer seedlings as sources of variation. Some farmers systematically uprooted all manioc seedlings they encountered in their fields; others sometimes incorporated seedlings but seemed not to be aware of their nature, confusing them with sprouts from abandoned cuttings; yet others were aware of their nature and curious about their traits. In contrast to the situation among Amazonian Amerindian manioc farmers, who share a common store of folk knowledge about volunteer seedlings and regularly incorporate them into stocks of clones, in Gabon knowledge and practices both appear to be very heterogeneous (Delêtre 2010). Do these different cultural variants vary in their effects on sustainability of cultivation systems? Can the rarity of incorporation of recombinants lead to lower genetic diversity and decreased evolutionary potential of manioc populations? Will the diversity of behaviours be filtered, resulting in a greater degree of adaptation? Are we observing the coevolutionary process in action? Finally, do genetic differences between Amerindian and African human populations play any role in interactions with manioc and its products? Has the long association with manioc led to any genetic adaptations in Amazonian Amerindian populations? In Africa, are individuals that bear the ancestral allele of *TAS2R16* (and are thus less sensitive to the presence of cyanogens in food; Soranzo et al. 2005) less able than others to detect residual cyanogens in manioc and its products? The great genetic diversity within African populations may well include other instances in which genetic variation could interact with manioc to affect individuals' health.

New coevolutionary challenges

While manioc has thus been successfully integrated into many African farming systems, some practices and attitudes, such as the often limited interest of farmers in volunteer seedlings as sources of diversity, suggest that the "cultural domestication" of manioc in Africa (Delêtre

2010) has not yet been fully achieved. Historically, the problems of manioc toxicity have been greatest in areas of recent introduction. Today, problems occur where bitter varieties have been recently adopted as a result of changing socio-economic circumstances (Cliff et al. 1997; Ministry of Health, Mozambique 1984b; Nhassico et al. 2008). It appears that even in those regions within Africa with a very long history of manioc cultivation, farmers may sometimes lack knowledge about their crop that affects its potential adaptive value, if not now then in the future. For example, a survey in Nigeria estimated that over 90% of farmers and 70% of food processors did not perceive manioc or its products as toxic (Oluwole 2008). While this may be true—at least currently—in an area with a high degree of shared knowledge applied to the production of gari, via a process that detoxifies manioc more effectively than most other modes of preparation (Dufour 1994), there is a real danger in complacency. Even though konzo is rare in West Africa, TAN is present, and one study estimated that 9% of Nigerians suffered from low level cyanide toxicity (Akintonwa et al. 1994). Furthermore, in an era of rapid environmental change, detoxification processes and other cultural adaptations to this cyanogenic staple crop that are adequate today may not be adequate tomorrow (see below). Moreover, in some parts of Africa, maladaptive mismatches between manioc and humans are patently evident. In this section, we examine the causes of these current and future mismatches, which challenge our ability to fashion adaptive coevolutionary responses that ensure food security. *Our central conclusion is that these mismatches are not by and large due to lack of knowledge but to lack of choice by farmers.* Where their options have not been brutally limited by natural and social catastrophes, African farmers of manioc have proved to be just as ingenious in adapting to the advantages and drawbacks of this crop to meet their needs as have Amazonians. In a healthy social and environmental context, cyanogens in manioc can be a positive benefit for food security. War, poverty, degraded soils and famine tip the balance, synergizing the negative effects of cyanogens. This crop needs peace.

Manioc and food security: chemical ecology and its interactions with other factors

Factors governing food security are complex. Economic and social factors, agricultural practices, and changing environments and climates can all affect the durability of food-production systems (Gregory et al. 2009). Assessing the role of manioc in meeting global food demands in a time of significant global change depends on answers to several questions: Will the crop's growth rates be maintained? Will manioc be safe to consume? Changes in land use, ecology, climates and socio-economic environments can all affect not only the ability of manioc to produce calories but also its cyanogen levels. The ability of people to produce, or their capacity to buy, the protein and micronutrients required by dependence on this crop as a staple, and already often in precariously short supply, may also change (Liu et al. 2008). Will these different kinds of change interact, and if so, with what consequences?

It has been estimated that in the next 40 years global food production must rise by 70% to meet the demands of an increasing global population (FAO 2009). This projection assumes increasing affluence and hence increasing per capita consumption. Another projection (The Royal Society 2009) that does not include this assumption puts the needed increase in food production at 50%. Since this increase in demand will predominantly occur in the developing world, there is a need to focus on crops grown in these regions under local conditions. As more demanding crops are increasingly abandoned in some parts of the developing world subject to the combined pressures of land degradation and climate change, an increasing number of farmers will adopt manioc as a new crop (Nhassico et al. 2008; Liu et al. 2008). The area and total production of manioc have already increased more than threefold since 1980 in tropical Africa (Nhassico et al. 2008). In addition to its higher yields than other crops, the principal reasons for this are its ability to tolerate variable conditions and its low requirement for fertilizer (El-Sharkawy 2007). Like chemical defences, these are hallmarks of manioc's relatively resource-conserving strategy compared to many crop plants. We contend that if we are to achieve the necessary increases in food production, we will need to take into consideration the changing context in which crops will be grown: first, the changing ecological context, marked by rapid environmental change (IPCC 2007) and an increasingly uncertain supply of essential nutrients for crop growth such as phosphorus (Cordell et al. 2009); and second, the changing social context, marked by social unrest (itself not unrelated to environmental change), by the unfamiliarity of farmers with procedures for detoxifying a newly adopted and challenging crop, and by various economic constraints that limit the amount of time, water and other resources they would be able to mobilize for its detoxification, had they the requisite know-how. The AIDS epidemic also places increasing stress on poor rural households, favouring cultivation of manioc, which requires less labour than other crops. Increasingly, farmers of manioc in such regions are likely to be caught between the devil and the deep blue sea: unable to grow less-defended, more demanding crops than manioc, which are also often high-cyanogen varieties, yet lacking the information and time to detoxify manioc technologically and the protein to detoxify it physiologically. This mismatch is likely to intensify, with catastrophic consequences for

agricultural systems and for human health, unless we find ways of solving this problem in applied chemical ecology. To add to the challenge, changes in both climate and atmospheric composition have the potential to make current maladaptation even worse.

Management of nutrients for crop growth

Of this nexus of issues, the first one we will address is the management of nutrients for crop growth. Managing soil fertility and the physico-chemical properties of soils that determine their capacity to supply nutrients and water is crucial. First, soil quality determines the kinds of crops that can be grown and thereby people's ability to complement manioc with a range of other plant (or animal) foods. Second, soil quality affects not only productivity of manioc (as any other crop), but also its quality as food, by influencing its nutrient content and cyanogen concentrations in ways that are still poorly understood (Alves 2002; Bokanga et al. 1994).

Careful nutrient management will be essential in the sustainable production of manioc, and indeed any crop. Excessive (or poorly timed) application of nutrients, especially mobile nutrients such as N (Tinker and Nye 2000), is both costly and potentially environmentally damaging. For example, NO_3^- can be readily lost via leaching, resulting in contamination of water supplies, and via conversion into the potent greenhouse gas nitrous oxide (see Jackson et al. 2008 for recent review). How we supply N to increase crop production must take these factors into consideration. Since the chemical composition of plants is closely related to nutrient supply, excess N supply may increase the production of N-based defence compounds (see below). For example, it has been shown that increased N supply can result in increased cyanogen levels in a number of crops (Busk and Møller 2002; Briggs 1990; Forslund and Jonsson 1997). Similarly, N supply helps to regulate the synthesis of proteins, which are important in the detoxification of cyanide in human diets. Striking a balance between these factors will be challenging but important. One solution may be to increase diversity in human diets (Johns 2003), but in times of drought, war and famine, when people have been forced to subsist on a monotonous diet of manioc and when konzo epidemics thus typically occur, this will be especially challenging.

While excessive supply of nutrients can negatively impact the sustainability of agroecosystems, many farmers, especially those in the developing world, in fact have limited access to fertilizers (Cardoso and Kuyper 2006). In addition to reducing crop yields, inadequate nutrient supply can alter the chemical composition of plants, including manioc. With increasing atmospheric concentrations of CO_2, this issue may become ever more significant, as plant N:C ratios are further reduced (see below). Taken together, all these points make it clear that nutrient management plans will be required if we are to maximize yields, manage the nutritional value of plants and minimize the costly and potentially environmentally degrading losses of nutrients from more closed biogeochemical cycles. The potential to address the issue of soil fertility, for example through including legumes in crop rotations, or intercropping, needs to be explored.

Agricultural intensification and/or expansion into marginal lands will increase pressure upon already delicate soils (Jackson et al. 2008). For example, increased cultivation can lead to a reduction in the structural stability of soils, loss of soil organic matter, increasing soil erosion and decreasing water holding capacity. As has been shown for a number of crops, water stress can result in increased production of defence compounds (Gershenzon 1984; Gleadow and Woodrow 2002b; Gleadow et al. 2009c). This, coupled with projections of decreased rainfall in many (but not all) regions of the world (IPCC 2007), may result in changes in the chemical composition of important plants. Such changes could have particularly dramatic consequences in plants containing biologically active allelochemicals. It is clear that addressing these issues will require baseline information on the growth and nutrition of manioc across a wide range of geographical locations (especially sampling latitudinal gradients), farming systems and plant genotypes. This must also be coupled with information on food preparation, cooking and taste preferences (as they affect detoxification) of consumers of manioc.

Environmental and social catastrophes: their interactions with cyanogens

Drought and war have often precipitated agricultural crises and epidemics of konzo in the poorest manioc-dependent areas of Africa in recent decades (Cliff et al. 1997; Cock 1982; Ministry of Health, Mozambique 1984a; Nhassico et al. 2008). Konzo is also established in some areas, with frequent epidemics or sporadic cases, for example in Bandundu in the Democratic Republic of Congo (Banea et al. 1992) and Mogincual in Mozambique (Ernesto et al. 2002). Although not directly due to catastrophe, the persistence of konzo in some parts of Africa, together with underlying chronic cyanide intoxication in the population (Ernesto et al. 2002), reflects the chronic agricultural crisis in these areas. A change in circumstances, such as drought or displacement, may precipitate a konzo epidemic. What are the underlying reasons for this? What are the relevant social and environmental factors? In catastrophic circumstances, is it the lack of variety in the diet, or is it that the food itself contains more cyanogens, as a result of

increased concentration in response to environment, through preferential cultivation of bitter varieties, their better survival under catastrophic conditions, or indeed all three? It is important to try to unravel these possibly confounding factors if manioc is to be promoted as a viable option for subsistence farmers to maintain food security.

The discovery that konzo was associated with cyanide from manioc was a direct result of the investigation of a drought-associated epidemic (Ministry of Health, Mozambique 1984a, b). Drought-associated epidemics have also been reported from Tanzania (Mlingi et al. 2009), Democratic Republic of Congo (Boivin 1997) and continue to be episodic in northern Mozambique (Cliff 1994, 2009). All the prerequisites for konzo epidemics—the cultivation and use of bitter varieties, insufficient processing and a protein-deficient diet (Tylleskär 1994)—are exaggerated during droughts.

Social and economic factors such as reduced opportunities for trade with non-manioc growing areas and increased poverty may mean that less alternative food stuffs are available, particularly those with high protein content (Cliff 2009). Trade may also contribute to konzo epidemics. In Zaire (now Democratic Republic of Congo), the method of processing changed and shortened when a new road to the capital turned manioc into the dominant cash crop (Tylleskär et al. 1991). In Mozambique, farmers were caught short after they had sold their surplus to drought-stricken neighbouring Malawi (Cliff 2009).

Environmental factors include a preference for the cultivation of bitter manioc, and the physiological response by the plant resulting in an increased cyanogen concentration. Manioc is more drought-resistant than other crops, and bitter varieties are more resistant to drought than sweet (Bellotti and Riis 1994; Essers et al. 1992; Ministry of Health, Mozambique 1984b; Wilson and Dufour 2002). Thus, during drought, as other crops die out, communities become more dependent on bitter manioc and consequently their intake of cyanogens increases. As they face food shortage, people may then take short cuts in processing bitter manioc. For example, in the large drought-associated epidemic in Mozambique, they shortened the time of sun-drying (Ministry of Health, Mozambique 1984b). The manioc-dependent diet is low in protein and particularly deficient in the sulphur-containing amino acids that are essential for detoxifying cyanide in the body, thus compounding the effect of the high cyanide diet (Cliff et al. 1985). One study compared the cyanide levels in flour purchased in markets in northern Mozambique in a typical year with those in a drought year (Ernesto et al. 2002; Nhassico et al. 2008). The flour had on average 40 ppm cyanide during a 'normal' year. In a drought year, that concentration was of the order of 100–200 ppm cyanide, or 10–20 times the WHO recommended level. Urinary

thiocyanate concentrations, a marker of cyanide intoxication, were extremely high in apparently healthy schoolchildren in years following the catastrophic drought of 1981 (Cliff et al. 1985). Although high concentrations have persisted (Ernesto et al. 2002), they have not reached the levels found during the severe drought.

Increased cyanide in the flour as a result of less efficient processing is only part of the story. As discussed above, manioc itself becomes more cyanogenic when subject to water stress. Thus, a cultivar known to be relatively safe, and requiring a certain level of efficiency in processing, will almost certainly become more bitter under drought conditions (and thus require more effective processing to reduce cyanogens to the same concentration in the processed product). This response is not unique to manioc. Leaves of many cyanogenic plants are known to become more toxic under drought conditions (e.g. Gleadow and Woodrow 2002b; Nelson 1953).

Konzo has also been associated with displacement and war. For example, in Mozambique in 1992–1993, a large epidemic occurred among people displaced by war, and continued after they returned home with inadequate support. Communities turned to bitter varieties during the war, as they were more productive and had a shorter reproductive cycle. Importantly, they were more resistant to predation by monkeys and wild pigs (Cliff et al. 1997), as noted earlier by Cock (1982). More recently, konzo associated with war has been reported from the Democratic Republic of Congo (Chabwine et al. 2009) and among war refugees from Central African Republic in Cameroon (Ciglenecki et al. 2009). These latter examples show that when social catastrophes limit people's options, manioc-related public health problems can develop even in regions with long and successful experience in adapting to high-cyanogen varieties of the crop.

Climate change and food security: predicted changes in nutritional quality of manioc under changing climate and atmospheric composition

Food security encompasses both the availability and the nutritional quality of food (Pinstrup-Andersen 2009). Despite the vital importance of manioc to food security in many parts of the developing world, and the effects of residual dietary cyanide on human health, little is known about how cyanogen production in plants will be affected by climate change. Some areas where manioc is cultivated, although not all, will experience more frequent or intense droughts as a result of climate change, and this should lead to higher cyanogen levels (see above). To our knowledge, there have been no studies on the direct effect of elevated temperature on cyanogen production in manioc or any other species, so any comments would be speculative.

Increased temperatures are, however, usually associated with higher rates of evapo-transpiration which may lead to a physiological drought. Any promotion of manioc as the food of the future will need to be accompanied by the necessary education for processing, as planting less bitter cultivars appears not to be a solution. Farmers have good reasons for preferring bitter varieties (Boivin 1997; Chiwona-Karltun et al. 1998, 2002).

An overlooked aspect of the food security debate is the direct effect of elevated atmospheric CO_2 on the nutritional quality of plants (Stiling and Cornelissen 2007). All four aspects of the nutritional quality of manioc (protein, cyanide, micronutrients and calories) are likely to be affected. Plants grown at higher CO_2 have reduced foliar protein levels, with mean reductions of around 16 and 7% in C3 and C4 plants, respectively (Jackson et al. 2008; Leakey et al. 2009). The reason for this is the tendency for plants to down-regulate the photosynthetic machinery in response to the increased efficiencies allowed by higher atmospheric CO_2 (Gleadow et al. 1998; Jackson et al. 2008). Elevated CO_2 experiments suggest that the response in manioc is at the low end of the range (Fernandez et al. 2002; Gleadow et al. 2009b). Manioc roots are already extremely low in protein (El-Sharkawy 2004), and must be supplemented with protein from other sources. Thus, any decrease in dietary protein in manioc-dependent areas is more likely to come from the decrease in protein of the alternative foods. Protein levels in wheat, barley and rice are expected to be 10–15% lower by 2030 as a direct result of increasing CO_2 (Erbs et al. 2010; Gregory et al. 2009; Taub et al. 2008; Wieser et al. 2008), and, indeed, may have already decreased in the past 50 years (Taub et al. 2008). It is anticipated that any decrease in protein concentration of tropical C4 crops such as maize, millet and sorghum will be half that of C3 plants such as wheat (Leakey et al. 2009).

As discussed above, an important determinant of nutritional value in a manioc-dominated diet is the overall ratio of protein to cyanide in the diet. If the overall protein intake from grains and legumes is expected to decrease, what will be the overall ratio? The only study, to our knowledge, on this ratio in manioc showed a large increase in cyanogenic glucosides in the leaves of plants grown at high CO_2 on a per mass basis, as well as relative to leaf protein (Gleadow et al. 2009b). Studies on other cyanogenic plants similarly show an increase in the cyanide:protein ratio in leaves (Gleadow et al. 1998, 2009a). While manioc leaves are frequently consumed as a protein supplement (Gomez and Valdivieso 1985), it is the tuberous root that is the primary food. This same study did not detect any change in cyanogen levels in the starchy core in plants grown at elevated CO_2, and no change in the protein:cyanide ratio. The peel, however, was more

cyanogenic in plants from the high emissions scenarios (R. Gleadow et al., unpublished data). While the peel is not usually consumed by humans (except under extreme circumstances; Ministry of Health, Mozambique 1984b), it is often used in stock feed, and if not processed correctly it could decrease animal production (Chauynarong et al. 2009; Ofuya and Obilor 1993) and thereby protein supply. Cassava peel is commonly fed to village chickens. Its impact has not been studied, but broilers consuming cassava diets commonly show depression in growth rates (Tewe 1992). Any consequent decrease in the consumption of animal protein by humans would have an adverse effect on food security for many reasons, among them the need for protein to detoxify cyanide. Problems of increased ingestion of cyanogens and less protein are likely to be exacerbated by social unrest and migration as a consequence of changes in rainfall patterns and availability of arable land in the future. With the decrease in availability of alternative food sources together with the decrease in protein of those foods, cyanide-induced diseases such as TAN and Konzo are likely to increase in the coming century.

Manioc is also notoriously low in essential micronutrients, aspects that are already the object of intensive plant improvement programs (e.g. Fauquet and Tohme 2004). Micronutrient deficiencies are less obvious than lack of calories, so they are sometimes referred to as the "hidden hunger". With more than half of the world's population suffering from inadequate dietary intake of essential nutrients, and many with inadequate protein, there is a need to consider the impacts of climate change on the overall nutritional value of plants (e.g. Ziska and Bunce 2007). Hidden hunger problems are likely to become worse in the future: plants grown at elevated CO_2 contain 5–20% lower concentrations of K, Ca, S, Mg, Fe, Zn, Mn and Cu (Loladze 2002), compounding the existing problem of micronutrient malnutrition in those deriving most of their nutriment from manioc.

The fundamental determinant of food security is crop yield. Predictions of yields for crops in the coming century take into account the effects of climate change (especially temperature and episodic drought) as well as the stimulatory effect of CO_2 on photosynthesis (Jackson et al. 2008; Ziska and Bunce 2007). Assuming a business-as-usual approach to agriculture and expected population increases, Lobell et al. (2008) predict that by 2030 there will be an overall reduction in per capita calorie availability in sub-Saharan Africa. Increased cultivation of manioc may help bridge the gap. With its high optimum temperature and ability to tolerate drought, manioc is expected to be little affected by climate change compared with crops such as wheat and rice (Lobell et al. 2008; Liu et al. 2008; Taub et al. 2008). There are, however, significant health risks

from cyanide toxicity associated with an increased reliance on manioc for calories, and any promotion of manioc must be coupled with the know-how for detoxification. It is possible that manioc will not be able to meet the demand for calories. Gleadow et al. (2009b) found that rather than stimulating the production of tuberous roots, manioc grown at twice-ambient CO_2 produced fewer and smaller tuberous roots, and a significant reduction in yield. The jury is still out on whether this is a typical response of manioc to high CO_2 (see for example Fernandez et al. 2002; Imai et al. 1984) or the result of some third as yet unknown variable, but it does cast doubt on whether manioc will be able to deliver the promised yields. Even the most optimistic assessments for enhanced crop production (manioc or otherwise) are contingent on high inputs of fertilizers, especially nitrogen and phosphorus. With much of the world's population having limited access to costly fertilizers, achieving the potential improvements in yield from enhanced CO_2 is unlikely. At any rate, there is a need to include the impacts of elevated CO_2 and climate change in the manioc production equation.

Implications for other crops and agroecosystems

Although manioc is the most spectacular example, many other crop plants contain allelochemicals (e.g. Kliebenstein 2009; Osbourn et al. 2003; Wink 1988). The approach we employ may be useful in analysing other crops and agroecosystems.

Has interaction with allelochemicals driven local genetic adaptation in human populations?

Agricultural populations have evolved genetic, as well as cultural, adaptations to their evolving domesticates. Among the most spectacular examples are the evolution of lactase persistence in milk-drinking pastoralist groups of Eurasia and Africa (Swallow 2003) and the evolution of increased amylase copy number in farming populations, associated with increased efficiency in the use of starch-rich staple foods (Perry et al. 2007). Have plant allelochemicals also promoted human diversification (Jackson 1991, 1996)? How much genetic variation exists within and among human populations for the capacity to detect, or to tolerate, allelochemicals or their breakdown products? Is this variation driven by selection? The example of genetic variation at the bitter-taste receptor gene *TAS2R16* discussed above (Soranzo et al. 2005) is suggestive. Some other members of the *TAS2R* gene family present a somewhat similar pattern of variation, with widely divergent alleles, each often found at high frequency in only one region or continent (Kim et al. 2005). This has led to the

suggestion that variant alleles arose under local natural selection, allowing individuals who carry them to avoid consumption of toxic substances occurring in locally occurring plants (Drayna 2005). Testing this hypothesis will require knowing much more than we currently do about the specificity of different receptors, and of the products of different alleles at each locus, for bitter compounds that humans actually encounter (Hofmann 2009). Genetic variation at bitter-taste receptor genes was discovered serendipitously using non-natural bitter substances (Wooding 2006), and only recently have functional assay systems begun to "deorphanize" these receptors (Drayna 2005) by identifying the range of naturally occurring allelochemicals to which each is specific.

Even for the specific bitter-taste receptor genes for which there is good evidence for selection, important open questions remain. Variation at the *TAS2R38* locus determines phenylthiocarbamide (PTC) tasters and non-tasters (Wooding 2006; Wooding et al. 2004). The PTC gene was the first bitter-taste receptor to be "deorphanized". Its function (at least, that of the alleles conferring the taster phenotype) appears to be the detection of PTC-like naturally occurring compounds, i.e. those with a thiourea chemical moiety (Sandell and Breslin 2006). Tasters are more sensitive than non-tasters to glucosinolates, which have a thiourea moiety, and this presumably helps them to avoid these and other plant chemicals that may cause thyroid malfunction (Sandell and Breslin 2006). It has been suggested that taster phenotypes could enjoy a selective advantage in regions where low iodine availability results in high goitrogenic potential of glucosinolates (Boyce et al. 1976). However, variation at the PCT locus shows no geographical patterns that suggest local adaptation in regions of high goitrogenic potential, or of high consumption of glucosinolate-containing plants. Glucosinolates are taxonomically restricted in their occurrence (Halkier and Gershenzon 2006; Wink 2008), and the most common glucosinolate-containing plant family, Brassicaceae, are primarily temperate-region herbs. The two PTC phenotypes, however, are maintained at near intermediate levels in many populations worldwide. This pattern not only indicates ubiquitous selection pressures but also strongly suggests balancing selection, molecular evidence for which was found by Wooding (2006) and Wooding et al. (2004). Balancing selection in turn indicates that the allele (AVI) responsible for the "non-taster" phenotype is not non-functional, but confers the ability to detect other, as yet unidentified aversive compounds, so that heterozygotes are sensitive to a greater range of compounds than either homozygote (Drayna 2005). What other compounds could be among the key tastants that have driven selection at this locus? We find intriguing the chemical similarity between thiourea and thiocyanate. The latter is not only a

degradative product of glucosinolates (Halkier and Gershenzon 2006) but is also produced by the reaction by which many organisms, including many plants, use the enzyme rhodanese to detoxify cyanide (Beesley et al. 1985), generated by a geographically widespread class of allelochemicals, cyanogenic glycosides (Jones 1998; Wink 2008). Degradative products of cyanogenic glucosides, including thiocyanate, can accumulate in plants (Okolie and Obasi 1993; Zagrobelny et al. 2004), although many plants, even some that possess rhodanese (e.g. manioc; Okolie and Obasi 1993), employ an alternative, nitrogen- and sulphur-sparing catabolic pathway via β-cyanoalanine synthase and cysteine synthase (Elias et al. 1997). Detecting thiocyanate could help herbivores avoid cyanogens, as well as thiocyanate itself, which, though less toxic than HCN, has a negative effect as a goitrogen and is a conceivable cause of konzo (Tshala-Katumbay 2009).

Secondary metabolites in plant domestication

Manioc is only one among the dozens of domesticated plant species with which humans have coevolved over the past 10,000 years. Whereas domestication has often led to reduction in chemical defences, many classes of allelochemicals are present in domesticated plants (Kliebenstein 2009; Osbourn et al. 2003; Wink 1988), and some, like cyanogens in manioc, appear to have increased in concentration over domestication, at least in some varieties (McKey and Beckerman 1993). How can we explain the diversity of fates of chemical defences during plant domestication?

Three selective pressures, acting singly or in combination, could confer advantages on crop plants with reduced allelochemical content. First, farmers prefer plants in which toxic and/or bitter-tasting compounds are absent from the parts used as food. Domestication has often entailed selection against toxic or anti-nutritional metabolites of plants, at least in the parts of these plants that are consumed by people (Wink 1988). Second, lower concentrations of defensive compounds in the non-harvested parts of cultivated plants are usually attributed to the reallocation of limited resources within the plant to increase yields (Denison et al. 2003; Rosenthal and Dirzo 1997). Farmers choose the best land available and attempt to augment resources for their crops. Cultivated habitats are thus usually characterized by higher resource supply and hence availability to plants, and lower risks of abiotic stresses than are the habitats of crop plants' wild ancestors. These changes favour shifts from resource conservation to resource acquisition along the continuum of plant growth/ defence strategies (McKey et al. 2010a). Selection for lower content of secondary metabolites has probably become more intense with crop improvement in recent decades (Gerber et al. 1999). In beans (*Phaseolus vulgaris* L.), for example, local landraces possess lower diversity of anti-fungal phytoalexins than do wild beans and are less resistant to fungal attack, but modern cultivars have even lower values for both traits (Lindig-Cisneros et al. 2002). Suggestive of a similar scenario is the finding by Köllner et al. (2008) that most North American maize varieties have lost the ability to produce (E)-β-caryophyllene, a damage-induced signal that attracts natural enemies of herbivores in teosinte, the crop's wild ancestor and in European maize lines. A third selective pressure, which has received much less attention than the other two, is relaxation of selection for direct chemical defences of crop plants because these are replaced by indirect defence, supplied by the crops' human protective mutualists. Humans not only provide indirect defence themselves, by scaring, guarding, pesticide application and other forms of active crop protection but also shape agroecosystems to enhance indirect defence provided by other organisms, and manage agrobiodiversity and patterns of crop phenology, field tenure and crop rotation to exploit opportunities for escape of crop plants in space and time from their herbivores and pathogens (Glass and Thurston 1978; Ruelle and Bruggers 1982).

However, each of these selective pressures favouring the loss of allelochemicals in crop plants can be countered by other selective forces maintaining them. First, by conferring resistance to pests (Kliebenstein 2009), toxic or otherwise anti-nutritional plant defence compounds may continue to confer advantages, even if they are present in plant parts consumed by humans, if they are removed during food preparation (Johns 1990; Jones 1998). Second, as discussed above, the distinction between "toxin", "nutrient" and "medicine" is often only a matter of dosage (Gerber et al. 1999). Delicate balance between costs and benefits in food of spices (which owe their properties to plant allelochemicals), for example, may explain latitudinal gradients in the number and concentration of spices employed (Billing and Sherman 1998; Sherman and Billing 1999) and differences in spiciness between meat and vegetable recipes of the same culinary tradition (Sherman and Hash 2001). Third, agricultural habitats vary greatly in their capacity to provide resources to plants and buffer environmental unpredictability. The optimal point on the resource-conservation/resource-acquisition continuum is thus likely to vary across crop plants and environments. Environments marginal for agriculture, owing to poor soil quality, drought stress, or other factors, may favour crop plants with more effective chemical defences than most. It is notable that, like manioc (McKey and Beckerman 1993), another crop well known for its high content of toxic compounds, grasspea [*Lathyrus sativus* L. (Fabaceae), which contains the neurotoxin β-N-oxalyl-L-α,β-diaminopropionic

acid], is also prized for its ability to provide economically viable yields in poor or drought-prone soils (vaz Patto et al. 2006). Fourth, while resource availability may be higher and unpredictability of abiotic environmental factors lower in cultivated than in wild environments, other features of cultivated environments may favour maintained, or even increased, levels of defences in crop plants. For example, while low species diversity in agroecosystems, or low intra-specific genetic diversity in crop populations, confers farm-management advantages, it could also make crop plants more apparent to herbivores (Feeny 1976) and more prone to pest epidemics, thus favouring the maintenance of defence.

Finally, while protection by humans (indirect biotic defence) can sometimes compensate for the loss of crop direct defences, this compensation is likely to be only partial. Crop plants and farm environments vary in the extent to which farmer vigilance can "replace" direct chemical defences (Ruelle and Bruggers 1982). As discussed above for manioc, crops planted in home gardens can be looked after frequently, but those planted in scattered fields often far from the farmers' homes—for example, crops in long-fallow shifting-cultivation systems—cannot receive such frequent attention and are more likely to require direct defences. In some crops, phenology may result in narrow temporal windows of vulnerability to enemies, permitting farmers, or those they employ, to hold vigil in their farms (Ruelle and Bruggers 1982). Production of vulnerable plant parts in concentrated pulses could also lead to herbivore satiation, and farmers sometimes manage crop phenology to this end (Lansing and Miller 2005). However, when a crop is vulnerable to herbivores and pathogens over a prolonged period, providing indirect defence is much more difficult. Roots, tubers and other underground storage organs are often present in fields over very long periods. Inability to escape herbivores and pathogens in time may mean that such "apparent" organs are more likely to require direct defence. In fact, many tropical root crops are known for their content of toxic or anti-nutritional secondary metabolites. These include taro [*Colocasia esculenta* (L.) Schott] and other aroids (calcium oxalate raphides; Holloway et al. 1989), yams (*Dioscorea* spp., Dioscoreaceae), which contain saponins (Bradbury et al. 1995; Sautour et al. 2007) and manioc, which contains cyanogenic glucosides (McMahon et al. 1995). Crops grown for their leaves may also suffer prolonged vulnerability, favouring the maintenance of direct defence, especially in herbivore- and pathogen-rich tropical environments. A striking example of this is bitterleaf, *Vernonia amygdalina* Del. (Asteraceae), grown for its leaves in the African humid tropics. Among other secondary metabolites, its leaves contain high concentrations of sesquiterpenes that, based on their anti-microbial (Erasto et al. 2006) and antifeedant properties (Ganjian et al. 1983), should confer a degree of protection against herbivores and pathogens. Interestingly, *V. amygdalina* is also frequently used medicinally, both by humans (Erasto et al. 2006) and by chimpanzees (Huffman 2001), and is "believed to be very effective as a tonic food" (Koshimizu et al. 1993). To summarize, as in plant defence generally, we should expect to observe only rarely univariate trade-offs between crop direct defence and indirect defence supplied by farmers but rather syndromes of complementary, sometimes synergistic defences (Agrawal 2007; Agrawal and Fishbein 2006). Secondary metabolites continue to play important roles as chemical defences of many crop plants (e.g. Kliebenstein 2009; Osbourn et al. 2003). They, or their metabolic derivatives, are thus also potentially present in the foods people eat, with important effects, both positive and negative, on human health and nutrition.

The points discussed above all indicate that our findings on manioc can contribute insights for managing other chemically defended crops in an era of rapid global change. Particularly pertinent could be analysis of other crops which, like manioc, are characterized by conspicuous, agronomically and ecologically significant polymorphism in chemical-defence phenotypes. The best-known example, next to manioc, is sorghum. In this crop, pigmentation of seed coats reflects variation in tannin content. This variation affects not only how different varieties are prepared and used (Mukuru et al. 1992) but also their resistance to pests such as granivorous birds (Bullard 1988; Ruelle and Bruggers 1982) and fungal pathogens (Thakur et al. 2006). The occurrence in sorghum of another widespread class of allelochemicals, cyanogenic glucosides, makes this crop a particularly interesting target for studies of how to manage chemical-defence phenotypes under global change (Gleadow et al. 2009c).

Concluding remarks: The challenges of interdisciplinary research and the contribution of chemical ecology

What practical lessons can be learned from this exploration of the chemical ecology of interactions between people and manioc? First, millennia of cultural selection acting on Amerindian cultivators of manioc in Amazonia have conserved options that worked and winnowed out those that did not. The diversity of manioc germplasm and of ways of using it, closely adapted to varying soils, flooding regimes, farmers' lifestyles and the like, probably surpasses anything seen in Africa (the qualifier "probably" is needed because the few attempts at intercontinental comparison of manioc diversity have so far treated only neutral genetic

markers, not plant traits under farmer selection, and have hardly touched farming systems). Amazonian cultivators devised dietary combinations appropriate for dependence on bitter manioc, and created different ecological and cultural niches for sweet and bitter varieties. Furthermore, it appears that most or all Amerindian groups who cultivate manioc incorporate volunteer seedlings as a source of diversity (Rival and McKey 2008).

In Africa, cultures adapted over time to the advantages and constraints of this plant, creating niches for sweet and bitter varieties, as in Amazonia, and using polymorphism in toxicity to agronomic advantage. Knowledge on how to detoxify bitter manioc, a cultural trait under strong selection, probably spread rapidly. Today, however, lack of options often forces rapid switches to dependence on manioc. Transmission of detoxification know-how cannot keep pace. In other cases, so many other resources are lacking that knowledge is not the limiting factor.

Other cultural traits, such as interest in volunteer seedlings as a source of diversity, seem to have evolved at varying speed among African farmers, and often slowly (Delêtre 2010). While perhaps often selectively neutral today, interest in volunteer seedlings could be crucial in the future, as environmental change places a premium on genetic diversity and new adaptations. Here, Amerindian practices could inspire innovations in participatory plant breeding schemes.

Perhaps the most important lesson to be learned is that where peasant farmers—whether in Amazonia or in Africa—have had access to basic essential resources and have had enough time, they have responded to this complex plant by fashioning cultural adaptations whose ingenuity compares very favourably with what "modern" science can produce. We can learn much from people whose livelihood depends on exploiting the advantages of this chemically defended crop and adapting to the constraints it imposes. The number and diversity of the factors that farmers must take into account to accomplish this should make us suspicious of any single-factor approach. Strategies that minimize one risk—for example, minimizing intake of cyanogens by promoting low-cyanogen varieties—may augment another risk, loss of the crop to thievery or predators. Peasant farmers are perfectly conversant with such linkages. The neglect of peasant agriculture by both donors and governments is among the deeper causes of current crises, along with the increasing inequality that deprives them of secure tenure to land and other resources, reducing benefits they can expect to receive from stewardship of these resources.

For scientists, however, seeing such linkages is not always easy, even among different subdisciplines of biology. Enthusiasm among plant molecular biologists for developing genetically modified acyanogenic manioc

varieties (Jørgensen et al. 2005; Siritunga and Sayre 2003) continued for a long time despite cautionary warnings of ecologists (Kakes 1994; McKey and Beckerman 1993). This enthusiasm has only been dampened recently by the finding that cyanogens likely play a central role in nitrogen turnover and transport as well as in defence (Jenrich et al. 2007).This discovery was presaged by under-appreciated early work on physiological roles of cyanogenic glucosides in *Hevea* (Selmar et al. 1988). That this discovery comes as a surprise over 30 years after studies first began to draw attention to primary roles of secondary compounds (e.g. Seigler 1977) speaks volumes about the disciplinary compartmentalization of science that must be overcome if we are to come to grips with multifaceted problems such as food security.

The difficulty that different branches of biology have in framing an integrative approach for our discipline give some hint of the even greater challenges to be faced in working with social scientists to study feedbacks between ecological and social processes. We must have the humility and the broad vision to accept that our science can provide essential pieces, but only pieces, of viable solutions. "Modern" science can work in creative ways with folk knowledge. But no technological fix is a "magic bullet". We must also sensitize ourselves to the natural history of *Homo sapiens*, whose highly plastic behaviour towards plants, land and other resources is shaped by social as well as by ecological contexts. Innovations we propose may be useful in some settings but not in others, and it would be useful to be able to predict, or at least to understand, why.

An example of an innovation that might have broad applicability in helping solve manioc-related food-security issues is a new detoxification method developed by Bradbury and coworkers (e.g. Bradbury 2006; Bradbury and Denton 2010; Cumbana et al. 2007). The key idea is processing of the manioc-derived product (e.g. flour or gari). This may become increasingly necessary as a supplement to processing of manioc roots, because products sold in markets are often insufficiently processed. Increasing commercialization means that even poor families buy manioc-derived products, rather than growing their own. The new method decreases the amount of cyanide in food ready for consumption by around 85%, compared with the concentration in the original processed product. The process involves mixing the flour with an equal volume of water, then spreading it out in a thin layer, and letting it "incubate" for 5 h in the shade. An alternative is to leave the mixture for 2 h in the sun (Bradbury and Denton 2010). Enzymes naturally present in the tuberous root hydrolyse the glucosides, releasing HCN, which volatilizes. Even gari, which contains much less linamarin than other flours, can be processed in this way and the toxin essentially eliminated. There are two potential impediments. First, the

method requires water, and during droughts—when efficient processing is most crucially required—clean water may be in critically short supply. Although less water is needed for cooking the product, there is still some loss from evaporation, so that more water is consumed. Another impediment is that the method takes time and involves a change in the daily routine. Social customs surrounding food preparation are often resistant to change. But why this is so must be analysed, not just ascribed to "tradition", the invention of which is often surprisingly rapid (Hobsbawm and Ranger 1984).

The challenges to interdisciplinary research are considerable; each discipline brings its own jargon to the table. But complex problems need insights from multiple perspectives, and bridging communication gaps is worth the effort. Achieving a secure and safe food supply for those already on the edge is a goal that will never be attained if our purview does not include the entire food production pathway, from soil and climate to plants to people, now and in projected future environments. Participants in such an endeavour must apply their discipline's inherent rigour and at the same time recognize its assumptions and limits, and be open to linkages with findings from other perspectives. Local people should not be just objects of study but full-fledged participants, since their experience can help shape fundamental research questions.

Producing an integrative view of human/plant chemical ecology will not be easy. It will take chemical ecologists out of a "comfort zone", forcing them to join up with other disciplines to tackle questions for which their expertise is necessary, but not sufficient, to form responses and act upon them. Some chemical ecologists have learned how to decipher complex chemically mediated trophic relationships in ecosystems; others have decrypted the fates of allelochemicals in the bodies of herbivores. But few have been prepared by their training to address questions like those raised in this paper: How do land degradation, agricultural intensification, or increased reliance on synthetic fertilizers affect what crops people can grow and their allelochemical content, how do shifts to new crops affect allelochemical intake, and how does this affect human health? How do such changes interact with the impacts of climate change and of changing atmospheric composition on the chemical defence phenotypes of crop plants? Again, if we are to address the complex issues considered here, we will need to move out of our comfort zones, encountering scientists from other contributing disciplines who are ready to do the same, and identifying and addressing common questions.

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