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Potato Glycoalkaloids: Chemistry, Analysis, Safety, and Plant Physiology

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ABSTRACT: Potatoes, members of the Solanaceae plant family, serve as a major, inexpensive food source for both energy (starch) and good-quality protein, with worldwide production of about 350 million tons per year. U.S. per capita consumption of potatoes is about 61 kg/year. Potatoes also produce potentially toxic glycoalkaloids, both during growth and after harvest. Glycoalkaloids appear to be more toxic to man than to other animals. The toxicity may be due to anticholinesterase activity of the glycoalkaloids on the central nervous system and to disruptions of cell membranes affecting the digestive system and other organs. The possible contribution of glycoalkaloids to the multifactorial aspects of teratogenicity is inconclusive. Possible safe levels are controversial; guidelines limiting glycoalkaloid content of potato cultivars are currently being debated. This review presents an integrated, critical assessment of the multifaceted aspects of the role glycoalkaloids play in nutrition and food safety; chemistry and analysis; plant physiology, including biosynthesis, distribution, inheritance, host-plant resistance, and molecular biology; preharvest conditions such as soil composition and climate; and postharvest events such as effects of light, temperature, storage time, humidity, mechanical injury, sprouting inhibition, and processing. Further research needs are suggested for each of these categories in order to minimize pre- and postharvest glycoalkaloid synthesis. The overlapping aspects are discussed in terms of general concepts for a better understanding of the impact of glycoalkaloids in plants and in the human diet. Such an understanding can lead to the development of potato varieties with a low content of undesirable compounds and will further promote the utilization of potatoes as a premier food source for animals and humans.

KEY WORDS: potatoes, *Solanum tuberosum*, glycoalkaloids, chaconine, solanine, solanidine, analysis, nutrition, food safety, plant-host resistance, storage, processing, plant molecular biology, plant physiology, plant genetics.

I. INTRODUCTION

The Solanaceae family contains many plants important to man. These include such diverse agricultural crops as tobacco (*Nicotiana* spp.), sweet peppers (*Capsicum annuum*), eggplants (*Solanum melongena*), tomatillos (*Physalis ixocarpa*), tomatoes (*Lycopersicon esculentum*), and potatoes (*Solanum tuberosum*). The most important of these is the potato. The commercial potato is derived from wild species first do-

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mesticated in the Andes and transported to Europe by Spanish explorers in 1565 to 1570. Potatoes are now a major food crop grown throughout the world (Hawkes, 1988; Salaman, 1985; Spoerke, 1994; Woolfe, 1987). World production is about 350 million per annum (FAO, 1992). U.S. per capita consumption of potatoes has been steadily increasing and is now 61 kg/year (Willard, 1993).

Although potatoes are commonly perceived as a carbohydrate source, they are an equally good source of high-quality protein (Friedman, 1996a; McCay et al., 1987). Potatoes contain approximately 2% protein on a fresh basis, but the value increases to about 10% on a dry-weight basis. Thus, the protein content of dried potatoes is equal to that of most cereals. Markakis (1975) showed that based on amino acid composition, the calculated protein quality of potatoes is about 70% that of whole egg protein. In addition, potatoes provide an excellent source of lysine, but are low in sulfur amino acids (cysteine plus methionine), which limits their nutritive value. Human feeding trials suggest that potato proteins are of a very high quality, higher than indicated by the amino acid composition, possibly because protein utilization is enhanced by the high concentration of free amino acids and other metabolites present in potatoes. Nestares et al. (1993) found that the nutritional quality of potato concentrate was excellent when measured in terms of its protein efficiency ratio (PER = 2.90), biological value (BV = 79.5), and net protein utilization (NPU = 74.2). Kies and Fox (1972) fed human volunteers potato protein (derived from dehydrated flakes) with and without amino acid supplementation. Their results suggest that complementary diets consisting of potatoes, which are high in lysine but low in sulfur amino acids, and cereals, which are low in lysine but high in sulfur amino acids, should provide a well-balanced protein source.

With the increased interest in potatoes and potato products, plant breeders and geneticists are continually trying to improve the pest resistance, yield, quality, and processing properties of commercial cultivars by crossing them with wild potato species or by altering their genetic pattern through molecular biological techniques. Members of the Solanaceae family, and the *Solanum* genus in particular, synthesize a variety of alkaloidal compounds. The most frequently encountered are the commonly named glycoalkaloids, which are nitrogen-containing steroidal glycosides. In point of fact, many alkaloids occur naturally in the form of glycosides and are, therefore, glycoalkaloids. Historically, however, "solanine" was one of the first alkaloids to be isolated (Baumann, 1843; Baup, 1826; Desfosses, 1820) and to be recognized as a glycoside (Zwenger and Kind, 1861). It was not until 1954 that Kuhn and Löw (1954, 1955b, d) showed that "solanine" was actually a mixture of two compounds, α-solanine and α-chaconine. Thus, the term glycoalkaloids has generally referred to the steroidal glycoalkaloids found in Solanaceae and Liliaceae. Some researchers now refer to these compounds as *Solanum* glycoalkaloids (SGA) or potato glycoalkaloids (PGA), but this has not become widespread. At least 90 structurally different steroidal alkaloids have been isolated and characterized in over 300 *Solanum* species (Cordell, 1981; Fieser and Fieser, 1959; Osman, 1983; Prelog and Jäger, 1953, 1960; Ripperger and Schreiber, 1981; Schreiber, 1968, 1979; van Gelder, 1990).

In commercial potato cultivars, the primary compounds are α-solanine and α-chaconine, glycosides of the steroidal alkaloid solanidine. While there is some debate about the actual function of these compounds in the plant, these and similar compounds have been shown to have toxic effects in humans (Hansen, 1925; Harris and Cockburn, 1918; McMillan and Thompson, 1979;

Ripakh and Kim, 1958; Rühl, 1951; Terbruggen, 1936; Willimott, 1933; Wilson, 1959). Thus, care must be taken in producing new varieties of potatoes so that the level of glycoalkaloids does not rise to an unsafe level or that new, more toxic glycoalkaloids are not introduced into the commercialized germplasm.

To further complicate the picture, many factors other than variety can affect the glycoalkaloid levels in potatoes. Climatic differences at the growing area can cause wide variations in the glycoalkaloid content, even in the same cultivar (Mondy and Munshi, 1990b; Morris and Petermann, 1985; Sinden and Webb, 1974; Slanina, 1990b; van Gelder and Dellaert, 1988). In addition, tubers do not stop producing glycoalkaloids after harvest, and improper handling and/or storage conditions may cause a dramatic rise in these compounds (Salunkhe et al., 1972). Levels can be especially high in green or damaged potatoes. Potatoes that have turned green due to light exposure are now routinely discarded as being potentially unsafe. The literature reports that at various times 14 to 27% of the potato crop has been rejected due to greening (Morris and Lee, 1984). However, Sinden (1972) suggested that glycoalkaloid levels in potatoes can be affected more by mechanical injury than by light. Petersen (1993) concurs and suggests that injured potatoes should be rejected as are green potatoes.

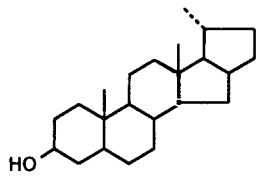
Processing may also affect glycoalkaloid content. While glycoalkaloids seem to be largely unchanged by cooking (Adams, 1991; Bushway and Ponnampalam, 1981; Jaswal, 1973; Stanley, 1991; Takagi et al., 1990), slicing, peeling, and other types of preparation may alter glycoalkaloid levels. Commercial chips and potato peel products can contain significant amounts of glycoalkaloids (as high as 200 mg/kg in one instance), but the glycoalkaloid content of these products can vary widely (Friedman and Dao, 1992). Slicing or otherwise wounding potatoes has been shown to cause an increase in glycoalkaloids over time (Ahmed and Müller, 1978; Wu and Salunkhe, 1978c), although according to Bergenstråhle et al. (1992b) this does not become significant until after 11 h.

Glycoalkaloid levels are not distributed evenly throughout the potato, but generally concentrate in the peel. However, as glycoalkaloid levels rise, this may not always be the case. This, as well as other factors affecting glycoalkaloid levels, are discussed in greater detail below. This paper presents overviews of glycoalkaloid chemistry, analysis, safety, and the complex pre- and postharvest aspects of plant physiology, which include biosynthesis, inheritance, plant resistance, varietal variations, and effects of light, mechanical injury, and storage. This overview is designed to illustrate general concepts and to suggest areas for future study. Its purpose is to leave the reader with a better understanding of the function potato glycoalkaloids have in plants and in the diet. This review strives to integrate information from the widely scattered literature on the multidisciplinary aspects of potato glycoalkaloids. These overlapping studies reveal a complex and fascinating interplay among the disciplines of genetics, plant science, chemistry, nutrition, and toxicology.

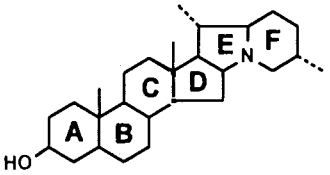
II. CHEMISTRY

A. Structure and Occurrence

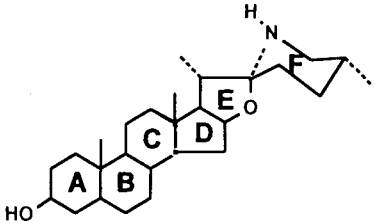
The major *Solanum* alkaloids of pharmacological and toxicological interest are steroidal alkamines, all of which possess the C_{27} steroidal skeleton of cholestane. They belong to one of five structural types as described by Schreiber in 1968 (Figure 1): (1) solanidanes, hexacyclic tertiary bases with fused indolizidine rings, such as solanidine;



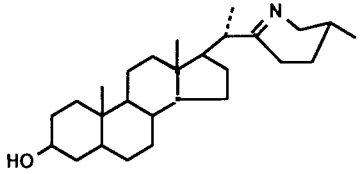
CHOLESTANE



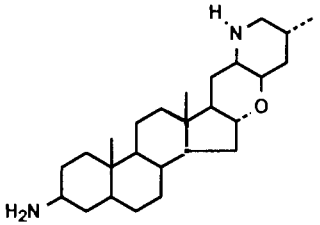
SOLANIDANE



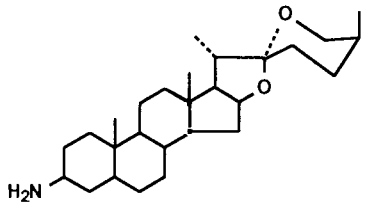
SPIROSOLANE



22, 26-EPIMINOCHOLESTANE



α-EPIMINOCYCLOHEMIKETAL



3-AMINOSPIROSTANE

FIGURE 1. Structures of alkamines found in Solanaceae.

(2) spirosolanes, spiroaminoketals, such as solasodine; (3) 22,26-epiminocholestanes, such as solacongestidine or etioline; (4) α-epiminocyclohemiketals, such as solanocapsine; (5) 3-aminospirostanes, such as jurubidine.

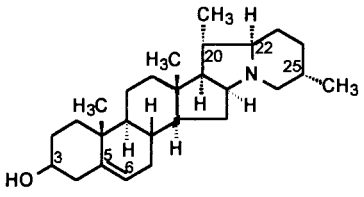
To date, the major glycoalkaloids found in various potato species are compounds of either solanidane or spirosolane aglycones, as shown in Figure 2. Solanidine is the aglycone portion of α-solanine and α-chaconine, the major glycoalkaloids found in commercial *Solanum tuberosum* cultivars.

Another solanidane is demissidine, isolated from Mexican wild potatoes, *S. demissum* Lindl. and later found in other potato species, including *S. chacoense,* as well as in some tomato varieties (Osman, 1980). Demissidine has been identified as 5,6-dihydrosolanidine. X-ray analysis of demissidine hydroiodide permitted complete stereochemical assignment of all the atoms in solanidine and demissidine. These natural solanidanes possess the 20S : 25S : NS stereochemical configuration. The hydrogen atom at C-22 is oriented toward the rear of the molecule, and the six-membered F-ring of the heterocyclic *trans*-indolizidine system has the chair conformation. This places the (25S) methyl group in an equatorial position.

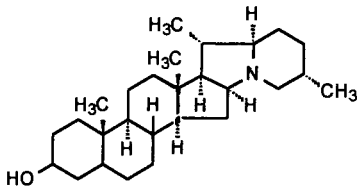
Two spirosolanes, solasodine and tomatidenol (Figure 2), have also been found in potato cultivars that have been crossed with wild species such as *S. berthaultii* and *S. vernei*, as well as in the wild species themselves (Schreiber, 1963; van Gelder et al., 1988). These two compounds are almost identical, differing only in the position of the heterocyclic nitrogen of the F-ring. Tomatidine, a 5,6-dihydrotomatidenol, has also been found in some *Solanum* species as the glycoside tomatine. Solasodine belongs to the 25R stereochemical series. Tomatidenol and tomatidine belong to the 25S series, with a reverse S-configuration at the spiro atom 22. These spirosolane alkaloids are widely distributed in numerous *Solanum* and *Lycopersicon* plant species.

The aglycones as such are found in potatoes only in trace amounts, possibly an artifact of the analytical method formed by hydrolysis. Only Zitnak (1961) has reported finding free solanidine in significant amounts in potatoes. The steroid alkaloids generally exist as glycosides, having various sugar groups attached to the aglycone backbone at the 3-hydroxy position (Figure 3). Both α-chaconine and α-solanine have a trisaccharide side chain attached to the 3-hydroxy group of solanidine (Kuhn and Löw, 1955c, d). α-Chaconine has a branched *bis*-α-L-rhamnopyranosyl-β-D-glucopyranose (chacotriose) and α-solanine has a branched α-L-rhamnopyranosyl-β-D-glucopyranosyl-β-galactopyranose (solatriose). The major solasodine glycosides, solasonine and solamargine, have the same trisaccharide side chains as α-solanine and α-chaconine, that is, solatriose and chacotriose, respectively. Likewise, the tomatidenol glycosides, the unfortunately named α-solamarine and β-solamarine (see below), are glycosides of solatriose and chacotriose. Solasonine and solamargine occur as the two major glycoalkaloids in more than 100 *Solanum* species, most notably different varieties of the bittersweet nightshade *Solanum dulcamara*. Van Gelder and Scheffer (1991) have found small amounts of the solasodine glycosides in *S. vernei* × *S. tuberosum* hybrids. Shih and Ku (1974) discovered α- and β-solamarines in Kennebec *S. tuberosum* leaves and aged tuber slices, whereas Sinden and Sanford (1981) found that wound-healed tuber tissue of 11 out of 123 commercial cultivars produced solamarines. Most of the solamarine-containing clones were derived from *S. demissum* crosses. Only one ("White Rose") was a pure *S. tuberosum* clone.

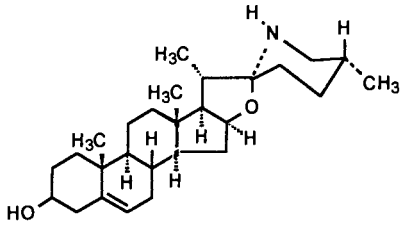
There are also two main glycosides associated with demissidine: demissine and



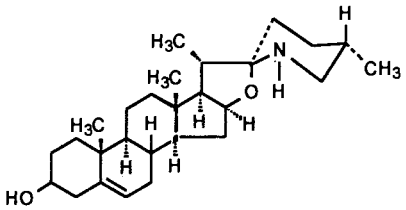
SOLANIDINE
(22αH, 25βH-SOLANID-5-EN)



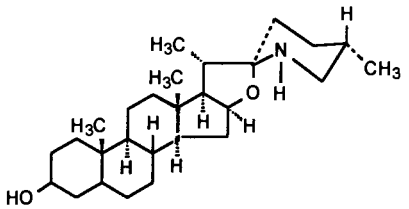
DEMISSIDINE
(5α,22αH, 25βH-SOLANIDAN)



SOLASODINE
((25R)-22αN-SPIROSAL-5-EN)



TOMATIDENOL
((25S)-22βN-SPIROSAL-5-EN)



TOMATIDINE
((25S)-22βN-5α-SPIROSOLAN)

FIGURE 2. Structures of aglycones found in potatoes.

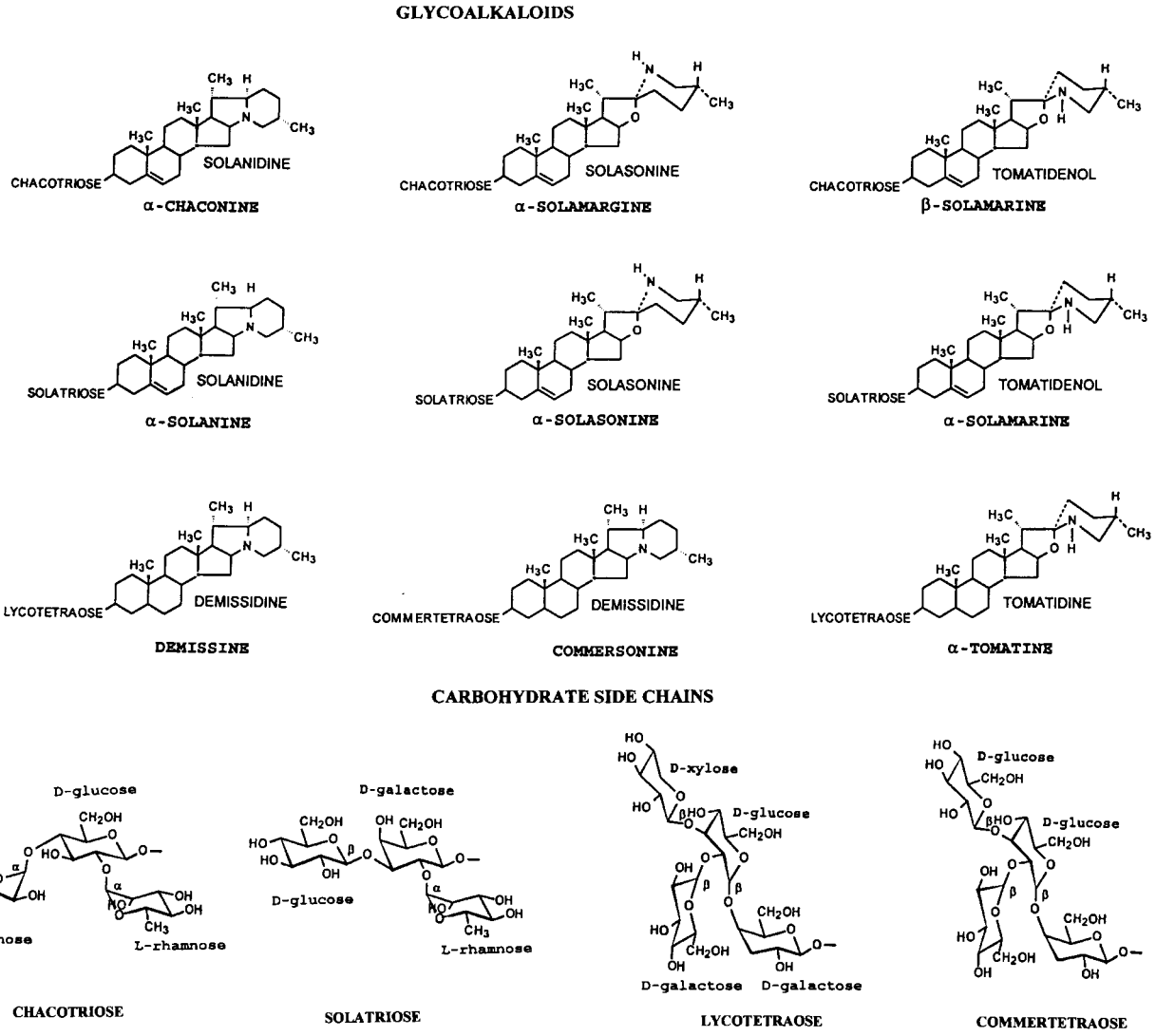


FIGURE 3. Structures of the common *Solanum* glycoalkaloids.

commersonine. Both have a four-sugar side chain attached at the 3-OH. Demissine was isolated by Kuhn and Löw (1947) from *S. demissum*. Demissine's glycoside is a lycotetraose, the same tetrasaccharide side chain found in α-tomatine, the major tomatidine glycoalkaloid found in tomatoes (Kuhn and Löw, 1957). Commersonine, first found and characterized by Osman et al. (1976) from accessions of *S. chacoense* and *S. commersonii* Dun., has a tetraose side chain not found in any other major glycoalkaloid.

Another group of closely related glycoalkaloids called leptines are present in a special accession of *S. chacoense* Bitt. (Kuhn and Löw, 1961 a, b). Figure 4 shows the structure of the leptine and leptinine glycoalkaloids and their corresponding aglycones designated as leptinidine (23-hydroxysolanidine) and 23-acetylleptinidine (leptidine). Stereochemically, the 23-OH or 23-OAc group is situated in the axial β-position of the ring. Because the leptines occur in only a few lines of *S. chacoense* (Sinden et al., 1986b), and occur at high levels only in the leaves and not the tubers, they have been little studied. In addition, because they are soluble at high pH — the most common method of precipitating glycoalkaloids for analysis — they would be lost in many analytical methods. Cultivars of *S. chacoense* with high levels of leptines have been found to be resistant to the Colorado potato beetle (Deahl and Sinden, 1987; Deahl et al., 1991; Sanford et al., 1996; Sinden et al. 1986a, b).

Finally, Nash et al. (1993) isolated a new class of alkaloids from potatoes called calystegines. Technically not "glycoalkaloids", these are structural derivatives of tropane. The skin of *S. tuberosum* cv. "Estima" contained 0.01% of these alkaloids. The rest of the tuber contained about one tenth of this amount. The significance of these compounds has yet to be determined.

While it is important to study and be aware of all alkaloids that may occur in new plant varieties, at least 95% of all the glycoalkaloids in commercial potatoes are α-solanine and α-chaconine. The remainder of this review concentrates on these two compounds.

B. Hydrolysis

It is current practice to name the naturally occurring glycoalkaloids as α-compounds. Stepwise cleavage of the individual sugars of the glycoside leads to β- and γ-compounds in the case of trisaccharide side chains and β-, γ-, and δ-compounds with the tetrasaccharides. (It is for this reason that the names α-solamarine and β-solamarine are confusing. β-Solamarine is not a hydrolysis product of α-solamarine but is rather, by this system, an α-compound on its own, that is, α-β-solamarine. It would be easier if the names of these compounds were changed to solamarine A and solamarine B or to solamarine S and solamarine C to differentiate the solatriose and chacotriose compounds.) Figure 5 shows the structures of α-, β_1-, β_2-, and γ-chaconines and the α-, β_1-, β_2-, and γ-solanines. While β_1-solanine can theoretically be formed, it has not yet been isolated.

In order to develop a chemical structure-biological activity relationship for the glycoalkaloids and to define the role of the carbohydrate side chain of α-chaconine and α-solanine in developmental toxicity, Rayburn et al. (1994) tested the parent α-trisaccharides, the β-disaccharides and the γ-monosaccharide as well as the aglycone, solanidine. The results showed that the biological activity was influenced by both the nature and the number of sugars making up the carbohydrate moiety attached to the 3-OH position of the aglycone. The embryotoxicity generally decreased with stepwise removal

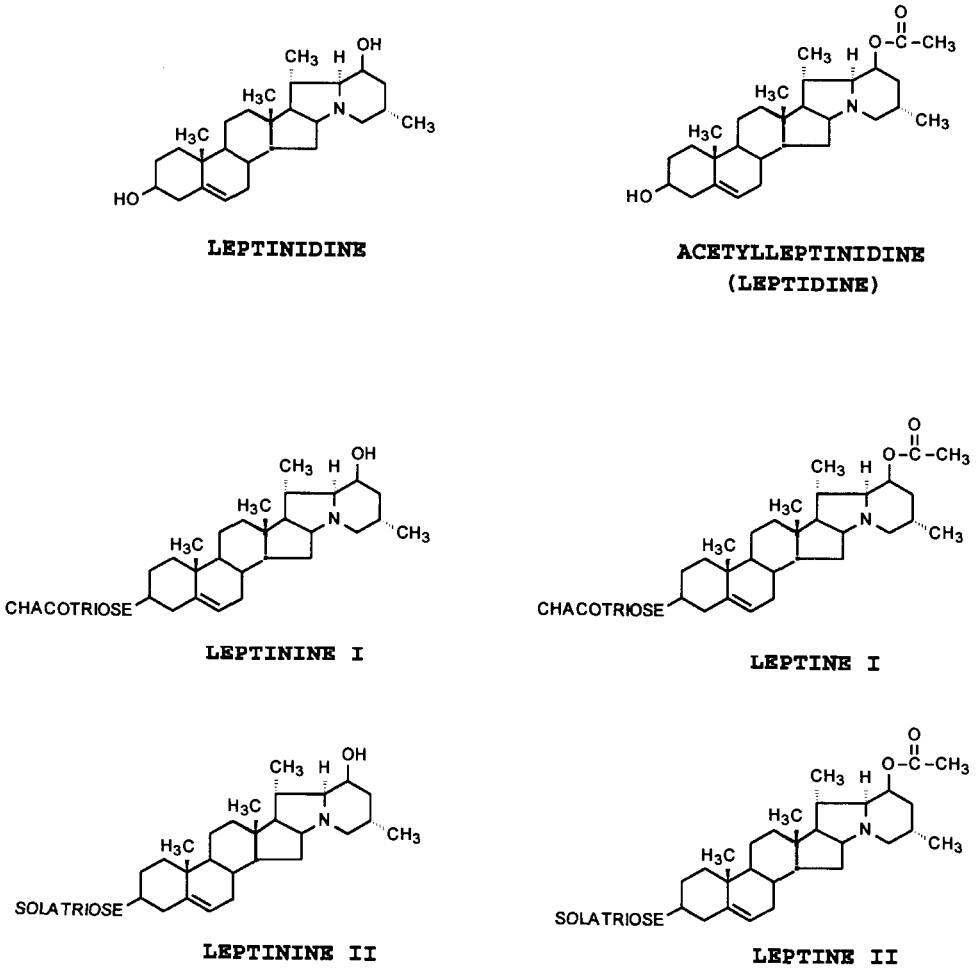


FIGURE 4. Structures of the leptines present in *S. chacoense.*

of sugar units from the chacotriose and solatriose side chains.

Indications are that potato sprouts contain the hydrolytic enzymes rhamnosidase, glucosidase, and galactosidase, which cleave rhamnose, glucose, and galactose residues, respectively, from the potato glycoalkaloids (Guseva and Paseshnichenko, 1957). Swain et al. (1978) confirmed previous reports of the nonstepwise hydrolysis of α-chaconine by an enzyme preparation from potato sprouts. The mixture cleaved the rhamnose side chain at the 2-position of the glucose residue in α-chaconine and further transformed the resulting β_2-chaconine to solanidine, apparently without producing the intermediate monoglucoside γ-chaconine that would be formed from the cleaving of the remaining rhamnose residue. However, the same enzyme mixture produced β-solanine by removal of the rhamnose, then γ-solanine by removal of the glucose, and finally solanidine by removal of the galactose. Related nonstepwise hydrolysis was also catalyzed by enzyme preparations isolated from potato tubers.

Bushway and colleagues (1988, 1990) attempted to purify and characterize rhamnosidases, which cleaved rhamnose units from α-chaconine and α-solanine. Par-

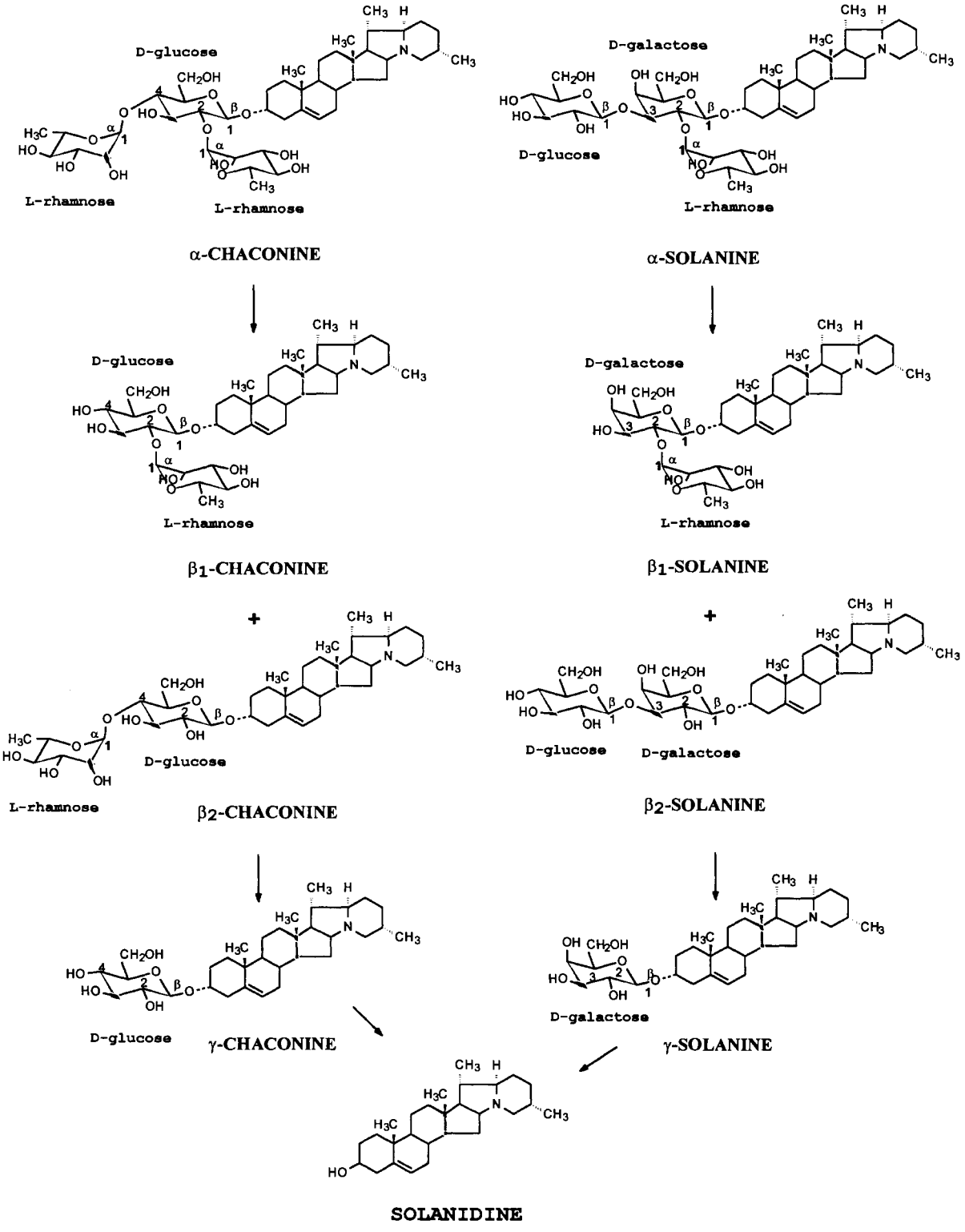


FIGURE 5. Structures of hydrolysis products of α-chaconine and α-solanine.

tial purification was achieved by ammonium sulfate precipitation of an extract of the peels of Kennebec and Wauseon potatoes. Additional studies are needed to purify the enzyme to homogeneity, to isolate the gene coding for the enzyme, and to determine the amino acid sequences, active sites, etc.

While these enzymes are present and work under laboratory conditions, they seem to have little activity in the intact mature potato tuber. Generally, only traces of the β- and γ-compounds have been found in tubers, although Morris and Petermann (1985) found significant amounts of β-chaconine in some varieties of Australian-grown, high-glycoalkaloid potatoes. Friedman and Dao (1992) also found β_2-chaconine in potato roots. Filadelfi and Zitnak (1982) and Zitnak and Filadelfi-Keszi (1988) have described a specific enzyme found in tubers and blossoms that converts α-chaconine to β_2-chaconine but has no activity for α-solanine. Friedman and McDonald (1995a) noted that after prolonged storage of sprouted potatoes at 3 to 4°C, all the α-chaconine in the sprouts was converted to β_2-chaconine, whereas the α-solanine was largely unaffected. What triggers this enzymatic activity is not known.

Crabbe and Fryer (1983a, b, c) developed a model system for acid hydrolysis of glycosides using solasonine. Gaši et al. (1984) studied optimal methods for the production of solanidine from potato sprouts by HCl hydrolysis, and Nicolic et al. (1993) examined hydrolysis by H_2SO_4. Friedman et al. (1993) carried out a detailed study on the effects of time, temperature, and acid concentration on hydrolysis. In general, hydrolysis rates increase with HCl concentration and temperature and decrease with the amount of water in organic solvent-water solutions. Under conditions of strong acid and high temperatures, solanidine formed from the hydrolysis of α-chaconine or α-solanine will further react to form solasodiene (solanthrene). Further study (Friedman and McDonald, 1995a) has revealed that the nature of the alcohol solvent strongly influences the rate and specificity of the hydrolysis, permitting optimal formation of specific hydrolysis products. Kling et al. (1986) have found various hydrolysis products, mostly β_2-chaconine, in potato distiller byproducts. Whether these products are the result of acidic or enzymatic hydrolysis was not determined.

Subject to possible enzymatic and/or acid hydrolysis after ingestion, the fate of the glycoalkaloids in the digestive tract is not yet fully known. Harvey et al. (1985a,b, 1986) found both glycosides and free solanidine in sera of men and women after ingestion of potatoes. Hellenäs (1994) found similar results and further states that while the α-compounds and solanidine were present, there were no intermediate β- or γ- glycoalkaloids.

III. ANALYSIS

Methods for quantifying the glycoalkaloids, like most analytical methods, consist of three parts. Coxon (1984), in his review of methodology, called them extraction, clean-up, and quantification. Jadhav et al. (1981), in their review, referred to them as extraction, separation, and analysis. Whatever they are called, the steps involve (1) extracting all the compounds of interest; (2) eliminating, if necessary, all other compounds that will interfere with the chosen method of analysis; and finally (3) determining the amount present. Some of the analytical methods may include another step, such as derivatization or hydrolysis, that might be called modification. Several colorimetric and gas chromatographic (GC) methods require conversion of the glycosides to aglycones before analysis. Some other GC methods require derivatization of the alkaloids. Several methods combine the extraction and modification steps. Extracting with strong

acid such as 3.5 *M* sulfuric acid (Coxon et al., 1979; Blincow et al., 1982) allows simultaneous extraction and hydrolysis.

The brief discussion of classic and current methods that follows examines each step separately. However, these steps cannot be adequately evaluated without taking the entire method into account. A new and "improved" method of quantification might be proposed, but if it also includes a new or modified extraction procedure, it is sometimes difficult to know which step is more responsible for the improvement.

The following example, as detailed by Coxon (1984), illustrates the difficulty of evaluating methodology. Fitzpatrick and Osman (1974) introduced their comprehensive method for glycoalkaloid determination. The original method involved extraction with the chloroform-methanol solvent of Wang et al. (1972). Aqueous Na_2SO_4 was added to effect a phase separation and the chloroform layer was discarded. Aliquots of the methanol-water layer were evaporated and the solid redissolved in absolute methanol. The undissolved Na_2SO_4 was filtered off and the methanol was again evaporated. The residue was hydrolyzed in 2 N sulfuric acid on a steam bath. The solution was then neutralized and extracted with benzene. The benzene was evaporated and redissolved in methanol. This solution was titrated with a bromophenol blue-phenol solution and compared against a standard curve. Other researchers reported poor recoveries of spiked samples. Fitzpatrick et al. (1978a) modified the cleanup procedure to either eliminate the solid Na_2SO_4 filtration or include sonication. Recoveries were still poor, however. Mackenzie and Gregory (1979) attributed losses to glycoalkaloid being discarded in the chloroform layer and being degraded in the hydrolysis step. Bushway et al. (1980c) substituted ammonia precipitation for the phase separation and eliminated the hydrolysis completely. Finally, Speroni and Pell (1980) noted difficulty extracting freeze-dried samples and substituted 5% acetic acid for the chloroform-methanol extraction solvent. They also used ammonia precipitation, but kept the hydrolysis step. With all these changes, the titration procedure remained substantially unchanged.

With the advent of alternative methods for determining glycoalkaloids, it has become possible to compare the results of the different methods. Colorimetric and titrimetric results have been found to be consistently higher than those obtained by GC or HPLC. The reason for this has not yet been determined.

A. Extraction

All of the glycoalkaloids except the leptines are only sparingly soluble in aqueous solutions at pH 7 or above. Extraction solvents are thus either nonaqueous or acidic or both. The literature describes over 20 different solvents used for extracting glycoalkaloids. Extractions are usually done by blending at room temperature. Any combination of acid and heat is usually avoided, as this can cause hydrolysis. However, some GC and colorimetric methods require hydrolysis before analysis.

Most studies involving these solvents also determined the recovery of added glycoalkaloids. However, recovery experiments can only ensure that there is little or no loss of glycoalkaloid in clean-up and analysis after extraction. Glycoalkaloids bound in a plant matrix may be more difficult to solubilize than those added to the surface of plant material. Thus, while recovery experiments may show that there is no significant loss after extraction, they may not reflect extraction efficiency.

Friedman and McDonald (1995b), in a preliminary study, evaluated ten solvent systems for extraction efficiency on dried, fresh,

and processed tubers using the same extraction and clean-up procedures and then measuring α-solanine and α-chaconine by HPLC. These solvents included: ethanol (Dabbs and Hilton, 1953); 2% acetic acid (Birner, 1969); 5% acetic acid (Speroni and Pell, 1980), 3% acetic acid in ethanol (Baker et al., 1955); methanol-acetic acid-water (94:1:6) (Jonker et al., 1992); 5% trichloroacetic acid (TCAA) in 50% methanol (Bretzloff, 1971); 5% TCAA in 75% methanol (Smittle, 1971); methanol-chloroform (2:1) (Wang et al., 1972); chloroform-acetic acid-methanol (10:1:9) (Shih and Kuč, 1974); tetrahydrofuran-water-acetonitrile-acetic acid (5:3:2:0.1) (Bushway et al., 1985); 0.5% sodium bisulfite in 2% acetic acid (Hellenäs, 1986); 0.02 *M* Na-1-heptanesulfonate in 0.17 *M* acetic acid (Houben and Brunt, 1994); and 0.4% 1-heptanesulfonic acid in 1% acetic acid (Carman et al., 1986). Results varied widely for α-solanine but less so for α-chaconine. The authors found the best solvent for dried samples was the 2% acetic acid of Birner (1969), reinforcing the results of Speroni and Pell (1980) and Bushway et al. (1985) that nonaqueous solvents do not work well with dried samples. In contrast, the best solvents for fresh samples were either the Wang et al. (1972) or Bushway et al. (1985) mixtures. Solutions of acetic acid in alcohol proved to be especially poor for extracting α-solanine.

B. Clean-up

Glycoalkaloids are commonly purified in one of three ways: (1) precipitation with ammonium hydroxide (Bushway et al., 1979; Friedman and Dao, 1992); (2) partitioning with either aqueous Na_2SO_4 solutions (Wang et al., 1972) or water-saturated butanol (Crabbe and Fryer, 1980; Friedman et al., 1994); or (3) passing through a C_{18} ion-pair chromatography cartridge (Carman et al., 1986; Houben and Brunt, 1994; Kobayashi et al., 1989; Morris and Petermann, 1985; Saito et al., 1990). A combination of these techniques may also be employed.

A disadvantage of the ammonia precipitation method (ca pH 10) is that while α-solanine is insoluble in basic solutions, α-chaconine does seem to be partially soluble. With a large sample this loss should not matter, but on small-scale samples it could be significant. Similarly, leptines are still soluble at this pH and will be lost.

Some of the problems of partitioning as mentioned above (partial loss of glycoalkaloids in the discarded layer or through occlusion on formed salts) can be avoided by using water-saturated *n*-butanol. It works very well with pure hydrolyzed systems (Friedman and McDonald, 1995a) and acetic acid extracts of freeze-dried samples (Friedman and Dao, 1992). It is less successful, however, with fresh samples or samples extracted with nonaqueous solvents as interfering compounds may remain.

The most popular clean-up method for glycoalkaloid determination by HPLC is solid-phase extraction (SPE). Carman et al. (1986) and Hellenäs (1986) used commercial C_{18} cartridges for clean-up prior to determining potato glycoalkaloids by HPLC. Houben and Brunt (1994) used SPE for determining glycoalkaloids in potato tubers. Jonker et al. (1992) recommended using SPE-CN cartridges for clean-up. Saito et al. (1990) recommended the use of C_{18} and NH_2 cartridges for clean-up of low- and high-lipid samples, respectively. However, Magrini et al. (1989) found it very difficult to clean up methanol extracts, even using SPE. While C_{18} ion-pair chromatography cartridges seem to be the best choice for general clean-up, especially for HPLC, the selection of sample clean-up method relies to a large extent on the extraction solvent and the method of analysis. These cartridges may not be best for all procedures.

C. Analysis

For the first 100 years, "solanine" was determined gravimetrically following alkaline precipitation, as reviewed by Bömer and Mattis (1924). Now, precipitation is used only as part of the clean-up procedure. Paseshnichenko and Guseva (1956) used liquid chromatography (LC) and paper chromatography (PC) for qualitative and quantitative separation. At present, thin layer chromatography (TLC) has replaced PC. LC is used only for purification in preparative procedures. Methodologies in current use for the analysis of potato glycoalkaloids and related compounds include: (1) colorimetry; (2); TLC (3) gas-chromatography (GC); (4) high-performance liquid chromatography (HPLC); and (e) immunoassays (ELISA).

1. Colorimetry

Colorimetric methods include: (1) complexing with bromothymol blue (Balcar and Zalecka, 1962); (2) complexing with methyl orange (Birner, 1969); (3) titration with bromophenol blue-phenol (Fitzpatrick and Osman, 1974); (4) color reaction with antimony trichloride in HCl (Wierzchowski and Wierzchowska, 1961); (5) color reaction with formaldehyde in sulfuric acid (Dabbs and Hilton, 1953); and (6) color reaction with paraformaldehyde in 85% phosphoric acid (Clarke, 1958). Technically, method 3 is not a colorimetric method but rather is a titrimetric method, because the color change is not proportional to the amount of glycoalkaloid present but instead indicates when all the glycoalkaloids have been complexed with phenol.

Methods 1, 2, and 3 generally involve hydrolyzing the glycosides to aglycones, although Bushway et al. (1980c) described a modification of method 2 that determined the glycosides directly. Any method involving hydrolysis can expect to suffer some loss such as degradation of solanidine to solanthrene. For this reason, Coxon et al. (1979) and Blincow et al. (1982) in their modifications of the bromothymol blue method recommend applying a recovery factor determined by hydrolysis of spiked samples. Van Gelder (1984) introduced a two-phase hydrolysis method using a top layer of chloroform to prevent further reaction of the hydrolyzed aglycone. However, hydrolysis methods by their nature determine only total glycoalkaloids (TGA). They cannot, for example, distinguish α-solanine from α-chaconine.

Methods 4, 5, and 6 not only involve the use of hazardous reagents but are subject to interference. These methods will determine all steroid type compounds with Δ^5 unsaturation, most of which are difficult to remove from the samples. They will not detect glycoalkaloids such as demissine or tomatine that lack the double bond. Bretzloff (1971) and Smittle (1971), in evaluating extractions with various trichloroacetic acid mixtures, used method 4 as did Sanford and Sinden (1972) in their inheritance studies. Wang et al. (1972) used method 6 for detection in their development of a bisolvent extraction system. Bergers (1980a,b) and Love et al. (1994) used this reaction in developing a method for analyzing potatoes and potato proteins. Cadle et al. (1978) also used a modification of this colorimetric method, combining it with the extraction method of Shih and Kuč (1974), in evaluating their TLC method for determining glycoalkaloids in tubers.

Based on a comprehensive evaluation of nine colorimetric methods, Clement and Verbist (1980) concluded that the method of Wang et al. (1972), which used the paraformaldehyde-phosphoric acid colorimetric method of Clarke (1958) was preferable to the others. This may have reflected the use of a new extraction method as much as the detection method.

2. Thin Layer Chromatography

Early work on separating steroidal compounds by TLC was done by Schreiber et al. (1963), Bennett and Heftmann (1966), Rozumek (1969), Hunter et al. (1976), and Zitnak (1968). Shih and Kuč (1974) evaluated several solvent systems for separating glycoalkaloids and aglycones and used the results to identify and characterize the new glycoalkaloids α- and β-solamarine. Cadle et al. (1978) used TLC and densitometry as a quantitative method for glycoalkaloids in potato tubers. Jellema et al. (1979, 1980, 1981) evaluated several solvent systems and detection reagents for use in TLC of glycoalkaloids. They proposed the use of optical brighteners for densitometric measurement. Filadelfi and Zitnak (1983) described a system for separating the hydrolysis products of α-solanine and α-chaconine by TLC.

The most widely used solvent systems for separation of the glycosides are combinations of chloroform-alcohol-ammonia. Cadle et al. (1978) used chloroform-95% ethanol-1% ammonia (2:2:1). Jellema et al. (1981) recommended chloroform-methanol-2% ammonia (70:30:5). This was also used by Friedman et al. (1993). Filadelfi and Zitnak (1983) preferred using the lower layer of chloroform-methanol-1% ammonia (2:2:1). For separating the aglycones solanidine, solasodine, and tomatidenol, Shih and Kuč (1974) obtained the best results with benzene-methanol (5:1) or cyclohexane-ethyl acetate (1:3). Sinden et al. (1980) had success with ethyl acetate-pyridine-water (5:2:1) in separating the leptines.

Various methods of detection have also been used, including antimony trichloride (Cadle et al., 1978; Filadelfi and Zitnak, 1983), Dragendorff's reagent (Ahmed and Müller, 1978; Roddick and Melchers, 1985), anisaldehyde reagent (Friedman et al., 1993; Shih and Kuč, 1974), iodine vapor (Friedman et al., 1993; McCollum and Sinden, 1979), Clarke reagent (Coxon and Jones, 1981), and optical brighteners such as Blankophor® BA 267% (Jellema et al., 1981, 1982). Iodine vapor is certainly the easiest, and although it is relatively nonspecific, it is reversible, an advantage in preparative work. The optical brighteners are the most specific but require fluorescence to be seen. Anisaldehyde, like Dragendorff's, Clarke's, and the $SbCl_3$ reagents, is also nonspecific and corrosive, but it gives different colors with different glycosides and aglycones that may help in identification.

Although newer methods of analysis have rendered TLC somewhat obsolete as a quantitative procedure for glycoalkaloids, it is still used as a simple and quick means of screening large numbers of samples (Duan et al., 1995; Ferreira et al., 1993), especially when used as a qualitative method for determining the presence or absence of various glycoalkaloids in inheritance studies (McCollum and Sinden, 1979).

3. Gas Chromatography

Advances in GC have led to two general methods for determining glycoalkaloids: (1) determination of the aglycones after hydrolysis and (2) determination of the glycosides after derivatization. Herb et al. (1975) devised the first GC method for glycoalkaloids, later used by Osman et al. (1978) and Gregory et al. (1981), chromatographing the glycosides after permethylation. They were able to separate α-solanine, α-chaconine, β-chaconine, and solanidine. Most other investigators have preferred to hydrolyze the samples and separate the aglycones without derivatization. Osman and Sinden (1977) were unable to separate solanidine and demissidine glycosides directly but obtained good separation of the corresponding aglycones. Coxon et al. (1979) and King (1980) developed similar methods for separating the aglycones.

Bushway et al. (1984) used the method of King with slight modifications.

Van Gelder (1985b) and van Gelder et al. (1988a, 1989) developed a method of capillary GC on hydrolyzed samples. Using a combination of flame ionization (FI) and nitrogen-source (NPD) detectors, they were able to separate a complex mixture of glycoalkaloids, sterols, and steroidal sapogenins. Lawson et al. (1992) described a capillary GC method using a combination extraction-hydrolysis step and tomatidine as an internal standard to separate and quantify solanidine, leptinidine, and acetylleptinidine. Other, less direct GC methods have also been reported. Siegfried (1976) hydrolyzed the glycosides and measured the sugars by GC after trimethylation. This suffers from being a long and involved procedure that may result in significant losses. Roddick (1979) complexed solanine and chaconine with stigmasterol and then measured the stigmasterol loss by GC, assuming the loss equaled total glycoalkaloid content.

There are several disadvantages to GC. It is relatively expensive compared with colorimetry and TLC. Due to the high temperatures involved (usually around 300°C or higher), the columns can run only 100 or fewer samples before needing to be changed. Run times are often long, and, as with all hydrolysis methods, no information on individual glycoside content is available. However, there is good separation of all compounds. Further, because GC has no carrier solvents, there are no solvent disposal problems, detection is relatively simple, and it is ideally suited to direct coupling with other instruments such as mass spectrometers (MS). GC-MS has proven to be of great value in structure elucidation and other studies (Chen et al., 1994; Evans et al., 1993; Osman et al., 1986; Price et al., 1985). Although MS is usually employed as a detector for GC or HPLC methods, Abell and Sporns (1996) have recently described the direct quantitation of potato glycoalkaloids by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOFMS) using α-tomatine as an internal standard.

4. High-Performance Liquid Chromatography

The most popular method for determining glycoalkaloids appears to be HPLC. Since the pioneering studies of Bushway et al. (1979), Crabbe and Fryer (1980), and Morris and Lee (1981), HPLC has been continuously improved with respect to sample preparation and clean-up, column selection, and peak detection. Its use is increasing because it can distinguish individual glycoalkaloids and aglycones directly without derivatization.

Hunter et al. (1976) first used HPLC as a preparative method for collecting various aglycones. Bushway and colleagues (1979) were the first to describe an HPLC method for separating α-solanine and α-chaconine with a bonded-phase column using tetrahydrofuran-water-acetonitrile mixtures for the mobile phase. In a series of papers, they have described continuing improvements to their method (Bushway, 1982a,b,c; Bushway et al., 1980d, 1986). Crabbe and Fryer (1980) developed an HPLC method for separating partial hydrolysis products using buffered aqueous methanol solutions with bonded- and reverse-phase columns. They were able to separate combined solanine and chaconine α, β, and γ products as well as the aglycones. Morris and Lee (1981), using radially compressed reverse-phase cartridges and adding ethanolamine to their acetonitrile-water (35:65) eluent, were able to separate all the partial hydrolysis products of either solanine or chaconine as well as solanidine and solanidiene. However, β_1-chaconine and γ-solanine were not separated from a mixture of hydrolyzed solanine and chaconine. Eldridge and Hockridge (1983), using this

method, separated α- and β-solamargine, α-solanine, α-chaconine, and solasonine.

The choice of mobile phase is dependent on the type of HPLC column used for analysis. Several current methods involve the use of a reverse-phase C_{18} column, although Jonker et al. (1992) found the C_8 columns to be faster than C_{18} columns with acetonitrile-Tris-buffer (3:2) as the mobile phase. Friedman and Levin (1992) used 35% acetonitrile in 100 m*M* ammonium phosphate buffer to separate α-chaconine and α-solanine on a C_{18} column. These authors also evaluated 13 different C_{18} columns for optimal separation of glycosides and hydrolysis products. Magrini et al. (1989) separated solasonine and solamargine using 33% acetonitrile in 10 m*M* diammonium phosphate with 0.02% triethylamine. Asano et al. (1996) used 33% acetonitrile in 20 m*M* phosphate buffer with a C_8 column and detection at 205 nm to determine glycoalkaloids in various parts of the potato plant. Houbun and Brunt (1994) used 40% acetonitrile to determine α-chaconine and α-solanine on a C_{18} reverse-phase column with reduced silanol groups. Kobayashi et al. (1989) separated these two compounds using ethanol-acetonitrile-0.005 *M* potassium dihydrogenphosphate on an NH_2 column. Saito et al. (1990) evaluated the interactions of column capacity, temperature, and pH and reported optimal separation of α-chaconine and α-solanine with acetonitrile-20 m*M* potassium dihydrogenphosphate on an amino column. Osman and Sinden (1989) and Ghazi and Matthees (1989) both found it easier to separate the aglycones after hydrolysis of the glycosides than to separate the glycosides directly.

Almost all of the above cited methods used UV detection between 200 and 215 nm. This has several implications. First, the choice of eluent is severely limited to compounds transparent to UV in that region, namely, water, methanol, ethanol, acetonitrile, and tetrahydrofuran. Second, the elution should be isocratic to maintain a stable baseline. Finally, the clean-up procedure becomes very important, as many compounds may interfere in this UV range. The most widely used clean-up procedure in current practice for HPLC involves the use of disposable C_{18}, CN, or NH_2 cartridges. They are relatively fast and inexpensive and can normally be reused several times. However, some interfering compounds may still remain, depending on the method of extraction. Osman and Sinden (1989) had some success in overcoming this interference by using a refractive index (RI) detector for determination of the aglycones. Drewes et al. (1992) suggested benzoylation of solasodine before HPLC so that a wavelength of 254 nm could be used. However, this reaction gave two products and the area of two peaks needed to be combined. In addition, loss during reaction adds another possible source of error. Friedman et al. (1994) and Friedman and Levin (1995) used pulsed amperometric detection (PAD) for tomatine determination. This system may be used for determining other glycoalkaloids but requires much more care than simple UV detectors.

The usual elution solvent for the above methods is therefore usually a mixture of acetonitrile-water or acetonitrile-alcohol. With reverse-phase columns salt or acid pH or both is normally added to speed up elution and improve separation.

There are several advantages to using HPLC. It is run at room temperature, it can analyze both glycosides and aglycones without derivatization, and it can give an almost complete picture of the pattern of individual glycosides present in one determination. Major disadvantages are the expense of the equipment, the need for extensive clean-up of samples, and the use of organic solvents that need to be purchased and disposed of safely. A compromise must also be made between speed and complete separation of some compounds. The methods of Bushway et al. (1986), Kobayashi et al. (1989), and Saito et al. (1990), for example, give good

separation of α-solanine and α-chaconine, but either do not separate the hydrolysis products or take considerable added time per run to do so. Methods like those of Carman et al. (1986), Friedman and Levin (1992), or Hellenäs (1986) separate all of the products in 10 to 12 min, but do not give baseline separation of all peaks, including α-solanine and α-chaconine at higher levels (> 50 μg/ml). This may lead to a slight inaccuracy in the α-solanine/α-chaconine ratios but should have little effect on the determination of total glycoalkaloids.

5. Immunoassays

Immunochemical assays are rapid, simple in design, and do not require expensive instrumentation. These assays require serum antibodies reactive to a compound or to a conjugate of that compound and a means of labeling that compound. Methods of labeling that have been used for glycoalkaloids are radioimmunoassay (RIA), enzyme linked immunosorbent assay (ELISA), and fluorescence polarization immunoassay (FPA).

Early studies involved RIA. The first-such successful method using radioactive labeling was developed by Vallejo and Ercegovich (1978). It could detect amounts of solanidine as low as 150 pg but was less successful with glycoalkaloids. Matthew et al. (1983) and Harvey et al. (1985a,b) reported on similar RIA methods for measuring solanidine in human serum and saliva. While the methods were quite sensitive, the results seemed to be somewhat random. A further disadvantage to RIA is the need for strict monitoring and controlling radioactive material.

ELISA methods, which use a second antibody, are generally easier and require less expensive equipment. Morgan et al. (1983) developed an ELISA method using an antiserum from bovine serum albumin-solanine conjugate that was specific for glycoalkaloids. They compared this method with conventional methods of glycoalkaloid analysis and found good agreement (Morgan et al., 1985a,b). Ward et al. (1988) studied colors produced by three different antibodies and recommended the use of horseradish peroxidase conjugate. Plhak and Sporns (1992, 1994) describe polyclonal antisera raised using immunogens produced by sodium borohydride cleavage of the sugars and discuss the production of monoclonal antibodies for glycoalkaloid determination. Thomson and Sporns (1995) described a method of using fluorescence polarization immunoassay as a label for determining potato glycoalkaloids.

Stanker et al. (1994, 1996 a,b) developed a panel of 11 monoclonal antibodies (Mabs) following immunization with a solanidine protein conjugate and cell fusion experiments that bound either α-solanine, α-chaconine, tomatine, solanidine, or tomatidine. Some of these monoclonal antibodies bound solanidine and the potato glycosides α-solanine, and α-chaconine with equal affinity. Others bound only solanidine, and still others bound the tomato glycoside α-tomatine and the corresponding aglycone, tomatidine. None of the antibodies showed any affinity for steroids lacking ring nitrogen atoms such as cholesterol, digitonin, β-sitosterol, and stigmasterol. Fifty percent inhibition of control values in a competition enzyme-linked immunosorbent assay (ELISA) ranged from 30 to 1500 ppb.

ELISA has the potential for the production of field kits that could be of great use to plant breeders and harvesters. Thus far, however, ELISA has failed to find general use in the potato industry.

D. Assessment

Evaluating methods for potato samples is not a simple task. Optimizing one part of the procedure may cause problems in an-

other part. For example, the most efficient extraction solvent may also extract compounds that will interfere in the chosen method of analysis or create the need for extensive clean-up. Other solvents might avoid these problems but might also be less efficient in the extraction of the glycoalkaloids. As yet, the perfect method of glycoalkaloid analysis for all types of samples has not been discovered. Analysts must be aware of the limitations of any of the methods or parts of the methods chosen. Another limitation is the number of samples involved. Breeding programs or checking harvested potatoes for high glycoalkaloid levels can generate too many samples for complete analysis. It may not be practical, or even possible, to use a relatively involved and time consuming method, even if it is the most accurate. A quicker and simpler screening method might be chosen, although it should still be comprehensive enough to keep any unsafe products from reaching the public.

An ELISA test kit for glycoalkaloids having good reproducibility and sensitivity would certainly provide a simple and quick method for screening large numbers of samples. Ideally, the test kit would work on a crude extract, or even directly on a suspension of potato or plant material. Selected samples of interest could then be analyzed more extensively as time permitted. Freeze-drying the samples would allow even more time for subsequent analysis.

Freeze-drying offers several advantages: (1) it stops enzyme-catalyzed, wound-induced, and moisture-dependent compositional changes that may affect glycoalkaloid content; (2) it permits storage and transportation of samples for analysis at different time periods and by different investigators; and (3) it makes it possible to relate composition to nutrition and safety, that is, portions of the same samples can be used for both analysis of composition and incorporated into diets for animal feeding studies. Additionally, extracts of freeze-dried samples are much easier to clean up, as they do not undergo browning during handling as fresh samples do. If 2% acetic acid should prove to be a good extraction solvent, this would eliminate the use of large quantities of organic solvents such as methanol and chloroform that present safe-disposal problems. However, a more comprehensive evaluation of extraction procedures is needed to ensure complete extraction of the glycoalkaloids from freeze-dried samples. One major disadvantage of freeze-drying a large number of samples is that it adds time, effort, and equipment costs.

Future studies should evaluate various extraction and purification techniques on a variety of potato cultivars and potato products, determining whether one method can be used for such different samples as tubers, processed and/or cooked potato products (flakes, chips, fries, etc.), other parts of the potato plant (leaves, roots, etc.), and blighted potatoes. Such studies can help establish guidelines for which methods can be used for different types of samples.

IV. SAFETY

A. Physiological Effects

1. Human Studies

Physicians have been aware for many years that the ingestion of blighted or sprouting potatoes and other parts of the potato plant, especially the leaves and berries, could cause illness and even death. Reviews on the toxic effects of glycoalkaloids include Baker et al. (1991), Dalvi and Bowie (1983), Huxtable (1987), Jadhav et al. (1981), Morgan and Coxon, (1987), Morris and Lee (1984), Sharma and Salunkhe (1985), van Gelder (1990), and Velísek and Hajšlová (1995). The symptoms of "solanine" poisoning include nausea, vomiting, diarrhea, stomach and abdominal cramps, headache, fever,

rapid and weak pulse, rapid breathing, hallucinations, delirium, and coma.

Harris and Cockburn (1918) described a case affecting 61 people, including the death of a 5-year-old boy after they had eaten potatoes that had begun to sprout. Those who refrained from eating the potatoes were unaffected. Hansen (1925) reported on the death of two women after they had eaten greened potatoes. Willimott (1933) described an incident where 60 people became ill after eating boiled potato leaves; one child died. Terbruggen (1936) and Rühl (1951) discussed separate cases of a child dying after eating a potato berry. Ripakh and Kim (1958) reported and described clinical symptoms of 382 cases of solanine poisoning from potatoes in North Korea during 1951 to 1953. Wilson (1959) reported on the case of a family who kept getting sick after Sunday dinner. They always ate potatoes, including skins, at this meal. The only member who did not become ill did not eat the skins, whereas the member who usually had three potatoes exhibited the most severe symptoms. A report in the *Canada Diseases Weekly Report* (Anon., 1984) mentioned that over 60 of 109 schoolchildren and teachers showed signs of poisoning after eating baked potatoes high in "solanine". Gonmori and Yoshioka (1993) described the symptoms of a woman who fell ill after ingesting potato juice as a folk remedy.

The case usually cited when discussing glycoalkaloid poisoning is that reported by McMillan and Thompson (1979). After a long school break, 78 schoolboys between the ages of 11 and 13 became ill after eating lunch. Seventeen of the boys were sick enough to require hospitalization and three were in critical condition. The common symptoms were nausea, vomiting, diarrhea, and abdominal pain. Most had fever and were confused or drowsy. The severely ill had weak rapid pulses, difficulty in breathing, high fever, and low blood pressure. The critically ill were unconscious. The symptoms declined after 1 to 2 weeks and the boys were discharged. It was noted that even after 6 d, plasma cholinesterase levels were extremely low. Investigators traced the problem back to potatoes that had "gone bad" over the long holiday. Remaining potatoes were found to contain around 330 mg/kg of glycoalkaloids.

Morris and Lee (1984) calculated the actual doses received in these and other cases *a priori* and concluded that 2 to 5 mg/kg body weight (BW) was a toxic dose, whereas a fatal dose was around 3 to 6 mg/kg BW. If true, this toxicity is comparable to that of strychnine. Although these dosages are approximations, nothing in the limited human studies has shown them to be overstated. Indications are that the toxic effect level is closer to 1.0 mg/kg BW.

Pfühl (1899), in studies with prisoners, reported that administered doses of solanine above 200 mg produced symptoms of solanine poisoning. Bushway (1987, private communication cited by van Gelder, 1989) conducted limited experiments with volunteers. Six males became nauseated after ingesting potatoes containing glycoalkaloids. Several had diarrhea and one experienced vomiting. Doses were estimated at 1.7 to 2.6 mg/kg BW. Symptoms appeared after 2 to 4 hours and disappeared after 8 to 10 hours. Hellenäs et al. (1992b) conducted similar experiments with seven volunteers. He had the subjects abstain from eating potatoes for 2 d. They were then given amounts of potatoes containing glycoalkaloids such that the dose would be equal to 1.0 mg/kg BW for each subject. Six of the seven volunteers experienced a burning sensation of the mouth and light to severe nausea. There was one case of diarrhea. Symptoms appeared after 30 min and lasted for about 4 h. These findings are in line with other results that have shown glycoalkaloid levels of 1 to 2 mg/kg BW to induce toxic effects.

Hellenäs et al. (1992b) also used a human study to determine levels of glyco-

alkaloids in blood serum. They determined that α-solanine and α-chaconine had biological half-lives of 10.7 and 19.1 h, respectively. Levels peaked at 4 to 8 h. Plasma levels ranged from 3 to 11 ng/ml for α-solanine and 6 to 21 ng/ml for α-chaconine. Solanidine was also present but at levels below 4.0 ng/ml. No other hydrolytic intermediates were found.

Claringbold et al. (1980, 1982) conducted similar experiments with solasodine and solanidine on plasma and blood but used intravenous (IV) injection to introduce the alkaloids. Solasodine was excreted slowly. After 3 d, only 25% was lost with some remaining in the blood and plasma after 8 d. Solanidine remained in the body even longer with a half-time excretion estimated at 34 to 68 d. These authors also examined postmortem livers of human cadavers and found quantities of solanidine and glycoalkaloids at levels in excess of 200 ng of glycoalkaloid equivalent. They suggested that these glycoalkaloids from the diet that were stored in the liver and other organs might be mobilized at times of increased metabolic stress (pregnancy, starvation, debilitating illness) with deleterious effects.

Harvey et al. (1985a,b, 1986) examined several hundred people for glycoalkaloids. They found glycosides and aglycones in the sera and determined that the concentrations were proportional to the amount of potatoes eaten. For two subjects who subsequently abstained from eating potatoes, serum glycoalkaloid levels dropped 35 to 55% after the first week.

2. Animal Studies

Although humans are especially susceptible to the effects of glycoalkaloids, these compounds can affect other animals. Most studies have concentrated on rats, mice, hamsters, rabbits, and occasionally monkeys, but cows, sheep, horses, pigs, and dogs have also exhibited symptoms of glycoalkaloid poisoning.

Early studies on absorption of the glycoalkaloids in animals showed that they were relatively slow to enter the bloodstream after oral administration. For example, Nishie et al. (1971, 1975) found that 78% of α-solanine was excreted by mice after 24 h, and that 94% was eliminated after 4 d. When these authors conducted studies using intraperitoneal (IP) injection, they found a striking difference. The residence time of the glycoalkaloids was considerably longer. The estimated lethal dose for 50% of all animals (LD_{50}) for α-solanine administered orally was over 1000 mg/kg BW. In contrast, the IP LD_{50}s for solanine, chaconine, and tomatine in mice were 27, 30, and 34 mg/kg BW, respectively. Rabbits had LD_{50}s of about double those for mice following IP injection of the same compounds. Gull et al. (1970) and Patil et al. (1972) compared oral intake to IP intake of glycoalkaloids. Their numbers were 590 vs. 75 mg/kg BW for rats (Gull) and 590 vs. 32 mg/kg BW for mice (Patil). Alozie et al. (1978, 1979a) and Norred et al. (1976) obtained similar results using tritiated α-chaconine to study uptake and excretion patterns after IP injection. Dalvi (1985) compared effects of oral intake to IP intake of solanine on liver damage in rats and found, not surprisingly, that oral consumption was considerably less toxic. Other investigators have used monkeys (Swinyard and Chaube, 1973), sheep (König and Staffe, 1953), and pigs (Sharma et al., 1978) to evaluate IP injection of glycoalkaloids and have found similar toxic effects.

Although there are few studies on oral intake of pure compounds, several generalities can be established. For most animals, the IP LD_{50}s of the various glycoalkaloids are around 30 to 60 mg/kg BW. Limited studies (König and Staffe, 1953; Nishie et al., 1971) would seem to put the intravenous (IV) LD_{50}s at around 10 to 20 mg/kg BW. The oral LD_{50}s are around 500 to 1500 mg/kg

BW. These values are considerably higher than the estimated oral lethal dose of 3 to 6 mg/kg BW for humans. However, studies with hamsters have shown them to have a sensitivity to glycoalkaloids nearer to that of humans. Thus, Alozie et al. (1978, 1979a) found much higher uptakes of tritiated α-chaconine in hamsters with only 24% being excreted after 7 d. Baker et al. (1987, 1988) and Groen et al. (1993) have also found increased sensitivity in hamsters to gavaged and orally administered glycoalkaloids. Due to this increased sensitivity, van Gelder (1989) recommended that researchers consider using hamsters as the preferred animal model.

As the above discussion indicates, although IP and IV studies are generally easier and require less material, and they provide valuable information on relative potencies and mechanisms of toxicity, they may not be indicative of what is actually occurring after ingestion. Since the early studies of Nishie et al. (1971) indicated poor absorption of the glycoalkaloids, there have been surprisingly few oral studies, due in part to the large quantities of material needed to evoke a reaction and difficulties in determining glycoalkaloids at low levels in tissues and body fluids. Oral studies with hamsters highly sensitive to glycoalkaloids could be the next best method to human feeding studies. Oral studies are still needed to elucidate many of the questions of glycoalkaloid toxicity relevant to the human diet.

The major toxic effects of glycoalkaloids are cell membrane disruption and acetylcholinesterase inhibition. Other possible effects are liver damage, heart damage, teratogenicity, and embryotoxicity.

3. Cell Membrane Disruption

The first effects of a toxic dose of glycoalkaloids are a burning sensation in the mouth, nausea, vomiting, abdominal cramps, and diarrhea. There may also be internal hemorrhaging, fluid build-up, and production of stomach lesions. IP injections have caused bleeding from the eyes and nose. All these symptoms can be attributed to the cell membrane-disrupting properties of the glycoalkaloids, similar to the lytic surface effects caused by saponins. They also have the ability to bind with sterols. Schlösser (1969) showed that the hemolytic activity of α-solanine and α-tomatine was reduced significantly in the presence of cholesterol. Roddick (1979) suggested that it may be a combination of properties that causes cell disruption, although Roddick and Rijnenberg (1987) later demonstrated that β_2-chaconine, which has similar surfactant properties, had no hemolytic activity with artificial liposomes. Roddick and colleagues (Roddick and Drysdale, 1984; Roddick and Rijnenberg, 1986, 1987; Roddick et al., 1988, 1992) have demonstrated that α-chaconine caused lysis of liposomes, erythrocytes, beet cells, and protoplasts, while α-solanine had little effect on these cells. An interesting question is why cell disruption is prevented by slight differences in the sugars of the triose, or the loss of one rhamnose from the lysis-active chacotriose, as in β_2-chaconine. α-Tomatine and solamargine have lytic effects on liposomes similar to α-chaconine, while solasonine is inactive. Although α-solanine and solasonine have no effect by themselves, they can act synergistically with α-chaconine or solamargine (discussed below). Roddick et al. (1990, 1992) noted that only liposomes with free sterols seemed to be affected and they could find no correlation between the *in vitro* sterol-binding ability of a compound and the amount of lysis caused. They cautioned against extrapolating *in vitro* results to actual membranes until more information becomes available. Oral *in vivo* studies are needed to clarify these results. Keukens et al. (1992), using a model membrane from egg, reported finding a dual

specificity in binding for aglycones and sterols. This may involve a lectin-like binding to a receptor.

The membrane potential of a cell is affected by the ionic concentration inside and outside the cell and by the carriers and ionic pumps located near the cell membrane. If either is disrupted, the membrane potential across the cell will change. Michalska et al. (1985) and Toyoda et al. (1991) have shown that there is a direct correlation between glycoalkaloids and inhibition of Ca^{2+} transport across cell walls.

Blankemeyer et al. (1992) developed a method of measuring membrane potential using the embryos of the South American clawed frog, *Xenopus laevis*. They found that α-chaconine and α-solanine changed the membrane potential of some or all of an embryo's cells.

Blankemeyer et al. (1995) also developed a method using frog skin to measure *trans*-epithelial active transport of sodium. They found that α-chaconine and α-solanine reduced interstitial short-circuit current (ISC), the measure of active transport of sodium.

Gee et al. (l996) observed changes in membrane integrity following exposure of cultured cell lines of rat and human intestinal mucosal epithelium to potato glycoalkaloids, as evidenced by leakage of the enzyme lactate dehydrogenase in a system relevant to the whole gut. A synergistic effect between α-chaconine and α-solanine was also observed. Related histochemical changes in gut tissue of mice were observed by Friedman (l992) following oral administration of the aglycone solasodine.

Phillips et al. (l996) found that a single peritoneal injection of a 1: 1 mixture of α-chaconine and α-solanine induced gut bleeding and was lethal to Syrian hamsters. Bleeding may be a consequence of membrane disruption in gut cells. In contrast, oral administration of 50 mg of glycoalkaloids per kilogram body weight had no adverse effects, or were adverse effects apparent following oral administration of potato tops to rats, mice, and Syrian hamsters.

Kupchan et al. (1965) reported that α-solamarine exhibited tumor-inhibiting properties. Cham and colleagues (Cham and Meares, 1987; Cham et al., 1987, 1991) have used the lytic properties of glycoalkaloids, solamargine in particular, to treat skin cancer. Cham and Daunter (1990) and Daunter and Cham (1990) reported that the glycoalkaloids might be used to attack cancer cells while leaving normal cells unharmed. This is certainly a possibility worth exploring. Similarly, Thorne et al. (1985) found that α-chaconine, α-solanine, and α-tomatine inhibited Herpes simplex virus type I in tissue culture. Whether glycoalkaloids can inhibit growth of other viruses merits further study.

4. Anticholinesterase Activity

The symptoms of glycoalkaloid poisoning associated with the central nervous system, such as rapid and weak pulse, rapid and shallow breathing, delirium, and coma, are due to the glycoalkaloids ability to inhibit acetylcholinesterase (AChE). Early work on AChE inhibition by potato foliage extracts was done by Orgell et al. (1958), Orgell and Hibbs (1963), and Zitnak (1960). AChE inhibition was also found with solanine (Abbott et al., 1960); solanine and solanidine (Harris and Whittaker, 1962); solanine, demissine, and leptine I (Orgell, 1963); and α-chaconine (Alozie et al., 1979b). Bushway et al. (1987) and Roddick (1989) reported AChE inhibition with *in vitro* studies. Another *in vitro* study revealed that a potato sprout glycoalkaloid extract inhibited 63.1% of human cholinesterase and α-solanine, α-chaconine, and solanidine, caused 52.1%, 41.2%, and 11.4% inhibition, respectively (Duan, 1994). These studies indicated that α-solanine and α-chaconine were strong inhibitors. Patil et al. (1972) observed an inhibitory effect in mice but classified it as weak to moderate.

They also observed that injections of atropine sulfate reduced the toxic effects by half. Aldous et al. (1980) found no correlation between lethal doses in rats and concentrations of acetylcholine and other neurotransmitters but did find significant changes in heart rates and respiration. Baker et al. (1988) found little decrease in AChE levels of hamsters following gavaging with potato sprouts and attributed death to formation of stomach lesions. Whether death from glycoalkaloid poisoning is generally due to damage to the central nervous system has not been completely established.

Part of the problem may lie in the fact that different animals may have different susceptibilities to AChE inhibition. Indeed, members of the same species may not react in the same manner. For example, Harris and Whittaker (1962) found that different populations seemed to have different levels of inhibition. They divided people into three types that they called usual, intermediate, and atypical. In a study on AChE inhibition by α-chaconine in Colorado potato beetles, Wierenga and Hollingworth (1992) found both a susceptible and a resistant strain of beetles.

Another area of discrepancy is the potency of solanidine. Early studies seemed to show it was almost as potent as solanine in inhibiting AChE. Later studies reported it to be about one tenth as effective as α-solanine or α-chaconine. Roddick et al. (1988) suggested that purity problems of the aglycones in the earlier work may have been responsible for the conflicting results. Glycoalkaloid extracts or precipitates used in some earlier studies were of dubious purity. Thus, compounds other than glycoalkaloids cannot be eliminated from contributing to the observed effects.

Roddick (1989) also reported that α-solanine and α-chaconine are about equal in effect on *in vitro* inhibition of bovine and human AChE and they do not act synergistically. β_2-Chaconine was as effective as α-chaconine. Tomatine was less inhibitory and solasonine and solamargine were even less so. The aglycones solanidine, tomatidine, and solasodine had little or no effect.

5. Damage to Liver and Other Organs

Glycoalkaloids seem to concentrate most in the liver but high concentration have been found in other major organs of the body including kidney, heart, lungs, and brain. Sharma et al. (1979) reported renal and hepatic congestion and leukocytic infiltration in mice after IP injection of solanine and chaconine. Azim et al. (1982) reported a significant increase in liver size after feeding rabbits for 30 d with potatoes high in glycoalkaloids. Dalvi (1985) and Dalvi and Jones (1986) found significant increases in cholinesterase and liver enzyme activities in male rats after administration of solanine orally and intraperitoneally. Kusano et al. (1987) reported that aglycones inhibited rat liver enzymes involved in cholesterol metabolism. Friedman (1992) found dose-related increases in liver enzyme activities in mice fed a normal diet supplemented with several levels of solasodine.

Caldwell et al. (1991) demonstrated that α-chaconine and α-solanine induced ornithine decarboxylase (ODC) activity — a marker of cellular proliferation — in rat livers after intraperitoneal administration. ODC activity induced by α-chaconine was higher than that induced by α-solanine, while the aglycone had no effect. ODC induction and measurement provide a bioassay that is quantitative and short-term and needs far less material than a long-term feeding trial. An unanswered question is whether ODC activity is induced by oral ingestion of the alkaloid as part of a normal diet.

Friedman et al. (1996) found that dietary consumption of steroidal glycoalkaloids resulted in decreases in mouse liver weights.

In contrast, consumption of the aglycones caused increased liver weights (hepatomegaly) in mice. The increases induced by solanidine and solasodine were apparently reversible in that liver weights returned to normal values when the mice were taken off the aglycone-containing diets. These results suggest that aglycone-induced liver enlargement may be an adaptive rather than a toxic response.

Azim et al. (1982) fed greened potatoes to rabbits for 30 d. They noted enlarged livers and hearts, increased blood cholesterol and glucose levels, decreased blood protein, increased plasma calcium and decreased plasma sodium and potassium levels, as well as other effects. Bergers and Alink (1980) found that solanine and tomatine were toxic to neonatal rat heart cells and Aldous et al. (1980) found changes in heart rate and respiration in rats given IP injections of α-chaconine at various levels. Doses of 8 to 10 mg/kg BW produced respiratory impairment and constriction of abdominal muscles. Strangely, doses of 10 mg/kg or 40 mg/kg produced rapid heart rates (tachycardia), but intermediate doses (20 to 30 mg/kg) produced slowed heart rates (bradycardia). The authors also observed an increase in low-frequency activity in electroencephalogram patterns.

The exact mechanism(s) of organ damage has not been determined. This damage may be due in whole or in part to membrane disruption effects or it could be caused by other, as yet undefined, mechanisms involving inhibition or potentiation of essential enzymes or both. Glycoalkaloids do not seem to damage the DNA or chromosomes of bacteria and animals, as evidenced by negative Ames and micronucleus assays (Friedman and Henika, 1992; Ness et al., 1984)

6. Teratogenicity

One of the more hotly debated issues is whether glycoalkaloids are teratogenic. Renwick (1972a) reported that there was a correlation between the incidence of potato blight and occurrences of spina bifida (the defective closure of the vertebral column) and anencephaly (absence of part of the brain and skull). He concluded that some component(s) of the blighted potatoes was responsible. This caused immediate concern. Spina bifida is one of the most serious neural tube defects. The malformation is fairly common in the North American white population, with an incidence of about 1.5 per 1000 live births. It can be much higher (7 to 8 per 1000 births) in other parts of the world. The incidence is 10 to 20 times greater in spontaneously aborted fetuses (Slattery and Janerich, 1991). Other investigators (Elwood and MacKenzie, 1973; Emanuel and Sever, 1973; Field and Kerr, 1973; Kinlen and Hewitt, 1973; McMahon et al. 1973; Spiers et al, 1974) conducted similar studies of records, but none could find any correlation similar to Renwick's.

Still, the implications were of such importance that clinical studies were needed to test Renwick's hypothesis. Immediate attention fell on the glycoalkaloids, which were known to be high in blighted potatoes and to have other toxic effects.

Nevin and Merrett (1975) in a study on pregnant women actually found a lower incidence of spina bifida in mothers who ate potatoes (2 out of 23) than in those who refrained (2 out of 56). This study is often cited to dispute Renwick's original hypothesis, but the sample size was not large enough to be conclusive. Also, the levels of glycoalkaloids involved were not known, but it is doubtful they were as high as would be found in blighted potatoes. However, it does seem to contradict Renwick's later assertion (1972b, 1973) that if pregnant women simply abstained from eating potatoes, incidence of spina bifida would drop by 95%. Harvey et al. (1986) found lower levels of glycoalkaloids in the serum of mothers carrying a fetus with a neural tube

disorder than in mothers carrying a normal fetus.

Numerous animal studies have been conducted, but the results are inconclusive. Chaube et al. (1973) and Ruddick et al. (1974) fed rats blighted potatoes up to 25 mg/kg BW and could find no teratogenicity. Similar results were reported by Keeler et al. (1974) and Kuč (1975), who used blighted tubers or extracts from tubers. Bell et al. (1976) and Chaube and Swinyard (1976) studied the effects of IP injections of α-solanine or α-chaconine on pregnant mice and rats and reported no apparent teratogenicity. Allen et al. (1976) had similarly negative results with rhesus monkeys and marmosets, as did Keeler et al. (1975) in rats, rabbits, hamsters, and mice. Slanina (1990a) introduced α-chaconine into pregnant rats by stomach pump, maintaining a serum level of glycoalkaloid equivalent to ten times that found in the serum of men who had ingested 200 mg total glycoalkaloids. No teratogenicity was observed. Hellenäs (1992a) observed no teratogenicity or embryotoxicity in rat fetuses when the mother was given 1.7 mg/kg BW/d by I.V. infusion on days 6 to 13 of the pregnancy. Blood serum levels reached an average of 340 ng/ml, a level stated to be 20 times that found in a man having ingested enough potatoes to have consumed the upper safe level of glycoalkaloids.

Several studies have produced mixed results. Poswillo et al. (1972) found higher than normal cranial abnormalities in marmosets. Poswillo et al. (1973a,b) observed no significant cranial effects but did observe behavior anomalies. Swinyard and Chaube (1973) found that gavaging blighted potatoes or IP injection of α-solanine or other glycoalkaloids induced minor skeletal and kidney malformations but no neural tube defects. Keeler (1973) found that solasodine was nonteratogenic in rats, but Keeler et al. (1976b) found that higher doses were teratogenic in hamsters, as were potato sprout glycoalkaloids (Keeler, 1984, 1986; Keeler et al., 1978). Sharma et al. (1978) fed freeze-dried blighted potatoes and their extracts to hamsters, rabbits, and miniature swine. No teratogenicity was found in hamsters, but anencephaly was observed in swine and a subclinical malformation similar to occult spina bifida was noted in rabbits. Sample sizes were too small for statistical significance.

Pierro et al. (1977) determined that α-solanine and α-chaconine at doses as low as 16 mg/kg BW when given IP caused significant neural tube defects in mice. Renwick et al. (1984) found that potato sprouts, α-solanine, and α-chaconine caused similar teratogenicity in mice and hamsters.

It should be noted that in the studies with positive correlations there were accompanying maternal mortality rates ranging from 11 to 48%. It is always difficult to distinguish between abnormalities of an embryo caused by a test substance directly and those caused by distress or failure of the mother's organ systems. The World Health Organization (WHO, 1987) stated in part that in testing for developmental toxicity, the highest doses given should only cause slight maternal toxicity, and that if birth defects occur only at levels causing toxicity in adults, there should be no special significance attributed to possible teratogenicity. Van Gelder (1989), citing this guideline, concluded that potato glycoalkaloids were not teratogenic at levels found in the common commercial cultivars. In contrast, pregnant hamsters gavaged with plant material from five *Solanum* species, including potatoes and eggplants, had a high incidence of craniofacial malformations in the offspring (Keeler et al., 1990, 1991). In some cases there was maternal toxicity and no malformation, whereas in others there was malformation and no maternal toxicity.

In the following studies on embryos where there was no maternal toxicity effect, the glycoalkaloids and potato extracts did

seem to exert a teratogenic effect, sometimes at very low levels. Nishie et al. (1975) tested solanine, chaconine, tomatine, and solanidine for embryotoxicity by injecting the compounds into fertilized chicken egg sacs prior to incubation. The lethal dose of α-chaconine was 1.0 mg, but all compounds were lethal at low levels. Mun et al. (1975) found that a preparation from blighted potatoes induced significant fetal abnormality and mortality in chick embryos at a level of 0.26 mg per egg. Jelinek et al. (1976) also found that doses as low as 0.3 mg of potato extracts and solanine caused teratogenicity in fertile eggs. There were no differences between extracts of blighted and healthy potatoes. In Friedman et al. (1991, 1992), studies on frog embryos by the FETAX (frog embryo teratogenicity assay — *Xenopus*) method indicated that α-chaconine, α-solanine, and tomatine induced embryotoxicity and teratogenicity. Further, related alkaloids such as jervine and cyclopamine found in *Veratrum* species are known to be teratogenic (Keeler, 1984).

Finally, although teratogenicity is still an open question, most researchers feel that glycoalkaloids can adversely affect fertility (Dixit et al., 1989). Swinyard and Chaube (1973) found that even proven breeder rhesus monkeys did not bear young while being fed glycoalkaloids. Chaube and Swinyard (1976) found increased resorption of fetuses with rats being fed glycoalkaloids. At the highest doses (160 mg/kg) there was 100% resorption. Studies by Keeler (1973) and Keeler et al. (1976a, b) revealed that solasodine and tomatidine caused increased resorption. Bell et al. (1976) noted resorption of fetuses in pregnant mice (26 to 100%) fed solanine or total potato glycoalkaloid mixture. Kline et al. (1961) reported an increased mortality in neonatal rat pups after feeding the mothers glycoalkaloids or potato sprouts, but they attribute this to lack of milk produced by the mother and not to a toxic effect on the pups. As no total amounts of glycoalkaloid ingested are given, it is difficult to evaluate the significance of this study. Moreover, many of the studies used blighted potatoes that may have been infected by fungi containing toxic and teratogenic mycotoxins such as nivalenol and zearalenone, which could potentiate the biological effects of glycoalkaloids (Griffin, 1994; Lotus-Zietkiewicz et al., 1990).

7. Relative Toxicities

Part of the problem in comparing glycoalkaloid toxicities is the fact that there are at least two, and maybe more, major toxic effects that have generally been combined into the overall category of lethality. Several studies cited, by their very nature or manner of introducing test compounds, have contrived to eliminate one or the other of these effects and have, thus, given a distorted picture of relative toxicity.

In overall toxicity, α-chaconine is the most toxic of the potato alkaloids. It exhibits the strongest cell disruption, as well as causing inhibition of AChE, organ damage, and teratogenicity in embryos. α-Solanine is somewhat less toxic. More specifically, it has little if any lytic properties by itself but is a strong inhibitor of AChE, similar in potency to α-chaconine. It is also less teratogenic to embryos than α-chaconine. This would seem to indicate that it is probably less damaging to organs, but more data are needed to demonstrate this possibility. The intermediate hydrolysis products of α-chaconine and α-solanine seem to lose toxicity as they lose sugar groups and the aglycone solanidine is the least toxic in all effects (Blankemeyer et al., 1992; Friedman et al., 1992; Rayburn et al., 1994). The solanidanes also seem to be more toxic than their corresponding spirosolanes — solamargine, solasonine, and solasodine. There is an ap-

parent relationship between chemical structure and biological potency glycoalkaloids (Brown and Keeler, 1978; Friedman et al., 1992, 1996; Gaffield and Keeler, 1984, 1993; Gaffield et al., 1991; Rayburn et al., 1994). This relationship might be used to predict potencies of new glycoalkaloids, possibly with the aid of computer modeling of molecular features responsible for toxicity.

Gaffield and Keeler (1996) determined the following relative oral teratogenic potencies for a series of alkaloids in Syrian hamsters: jervine, 100; 20(S),24(R)-solanidanes, 50; α-chaconine, 43; α-solanine, 32; 22(R),25(S)-solanidine, 32; solanidine *N*-oxide, 32; 5-α,6-dihydrosolanidine, 9; and tomatidine, 0. To what extent these results are relevant to whole foods such as potatoes, which contain more than one glycoalkaloid, awaits further study. See sections below on synergism and dietary considerations.

Friedman et al. (1996), in a study on liver enlargement (hepatomegaly) in mice, found that the aglycones solasodine and solanidine were more active than tomatidine. In addition, they fed dehydroepiandrosterone, which has A, B, C, and D rings identical to those of solanidine and solasodine. They concluded that the 5,6 double bond, lacking in tomatidine, had more effect on hepatomegaly than the structures of the E and F rings. Gaffield and Keeler (1993) also discuss the importance of this double bond in relation to teratogenicity.

An interesting finding of Chaube and Swinyard (1976) was that size of dose seemed to be more important than total glycoalkaloid intake. They observed that in IP injections of glycoalkaloids to rats, two daily doses of 40 mg/kg BW (80 mg total) were as toxic as eight daily doses of 20 mg/kg (160 mg total). Nishie et al. (1971) and Norred et al. (1976) also commented that as doses approached the toxic level, absorption seemed to increase much more rapidly.

If we accept the toxic and lethal levels determined by Morris and Lee (1984) as valid, we are left with this possible scenario for ingestion of glycoalkaloids. A single dose of less than 1.0 mg/kg BW enters the system, and most of it passes through without being absorbed. There is some disruption in the gut but not enough to be noticed. Some of the glycosides are hydrolyzed to solanidine. The small amounts of glycoalkaloids and aglycone entering the bloodstream do not cause significant damage and are eventually stored in the liver for slow detoxification. At a single dose of around 1 to 2 mg/kg, cell disruption becomes noticeable, causing nausea, diarrhea, etc., but levels in the bloodstream are still safe. However, if this is chronic, damaging levels of glycoalkaloids begin to collect in the liver and other organs. With a single dose of 3 to 4 mg/kg, cell disruption becomes extensive and membranes become permeable and allow most of the glycoalkaloids to pass into the bloodstream unchanged. AChE inhibition occurs as well as cell disruption, causing damage to the central nervous system and major organs, leading to rapid breathing, rapid pulse, delirium, etc. The body slowly recovers and is able to repair the damage. At an even higher acute dose, the damage is irreversible and may cause death.

B. Synergism

The first indication that glycoalkaloids might act synergistically was when Swinyard and Chaube (1973) reported that glycoalkaloid extracts seemed to have a greater toxicity than the combined total of α-solanine and α-chaconine individually. However, as these were crude extracts, this could have been due to the presence of another unidentified toxic component.

Since then, several different methods have been used to evaluate possible syner-

gistic effects. Roddick and colleagues (Roddick and Rijnenberg, 1987; Roddick et al., 1988, 1990, 1992) in *in vitro* studies on artificial liposomes, have found that α-solanine and α-chaconine do indeed act synergistically in their cell disruption effects. α-Solanine had no lytic effect by itself and α-chaconine had a strong effect. Some combinations of α-solanine and α-chaconine acted as strongly as pure chaconine. Maximum synergy was exhibited between 60:40 and 40:60 ratios. The authors have also found synergy between α-chaconine and solasonine and between α-solanine and solamargine. A combination of α-chaconine and solamargine had only an additive effect, and a combination of α-solanine and solasonine had no effect. The two synergistic pairs are both combinations of chacotriose and solatriose glycosides. Roddick et al. (1990) speculated that this may be the primary reason why the potato plant devotes a considerable amount of energy producing both glycoalkaloids and not just α-chaconine. This concept has application to many *Solanum* species, which seem to produce glycoalkaloids in matched pairs of a chacotriose and a solatriose (solasonine and solamargine, α-solamargine and β-solamargine, leptine II and leptine I). Roddick (1989) has also shown that there is no synergistic effect between α-chaconine and α-solanine for AChE inhibition.

Using a complex toxic unit (TU) analysis technique combined with FETAX studies, Rayburn et al. (1995b) showed that several combinations of α-chaconine and α-solanine acted synergistically in inducing embryotoxicity and teratogenicity in frog embryos. These results suggested that the synergism observed for a specific mixture cannot be used to predict the possible synergy of other mixtures with different ratios of the two glycoalkaloids.

Blankemeyer et al. (1992, 1995), using a method involving the membrane potential of frog skin, postulated that the fundamental mechanism governing teratogenicity may be disruption of cell membranes and changes in ion fluxes and interstitial currents of the membranes. That there is synergy between α-chaconine and α-solanine for teratogenicity gives credence to this idea. The same cell-disrupting mechanism(s) would be operating whether the outcome was lysis or teratogenicity. In fact, the anticarcinogenic and antiviral effects of glycoalkaloids mentioned earlier may result from the disruption of cell membranes, preventing cell division and/or killing the cells.

It is possible that the stronger cell-disrupting property of α-chaconine may be the reason why only α-chaconine is converted to the β-form in sprouts. The young plant may be protecting itself from the lytic effects of α-chaconine by converting it to the nonlytic β_2-chaconine. It does not convert α-solanine, as this has reduced lytic properties in the absence of α-chaconine. As the plant matures, it converts the stored β_2-chaconine back to the α-form in the single energy-efficient step of adding one sugar, rather than having to synthesize it from solanidine, which requires adding three sugars. Additionally, the α-solanine and β_2-chaconine will still provide the young plant a measure of protection against pathogens, as they are both strong acetylcholinesterase inhibitors, an effect that may be incidental to the plant and from which it has no need to protect itself.

An unresolved issue is why α-solanine and β_2-chaconine have little or no cell-disrupting properties but do inhibit AChE as effectively as α-chaconine. The mechanisms for the two effects must be very different. In the case of the cell membranes, the relative potencies seem to be governed by the nature of the carbohydrate side chains. The specific mode of action is unclear, but the possibilities include binding of the carbohydrate to receptor sites on the membranes or actually changing the membrane structure by altering fluidity. In contrast, the mechanism for

AChE inhibition seems to be governed more by the nature of the steroidal moiety, solanidine in the case of the three aforementioned compounds. A protonated solanidine moiety would be viewed by the active site of AChE as a quaternary ammonium compound, identical to the quaternary ammonium structure of acetylcholine, the normal substrate of AChE. This implies that other pairs of glycosides such as solamargine and solasonine would have equal AChE-inhibiting ability. It also implies that the inhibition is regulated by the pKa value of the steroid nitrogen atom. However, because the aglycone solanidine does not inhibit AChE as much as α-solanine, α-chaconine, or β_2-chaconine do, it must be concluded that the carbohydrate plays some part in the process. Similarly, because solamargine is less active in disrupting membranes than α-chaconine, even though they have identical sugar side chains, the steroidal moiety also appears to contribute to the disruption process.

C. Dietary Considerations

A relatively unexplored area of glycoalkaloid toxicity is the influence of other components in the diet. Studies on pure compounds or mixtures are necessary and instructive, but they do not reflect the normal manner of potato consumption. Obviously, glycoalkaloids in potatoes are consumed simultaneously with other components of the potato itself. Similarly, the potato is usually eaten along with other foods. How all these factors interrelate is still poorly understood and may never be completely defined.

For example, Roddick (1979) mentions that at least part of the glycoalkaloids' ability to disrupt membranes is due to sterol binding. Protonated glycoalkaloids, however, do not complex with sterols. Therefore, the pH of the digestive system may have an effect. Foods that do not require large amounts of stomach acid for digestion or that are acidic themselves might tend to lessen the toxicity of the glycoalkaloids by maintaining an acidic protonating environment. Also, if a high concentration of a sterol such as cholesterol were ingested at the same time, the glycoalkaloids might competitively bind to it rather than to cell membranes, especially in the alkaline environment of the duodenum. Thus, the old standard of "meat and potatoes" may include a built-in safety factor as far as glycoalkaloid toxicity is concerned. Bile cholesterol that enters the digestive tract via the enterohepatic circulation could also be complexed by dietary glycoalkaloids. Dixit et al. (1992) have reported that solasodine had an antiatherosclerotic effect on cholesterol-fed rabbits.

Another complicating factor is that if enough glycoalkaloids are ingested to cause membranes to become permeable by cell disruption to allow glycoalkaloids to pass into the bloodstream, these membranes would also allow other components of the diet to do likewise, causing unpredictable results.

Recently, Rayburn et al. (1995a) discovered that glucose-6-phosphate (G6P) and nicotine adenine dinucleotide (NADP) can reduce the developmental toxicity of α-chaconine in frog embryos. We have also discovered that folic acid protected frog embryos against α-chaconine-induced disruption in the integrity of frog embryo cell membranes (unpublished results). Renwick (1986) described protective effects of ascorbic acid against glycoalkaloid toxicity. These findings are significant in view of the apparent protective effect of folic acid against anencephaly in human fetuses (Herbert, 1992). It is certainly possible that these compounds and other dietary components could reduce the adverse effects of glycoalkaloids.

On the other hand, other parts of the diet could contain toxic compounds that act synergistically with the glycoalkaloids to increase toxicity. Potatoes themselves are known to contain sesquiterpenes and other stress-related compounds known as phytoal-

exins (see Pest Resistance section below). Several researchers feel that the glycoalkaloids are not sufficient by themselves to provide pest resistance and that phytoalexins or other compounds may be more responsible for resistance. Another possibility, however, is that the glycoalkaloids and the phytoalexins or other compounds act synergistically to increase pest resistance. This could have the effect of increasing toxicity when eaten by humans. Other plants have similar protective compounds, and the effects of such a complicated mixture would be almost impossible to predict.

D. Safety Guidelines for Potatoes

From the previous discussion, the minimum toxic effect level of glycoalkaloids for humans seems to be around 1 to 2 mg/kg BW. Lethal doses may be as low as 5 to 6 mg/kg. The common current guideline for potatoes establishes an upper level of 200 mg/kg fresh weight (FW) of glycoalkaloids, an official requirement in many countries but unofficial in the U.S. The average amount found in commercial potatoes is generally less than 100 mg/kg FW. The daily average amount of potatoes consumed varies considerably by country. In the UK it is 140 g (MAFF, 1993, as cited by Hopkins, 1995), in the U. S. 167 g (Willard, 1993), and in Sweden 300 g (Slanina, 1990b). At the highest "safe" level, this would be a daily glycoalkaloid intake of 28 mg, 33 mg, and 60 mg, respectively. If the above-mentioned toxic levels are correct, this would amount to the minimal toxic doses for a child or teenager. It is certainly possible that a person might consume 500 g of potatoes. At the "safe" level, this would be 100 mg of glycoalkaloids, a dose where a healthy, slightly overweight individual might feel some symptoms of toxicity.

Safety guidelines may also be affected by the difficult-to-control factor of biological variability. Van Gelder (1985a) in a survey of 521 samples of commercial Netherlands potatoes, found that, while most potatoes (84%) had glycoalkaloid levels below 100 mg/kg FW, 2% of these samples contained over 200 mg/kg. Davies and Blincow (1984) have found higher average levels (90 to 170 mg/kg FW) in potatoes in the U.K. Hellenäs et al. (1995b) report that the sale in Sweden of the widely consumed potato variety Magnum Bonum was banned because of its very high glycoalkaloid content. Additional studies on Magnum Bonum tubers showed that the α-chaconine plus α-solanine content of 300 commercial lots ranged from 61 to 665 mg/kg FW, an average of 254 mg/kg. Peeling did not significantly reduce the glycoalkaloid content when original values for the whole tuber were high. The authors reported circumstantial evidence of a few cases of temporary gastrointestinal disturbances caused by consumption of Magnum Bonum potatoes with glycoalkaloid concentration in the range of 310 to 1000 mg/kg FW. In the opinion of several researchers, this may be a relatively common occurrence, where the gastrointestinal problems are dismissed by the victim as "food poisoning" or "a touch of the flu" and never reported.

The observed tenfold variation in glycoalkaloid content among different samples of the same Magnum Bonum variety grown in the same season is striking and suggests that although the average glycoalkaloid content of a particular variety may be below the 200 mg/kg FW guideline, individual potatoes from the same variety may exceed this level. Hellenäs (1994) commented that safety margins for glycoalkaloids in normal potatoes must be regarded as unsatisfactory. The 200 mg/kg guideline should be considered a minimum requirement until acceptable levels have been adequately established.

Van Gelder (1989, 1990) critically evaluated safety aspects of *Solanum* glycoalkaloids and suggested that the currently accepted

guidelines limiting glycoalkaloid content in potatoes to less than 200 mg/kg are too high. The reasons for his conclusion are best stated in his own words:

> "Many authors have assumed without further evidence that levels below 200 mg/kg are safe. They ignore the fact that the 200 mg/kg [FW] level only relates to acute and/or subacute effects and not to possible chronic effects...
>
> Other authors have proposed lower acceptable levels because they took additional relevant facts into consideration. The content of solanidine glycosides in potatoes varies with the year and location of growth, an upper limit of 60–70 mg/kg is to be applied to cultivars to be selected for human consumption. Recently, the National Institute of Agricultural Botany (NIAB) at Cambridge (UK) recommended that the overall amount of SGAs [steroidal glycoalkaloids] ingested by the public should not be allowed to rise. NIAB therefore suggested 'the average SGA content over all eight maincrop recommended potato varieties', which was calculated (over years and locations) to be 60 mg/kg, as a guideline for potato breeders to bear in mind when submitting new potato cultivars for National List Testing (Parnell et al., 1984)."

Several other researchers have also expressed similar concerns that the guidelines are too high and need to be lowered (Morris and Lee, 1984; Potus and Adrian, 1995; Slanina, 1990b). There seems to be a need to do a quantitative risk assessment to determine whether the "safe" level of 200 mg/kg FW needs to be lowered.

E. Future Studies

Key questions regarding safety that need to be answered include:

1. What are the relative potencies of α-chaconine and α-solanine, the six possible partial-hydrolysis products with side chains of two or one sugar and their common aglycone, solanidine in relation to the several noted toxic effects?
2. Can combinations of different compounds act synergistically, both in pure form and in whole foods and do some food components act antagonistically? Because people do not eat individual glycoalkaloids but combinations of two or more along with other foods, this unexplored aspect probably has the most relevance to food safety.
3. Do short-term *in vitro* assays predict the mechanism of *in vivo* teratogenicity and its prevention?
4. Can the proposed studies be used as a guide by plant scientists to help develop new cultivars with low levels of the most toxic compounds allowing producers and consumers to minimize the glycoalkaloid content in the diet?

In summary, efforts should continue to measure the safety of glycoalkaloids individually and in combinations found in different potato varieties. Particular emphasis should be placed on the interaction of glycoalkaloids with potential antagonists such as glucose-6-phosphate and folic acid. The results will provide information on (1) the mechanism of action of glycoalkaloids at the cellular level, facilitating the development of improved potato cultivars; and (2) dietary factors that protect against glycoalkaloid toxicity.

V. PLANT PHYSIOLOGY

A. Biosynthesis

Biosynthesis of glycoalkaloids has been discussed in detail by Bergenstråhle (1995), Heftmann (1983), and Petersen et al. (1993).

The starting point for the glycoalkaloids is cholesterol, which is formed by the mevalonic acid pathway responsible for the production of steroids in general. Cholesterol does not accumulate in plants but is immediately and completely converted to other substances. Acetate reacts with coenzyme A, forming the intermediates of mevalonic acid, squalene, lanosterol, cycloartenol, and, finally, cholesterol. Guseva and colleagues (Guseva and Paseshnichenko, 1958, 1962; Guseva et al., 1960, 1961) studying glycoalkaloid synthesis in potato plants showed that active acetate and mevalonate are utilized for the biosynthesis of glycoalkaloids by potato sprouts, potato slices, and isolated potato chloroplasts. Bergenstråhle (1995) and Bergenstråhle et al. (1996) found that (1) accumulation of glycoalkaloids in potato disks parallels accumulation of cholesterol and (2) suppression of cholesterol biosynthesis by the inhibitor tridemorph or by the plant hormone ethylene results in a parallel decrease in glycoalkaloid formation. Related studies by Shih et al. (1973) and Tjamos and Kuč (1982) described the suppression of glycoalkaloid formation by arachidonic and eicosapentanoic acids produced by the late blight pathogen *Phytophthora infestans*. Ripperger et al. (1971) discussed the conversion of [26,27-^{14}C]cycloartenol and [26,27-^{14}C]lanosterol to solanidine by *Solanum* plants.

The exact pathway for the conversion of cholesterol to glycoalkaloids has not been fully proven. Kaneko and associates (1971, 1972, 1977a, 1977b), working with *Veratrum grandiflorum* on the synthesis of *Veratrum* alkaloids, have proposed the pathway shown in Figure 6. The nitrogen atom added in the formation of the F ring in the conversion of dormantinone to verazine originates from an amino acid such as arginine, glycine, or alanine. Kaneko et al. (1976) suggested arginine as the principal source of incorporated nitrogen. Once teinemine is formed, the E ring is closed in various ways to form solanidine, solasodine, or tomatidine.

Petersen (1993) postulated that the aglycones with a 5,6 double bond (solanidine, solasodine, and tomatidenol) and the saturated aglycones (demissidine, soladulcidine, and tomatidine) are formed by identical pathways (Figure 7), but that the starting compounds are either cholesterol or cholestanol (cholesterol with a saturated double bond). Another possibility is that the aglycones with double bonds are first formed from cholesterol and then saturated. One might then expect to find both the saturated and unsaturated compounds in the same plant. However, this does not seem to be the case in most *Solanum* plants studied. Obviously, more work is needed in this area.

A relevant study by Ehmke (1995) suggests that the biosynthesis of the aglycone solasodine in cell and shoot teratoma cultures of *S. dulcamara* is complete before glycosylation to solamargine and solasonine begins.

1. Glycosylation

The final step in glycoalkaloid synthesis, as suggested by Liljegren (1971), is the addition of the sugar side chain to the 3-hydroxy position of the aglycone. Jadhav et al. (1973) showed that labeled D-glucose was incorporated into glycoalkaloids in potato sprouts. Jadhav and Salunkhe (1973) showed that extracts from potato sprouts and slices convert solanidine to the β-glucoside, with UDP-glucose-U^{14}C acting as the glucose donor.

Lavintman et al. (1977) described an enzyme preparation isolated from potato tubers and sprouts that had the ability to catalyze the synthesis of all possible sugar derivatives, that is, α-, β-, and γ-solanine and α-, β-, and γ-chaconine. This enzyme preparation must synthesize UDP-glucose, UDP-galactose, UDP-rhamnose, and the

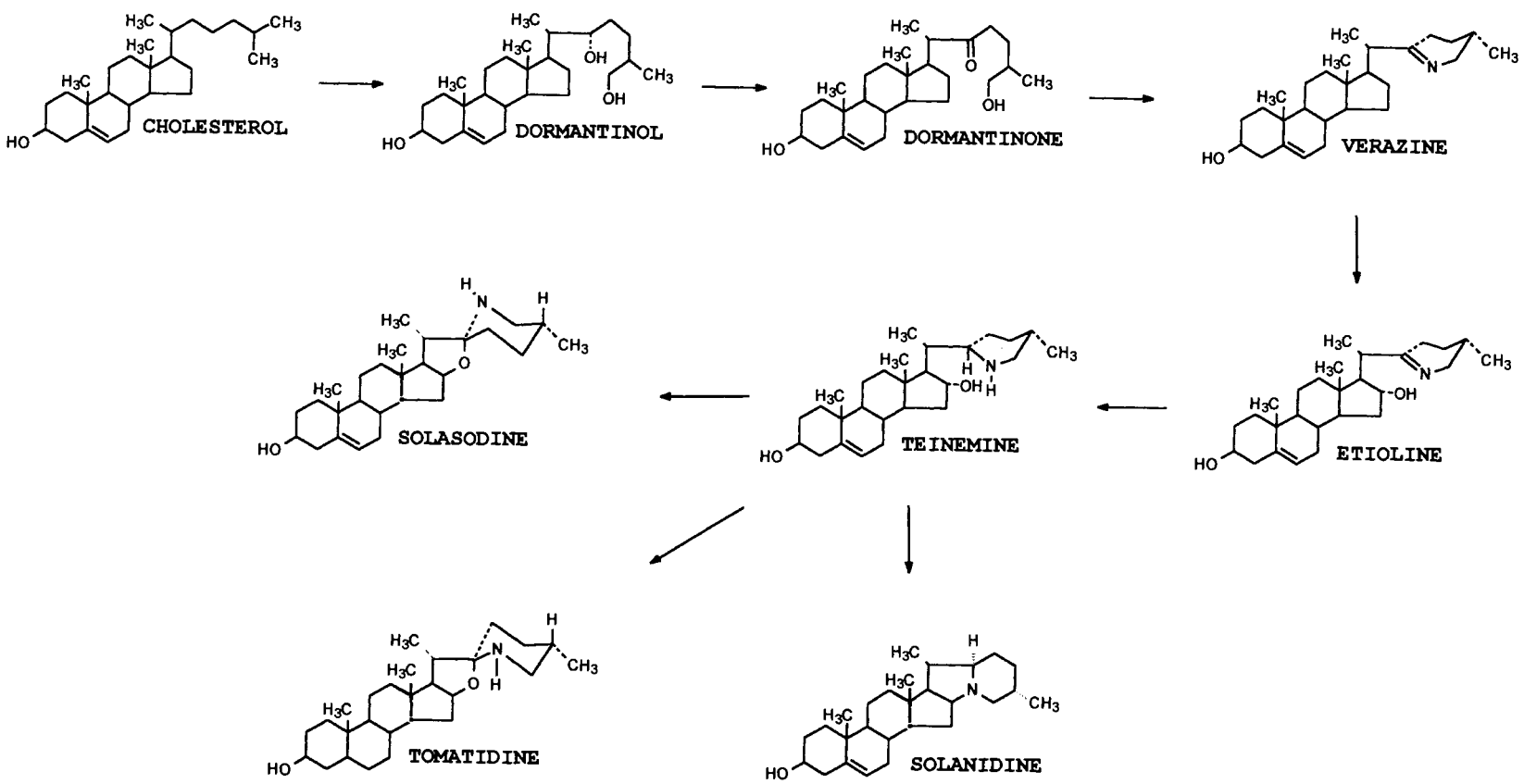


FIGURE 6. Possible synthetic pathways from cholesterol to aglycones. (Adapted from Kaneko et al., 1977a,b.)

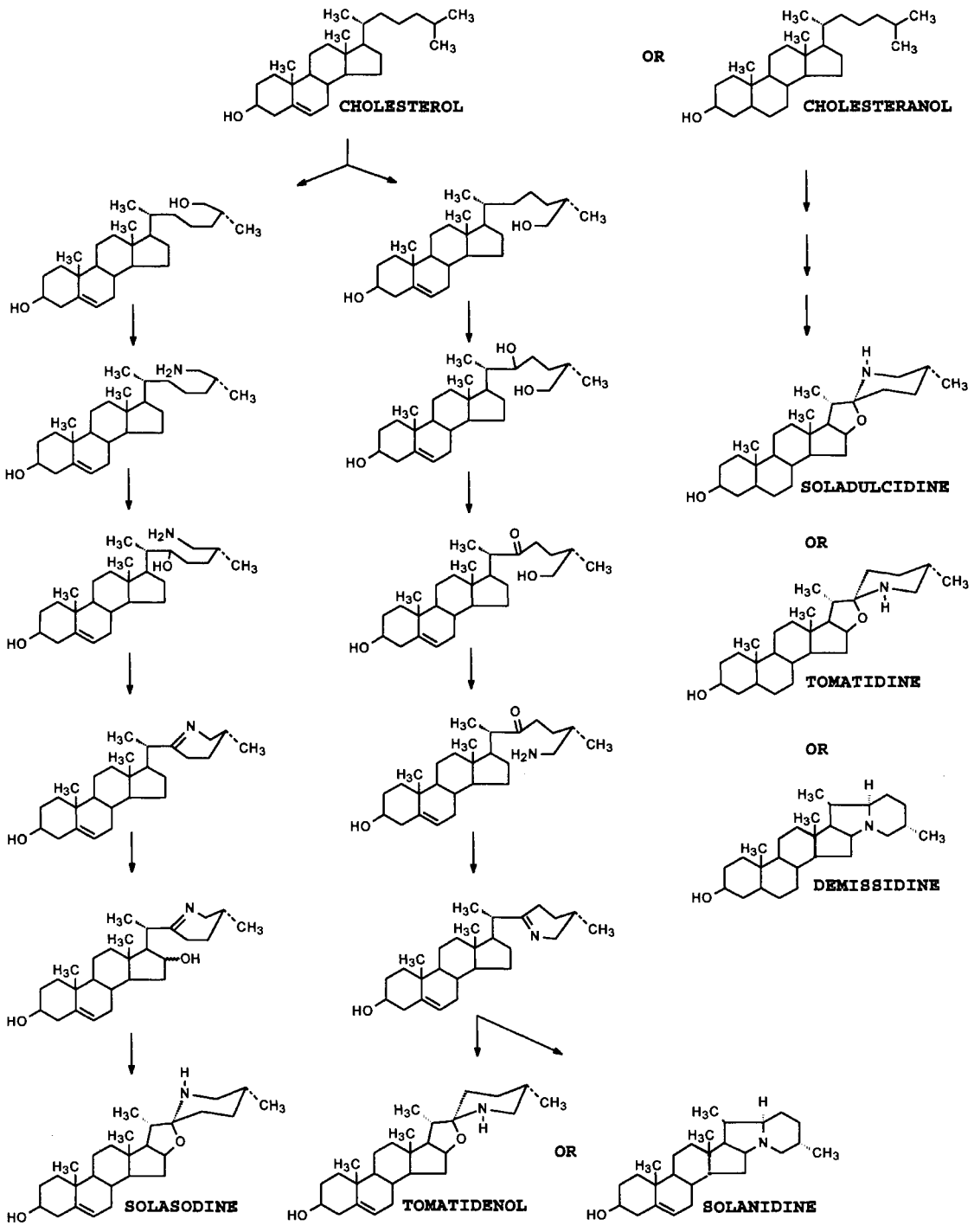


FIGURE 7. Possible synthetic pathways from cholesterol and cholesteranol to aglycones. (Adapted from Petersen, 1993.)

transglycosylases required for the transfer of the three sugars from the nucleotide to the acceptor molecule.

Osman and colleagues (Osman and Zacharius, 1979; Osman et al., 1980) isolated and characterized mono- and diglucosyl-solanidines, directly demonstrating the stepwise glycosylation of radioactive solanidine added to potato tuber tissue slices and cell suspension cultures.

Bergenstråhle et al. (1992a) concluded that the formation of γ-solanine and γ-chaconine was accomplished by two different glycosylating enzymes — a glucosyltransferase and a galactosyltransferase — rather than by a single glycosylating enzyme. All evidence seems to show that the aglycone was rapidly glycosylated in a stepwise manner after being formed. However, as studies by Bergenstråhle (1995), Paczkowski and Wojciechowski (1994), Stapleton et al. (1991, 1992, 1994), and Zimowski (1991, 1992, 1994) showed these enzymes occurred at very low concentrations in plant tissue and were difficult to purify because they were unstable after extraction from leaves, potato peels, and tubers. In addition, no definitive experiments have been possible as solanidine glucosyltransferase (SGT) could not be separated from epoxide hydrolase (Stapleton et al., 1994) or transaldolase (Moehs et al., 1996a).

Using an original approach, Moehs et al. (1996b, 1997) were able to overcome this problem. Based on the observation that the aglycone solanidine inhibited the growth of yeast (*Saccharomyces cerevisiae*), while its glycoside α-chaconine did not, they isolated a complementary DNA (cDNA) encoding SGT by functional expression in yeast. They transformed a library of cDNA into yeast. Certain cDNAs were found to encode an enzyme that glycosylated the aglycones, allowing the yeast to grow in the presence of normally inhibitory concentrations of solanidine, solasodine, or tomatidine. The messenger RNA (mRNA) encoding SGT was strongly induced in wounded potato tubers but less so in wounded leaves. This observation suggests that the concentration of induced SGT could serve as a biomarker of postharvest stress in potato tubers. This approach should also make it possible to characterize other enzymes involved in glycoalkaloid biosynthesis and to explore the effects of antisense constructs on glycoalkaloid levels in potatoes and other plants see also section on molecular genetics.

B. Distribution

Glycoalkaloids are synthesized in all parts of the plant. Table 1 lists the glycoalkaloid contents of the various parts of the potato plant as found by several investigators. Glycoalkaloid biosynthesis begins during germination and reaches a peak during the flowering period. The highest levels of glycoalkaloids are found in parts with the greatest metabolic activity, that is, new leaves, fruit, flowers, and sprouts. Indeed, Haard (1977) found that meristematic outgrowths (warts) of stems, roots, and tubers caused by *Synchtrium endobioticum* had high levels of glycoalkaloids. Generally, leaves attain a maximum glycoalkaloid concentration first, and as new growth occurs, glycoalkaloid levels in the older leaves decrease markedly. Kozukue et al. (1987) examined May Queen and Irish Cobbler plants and found that the upper leaves contained 587 and 358 mg/kg FW of total glycoalkaloids, while the lower leaves had levels of 359 and 226 mg/kg FW, respectively. Unripe fruits and flowers have higher glycoalkaloid concentrations and, while these levels may decrease somewhat at senescence, they remain high. For this reason, flowers have proven to be an excellent source for obtaining mass quantities of α-chaconine and α-solanine (Achterberg et al., 1979;

TABLE 1
Total Glycoalkaloid Content of Parts of the Potato and Parts of the Tuber (mg/kg Fresh Weight)

Plant part	Lampitt et al., 1943	Wood and Young, 1974	Kozukue et al., 1987	Friedman and Dao, 1992	Coxon, 1981
Roots	180–400	—	—	860[a]	
Stems	23–33	30	30–71	320–450[a]	
Leaves	550–610	400–1,000	230–1,000	1450[a]	
Flowers	2,150–4,160	3,000–5,000	3,000–5,000		
Berries	420	—	—	380	255–1,355
Sprouts	1,950	2,000–4,000	—	2,750–10,000[a]	
Skin	300–640	300–600	—	—	
Peel	150–155	150–300	13–400		
				850[b]	
Flesh	12–100	12–50	—	16–60, 110[b]	
Peel + eye	300	300–500	—	—	

[a] NDA1725-1, a cultivar known to be high in glycoalkaloids.
[b] Lenape, a cultivar known to be high in glycoalkaloids.

Bushway, 1983; Bushway et al., 1980b; Roddick, 1979). Sprouts contain the highest amounts of glycoalkaloids. Glycoalkaloids in roots and tubers are not transported upwardly and, in general, there is little or no transport of glycoalkaloids between different parts of the plant. Each of the parts appears to be responsible for synthesizing and degrading its own glycoalkaloids.

Van Gelder et al. (1987) compared the biosynthesis and metabolism of C_{27} steroidal alkaloids in leaves of potato plants grown in a greenhouse with those grown in a growth cabinet. There was a significant difference in the biosynthesis of the glycoalkaloids in greenhouse and cabinet-grown plants. The authors concluded that the concentration and composition of glycoalkaloids in potato leaves are influenced by genotype, developmental stage, and environment. The results suggested that in studies on the relationship between foliar and tuber glycoalkaloids and resistance characteristics, it might be necessary to establish biosynthesis patterns.

Table 1 also lists the glycoalkaloid levels found in various parts of the potato tuber. Glycoalkaloids are formed in and below compacted phellem cells, the parenchyma cells of the periderm and outer cortex of the tuber. There are generally no glycoalkaloids found in the central pith, and the inner cortex has very low levels (Lampitt et al., 1943; Reeve et al., 1969; Wünsch, 1989). Levels are higher at the bud end than at the stem end of the tuber. This seems to be due to the eyes that form at the bud end. Wünsch (1989) reported that if the eyes and closely surrounding tissue were removed, there was no difference in the glycoalkaloid content of the cortex at either end. The majority of the glycoalkaloids in commercial potatoes (80 to 95%) are found in the peel — the first 1.5 to 2.0 mm layer, composed of the skin and the outermost cortex (Kozukue et al., 1987; Uppal, 1987; Verbist and Monnet, 1979; Wolf and Duggar, 1946). Bushway et al. (1983) compared the glycoalkaloid content of peels in 12 potato varieties and found high variability among cultivars. Russet Burbank peels were lowest, ranging from 18 to 85 mg/kg FW, while Kennebec peels ranged from 828 to 1068 mg/kg. Wünsch also (1989) found one variety of tuber (Gusto) that had relatively high levels of glyco-

alkaloids in the inner cortex – about half that found in the peels. In tubers of cultivars with high initial levels of glycoalkaloids or in tubers that have accumulated high levels (in excess of 200 to 300 mg/kg FW) due to some kind of stress, the glycoalkaloids translocated and permeated the rest of the tuber, even the pith (Verbist and Monnet, 1979; Wang et al., 1972; Wood and Young, 1974; Zitnak, 1961; Zitnak and Johnston, 1970). In this case, peeling the potato eliminated only 30 to 35% of the total glycoalkaloids. After bruising tubers, Petersen (1993) removed both the peel and the wounded area and found that 60 to 70% of the glycoalkaloids still remained. Hellenäs et al. (1995a,b) in studying Magnum Bonum potatoes found that for tubers with the highest levels (over 500 mg/kg), peeling removed only about 20% of the glycoalkaloids.

The fact that most of the glycoalkaloids are present in the peel is probably responsible for the observation that early harvest and small potatoes are higher in glycoalkaloids than later, larger tubers (Bömer and Mattis, 1924; Sinden and Webb, 1972; Verbist and Monnet, 1979; Wolf and Duggar, 1946). Older, larger tubers, which have lower overall glycoalkaloid levels per unit weight, generally have a much lower skin-to-flesh ratio than the small tubers. It is possible that glycoalkaloid production may slow down as tubers mature, as occurs in the leaves. This is still an open question because many other factors influence glycoalkaloid production.

In a related study, Percival and Dixon (1996) compared glycoalkaloid levels in normal and aerial tubers of 14 potato cultivars. Aerial tubers form at the leaf axils in response to restriction of carbohydrate transfer from the leaves to the tubers. This restriction is associated with some form of injury. The tubers formed are usually quite small (1 to 3 cm) and highly colored (green to purple). The aerial tubers of stressed plants had greatly elevated glycoalkaloid levels compared with subterranean tubers, ranging from 301 to 1343 mg/kg FW, and the α-chaconine:α-solanine ratios were quite different. The increased glycoalkaloid levels may be due to a combination of factors: small size, reaction to the initial stress causing aerial tuber formation, and reaction to growing in light.

The reduction in glycoalkaloid biosynthesis seems to be genetically controlled and is not true in all varieties. Cronk et al. (1974) found that Katahdin tubers showed increased glycoalkaloid content at maturity. Similarly, Petersen (1993) found three cultivars of Danish potatoes that did not have lower glycoalkaloid concentrations at maturity. Certain rates of fertilization actually increased glycoalkaloid concentrations. In most cases when comparing glycoalkaloid content of various tubers, it is important to take this uncertainty into account. It is recommended that tubers of the same size and stage of maturity be used whenever possible in comparing glycoalkaloid levels.

Johnsson and Hellenäs (1983) and Jonasson and Olsson (1994) have suggested that plant breeders use the fact that different varieties may have greater or lesser concentrations of glycoalkaloids in the peel to breed a variety that has almost all its glycoalkaloids in the peel. This would impart maximum pathogen resistance during growth, and the consumer would ingest little or no glycoalkaloids simply by peeling the potatoes before cooking.

Because α-chaconine is generally more toxic than α-solanine, another area of interest is the ratio of α-chaconine to α-solanine. While normally around 40:60, it can range anywhere from 25:75 to 60:40 (Ahmed and Müller, 1978; Cadle et al., 1978; Fitzpatrick et al., 1977; Friedman and Dao, 1992; Guseva et al., 1960; Morris and Petermann, 1985; Osman et al., 1976). The stage of maturity of the tuber does not seem to effect the ratio. Chungcharoen (1988) found a consistent 60:40 ratio for Norland and Russet Burbank

tubers of all sizes. Large temperature fluctuations during light exposure increased the synthesis of α-solanine more than α-chaconine (Percival et al., 1993, 1994). Because not all ratios of α-chaconine to α-solanine show the aforementioned synergism in inducing biological effects, it might be worthwhile to develop potato cultivars with ratios that exhibit low synergy in humans and high synergy against phytopathogens.

C. Factors Influencing Glycoalkaloid Production

1. Inheritance

The history of the domestication of the potato from wild *Solanum* species has been reviewed by Hawkes (1990) and Woolfe (1987). Petersen et al. (1993) attempted to determine the history of the potato through chemotaxonomy. Ross (1966), studying German potato hybrids, concluded that suppression of glycoalkaloids was inherited, but later studies seem to have suggested otherwise. Sanford and Sinden (1972) and Sanford et al. (1995) demonstrated that the glycoalkaloid content of a specific cultivar was indeed genetically controlled and that production of high glycoalkaloid levels was heritable, as was the synthesis of other alkaloids.

Quantitative analysis of the alkaloids by GC-MS revealed that in addition to the standard *S. tuberosum* glycoalkaloids, solanine, and chaconine, foliar extracts of the Arabesque and Pimpernel varieties contained two solasodine-type alkaloids and two novel solanidane-type alkaloids that appeared to be inherited from their wild ancestors (van Gelder et al., 1987). Van Gelder et al. (1989) also found 11 glycosidically linked compounds in four different *Solanum* species. Van Gelder and Scheffer (1991) point out that desirable traits derived from potato breeding programs (such as resistance against pathogens, insects, and physiological stress) and processing traits (such as high solids or low sugar content) may be accompanied by the undesirable trait of transmitting high levels of known and unknown glycoalkaloids. These authors cited studies with *Solanum vernei* widely used in potato breeding for the introgression of new genes into the cultivated potato. They noted reduced contents of solanidine and solasodine glycosides in hybrids compared with *S. vernei*. This useful finding suggested that repeated backcrossing could create genotypes that were safe for consumption. The authors cautioned, however, that despite this apparent desirable trend, it was possible that *S. vernei* offspring could accumulate alien glycoalkaloids inherited from the wild species under cultivation conditions differing from those used in their research.

The classic case demonstrating why caution must be exercised is that of the Lenape cultivar. This was a result of crossing *S. tuberosum* with *S. chacoense*. Because *S. chacoense* had been shown to have increased insect resistance due to the presence of leptines (Stürckow and Löw, 1961), it was expected that this would be passed on to a commercial potato line. The Lenape potato did indeed have good insect resistance and a high solids content, both desirable characteristics (Akeley et al., 1968). However, there were reports of illness after ingestion of Lenape tubers. Zitnak and Johnston (1970) determined that Lenape had very high levels of glycoalkaloids, and the variety was never released for widespread commercial use. There was a similar problem in Sweden with the Magnum Bonum variety that was in commercial production and had to be withdrawn from the market (Hellenäs et al., 1995b). This cultivar had been available for many years and did not have any wild ancestors. It did, however, seem to be particularly sensi-

tive to environmental factors such as cold and wet weather.

Louwes et al. (1992) and Mattheij et al. (1992) somatically fused the cultivated potato *S. tuberosum* and the wild species *S. circaeifolium* in order to incorporate desirable traits into the potato gene pool. Some of the tetraploid hybrids were resistant to the fungus *Phytophthora infestans* and to *Globodera* spp. potato cyst nematodes. The amount and type of glycoalkaloids varied among tubers of the parents and the hybrids. The hybrids contained glycosides of solanidine, tomatidine, tomatidenol, and demissidine. The great range of variation of both the type and amount of glycoalkaloids present in the hybrids implied that selection for low glycoalkaloid content should be possible and that the gene pool of *S. circaeifolium* could be made accessible for potato breeding and research through sexual and somatic hybridization.

Osman et al. (1978) evaluated five wild tuber-bearing species for glycoalkaloid content. They found that *S. ajanhuiri, S. curtilobum, S. juzepczukii,* and *S. stenotonum* were suitable for crossing with commercial potato varieties but that *S. acaule* was not, due to its high demissine and tomatine content. Gregory et al. (1981) similarly examined 16 wild species for type and level of glycoalkaloids. Most wild species had relatively high levels of solanine, chaconine, solamarines, tomatine, demissine, and leptines. Deahl et al. (1993) obtained comparable results in their screening of 70 different *Solanum* species and six hybrids for foliar glycoalkaloids. They found that leaves of *S. tuberosum* crosses seemed more susceptible than tubers to transmission of high glycoalkaloid levels. Grassert and Lellbach (1987) found that the crosses between *S. tuberosum* and six wild species had high glycoalkaloid levels (120 to 1680 mg/kg FW), especially the crosses with *S. vernei, S. aracc-papa,* and *S. sparsipilum.* Backcrossing did reduce glycoalkaloid levels, but even after a fourth backcross, levels still remained unsafe for general consumption.

Several studies have used glycoalkaloid profiles to study the development of the potato. Johns (1986) and Johns and Galindo Alonso (1990) cite evidence in support of the hypothesis that selection for reduced glycoalkaloid levels occurred during the domestication of the potato. Specifically, they found that although the mean glycoalkaloid content of tubers of likely ancestral species ranged from 240 to 960 mg/kg FW, the most probable progenitor, *S. sparsipilum,* had the highest content (mean 960 mg/kg FW, range, 240 to 1960 mg/kg). Three of the five wild species known to have been eaten historically had potentially toxic levels of glycoalkaloids. Although detoxification appeared to have been important in the evolution of the edible potato, part of the reduction in glycoalkaloid content could have resulted from selection for increased tuber size. The authors speculated that co-selection for reduced toxicity and increase in tuber size, which resulted in a decrease in glycoalkaloid content relative to water and carbohydrates, reasonably explains the domestication events. A study of nine taxa of the *Solanum* series *Megistacrolobum* from western Bolivia found that three taxa exhibited anomalous glycoalkaloid patterns indicative of human influence (Johns and Osman, 1986). Johns et al. (1987) demonstrated a close interrelationship among *S. megistacrolobum, S. stentotum,* and *S. acaule* and their hybrids.

Morris and Petermann (1985) measured levels of individual glycoalkaloids in 40 cultivars and 50 breeding lines grown in Australia. This comprehensive study revealed that (1) cultivars with high glycoalkaloid content had a higher percentage of α-solanine at the expense of α-chaconine; (2) cultivars or breeding lines that contained β_2-chaconine had a higher glycoalkaloid content

(114 mg/kg FW) than did those without significant β_2-chaconine (69 mg/kg FW); (3) two of the cultivars (Lenape and Berita) had glycoalkaloid levels greater than the upper safety limits of 200 mg/kg FW; and (4) the content in several others ranged between 100 and 200 mg/kg FW. The authors suggested that caution should be exercised in growing these two cultivars, because cool weather, rough handling, and magnesium and nitrogen in the soil can increase the already high levels of glycoalkaloids.

Similar studies have been conducted on potato varieties grown in Australia (Bradley et al., 1978), Egypt (Ahmed et al., 1988), Germany (Lepper, 1949; Ross et al., 1978; Wünsch, 1989), India (Seth and Chatterjee, 1968; Uppal, 1987), Korea (Hwang and Lee, 1984), Netherlands (van Gelder, 1985a; van Gelder and Dellaert, 1988; van Gelder et al., 1988b), New Zealand (Lammerink, 1985; Patchett et al., 1977), Pakistan (Rahim et al., 1989), Poland (Mazurczyk, 1995), and the U. K. (Bhuva and Parnell, 1983; Bintcliffe et al., 1982; Parnell et al., 1984). These studies evaluated the effects of differences in growing area and time of harvest on glycoalkaloid content. The general conclusion was that although weather, area, and time of harvest may have an effect, sometimes even a dramatic impact, glycoalkaloid production is primarily genetically controlled. Under stress, low-glycoalkaloid potatoes will remain relatively low and high-glycoalkaloid potatoes may increase to potentially dangerous levels. Concentrations in commercially grown cultivars range from 10 to 350 mg/kg FW, while concentrations in wild potatoes range from 36 to 4320 mg/kg FW or up to 100 times more than in cultivated varieties (Sinden et al., 1984). Because these high levels of glycoalkaloids can be passed genetically to any progeny, care must be taken when using wild species in plant breeding programs. In addition to α-chaconine and α-solanine, wild species contain a number of other glycoalkaloids such as commersonine, demissine, solasonine, and solamargine whose safety is largely unknown.

2. Preharvest Changes

Although the nature and relative concentrations of glycoalkaloids are genetically determined, the total concentrations are certainly influenced by environmental factors during the growing period. Seasonal and climatic variations seem to markedly influence glycoalkaloid biogenesis. Glycoalkaloid biosynthesis may be influenced to a lesser extent by agricultural practices and soil composition, although this is not clear cut.

Weather seems to have a considerable effect on glycoalkaloid production, especially a combination of cold temperature, excessive rain, and lack of adequate sunshine. Bömer and Mattis (1924) reported that after such a poor growing season, potatoes were found to be high in solanine. There were increased incidents of gastrointestinal problems after ingestion of these potatoes. Hutchinson and Hilton (1955) and Sinden and Webb (1972), among others, have noted similar effects due to bad weather. Olsson and Carlsson (1993) found that heavy precipitation alone did not cause excessive glycoalkaloid synthesis. Similarly, Hellenäs et al. (1995b) stated that cold weather or excess water by themselves did not seem to raise glycoalkaloid levels significantly, but the combination may result in large increases in glycoalkaloids. Cold weather and rain is a common weather pattern in many of the northern climates where potatoes are grown, especially for early crops. Other researchers have suggested that immaturity of potatoes can cause high glycoalkaloid levels, stating that it was a function of size. However, the levels generally seem too high for this to be the sole cause. Rather, the increased

glycoalkaloid production seems to be the plants' reaction to stress.

In fact, the reaction to any kind of stress appears to be an increase in glycoalkaloids. There are reports of elevated glycoalkaloid formation caused by prolonged cold, extreme heat, too much water, too little water, too much sunshine, and too little sunshine (Shikina and Korzunova, 1955; Yaniv et al., 1984). Wolf and Duggar (1946) showed that increased exposure to light by growing potato plants led to higher levels of glycoalkaloids. Gosselin et al. (1988) examined the effects of two different irrigation methods and found that microjet misting increased glycoalkaloid levels in tuber-cortex tissue, whereas impact sprinkling had no effect. Love et al. (1994) evaluated the effects of fertilization, storage time and temperature, and cultivar on glycoalkaloid levels in tubers for 2 different years. While all these parameters seemed to have an effect on glycoalkaloid synthesis, the biggest difference was caused by cultivation in different years. Hellenäs et al. (1995a,b), O'Keefe (1978), Ross et al. (1978), and Sinden and Webb (1972) have reported similar annual variations.

Other factors, such as fertilization or soil type, seem to have varying effects on glycoalkaloid production. Maga (1980, 1994), Jadhav et al. (1981, 1991a,b), Sinden et al. (1984), and van Gelder (1989) conclude that these factors have little if any effect. Van Gelder and Dellaert (1988) found only slight differences between potatoes grown in sandy soil or clay. The reported consequences of added nitrogen were not obvious. Bömer and Mattis (1924) found no difference in glycoalkaloid content with increased nitrogen. Cronk et al. (1974), Mondy and Munshi (1990b), and Love et al. (1994) reported significantly higher glycoalkaloid levels with increased nitrogen fertilization, whereas Ahmed and Müller (1979) and Van Swaaij (1992) found decreased production of glycoalkaloids. Petersen (1993) had mixed results depending on the variety of potatoes grown. The results with added or reduced amounts of potassium are equally contradictory (Ahmed and Müller, 1979; Petersen, 1993; Van Swaaij, 1992).

The effects of added magnesium (Evans and Mondy, 1984), selenium (Mondy and Munshi, 1990a), and molybdenum (Mondy and Munshi, 1993) have also been investigated. Mg and Se fertilization increased glycoalkaloid formation, whereas foliar application of Mo decreased synthesis. Speroni et al. (1981) reported that glycoalkaloid content of ozone-treated plants was significantly lower than that observed in nonexposed plants when expressed on a fresh-weight. However, this was not the case when levels were expressed on a dry-weight basis, presumably because ozone treatment reduces moisture content but does not affect glycoalkaloid synthesis. Ponnampalam and Mondy (1986) found that foliar application of the plant growth hormone, indoleacetic acid, caused a significant decrease of glycoalkaloids in Katahdin and Kennebec tubers.

Wilson and Frank (1975) studied the effects of six systemic pesticides (three insecticides and three fungicides) on glycoalkaloid production. Only one, the insecticide carbofuran, showed significant differences. When applied at planting in the field, it decreased glycoalkaloid production in tubers of the three cultivars tested; when applied at the time of tuberization, glycoalkaloids increased, almost doubling in one cultivar. The significance of these findings is not clear, as the second test conducted used three different cultivars grown in a greenhouse.

The role of pesticides in general is difficult to evaluate because if the control plants are subjected to stress due to pathogen attack, there may be considerable dif-

ferences in glycoalkaloid levels. If the controls are relatively healthy plants, there may be little observable effect. (See also discussion in pest resistance section.)

Finally, there is the practice of vine or haulm killing. This involves the killing of the growing vine (the haulm) after the tuber has reached maturity, usually 7 to 14 d before harvest. This practice facilitates harvesting by loosening the stolons attached to the tuber. It prevents diseases from being transferred from the vine to the tuber and increases the tuber's resistance to mechanical injury by toughening the skin. Methods of vine killing include the use of herbicides and desiccants, pulverizing, pulling, flaming, and various combinations of these techniques. Little work has been done on the effects vine killing has on glycoalkaloid levels. Larsson (1992) compared glycoalkaloid levels in Bintje and King Edward tubers after several methods of haulm killing with varying results.

3. Postharvest Changes

Glycoalkaloids are usually present at low levels in commercial potatoes. However, because biosynthesis of glycoalkaloids in potatoes continues long after harvest, they can accumulate to higher levels. Factors that influence glycoalkaloid formation include light, storage conditions, and mechanical injury. Possible relationships of glycoalkaloid synthesis to other postharvest events, such as blackening, blighting, and browning, are not well defined. Agents or treatments that inhibit sprouting, such as γ-radiation or various chemical treatments, suppress glycoalkaloid production in potatoes. Obviously, potatoes with higher initial levels of glycoalkaloids are more likely to develop excessive amounts after harvest. What is unclear at present is whether the rate at which these potatoes produce glycoalkaloids is significantly different from the low-glycoalkaloid varieties.

a. Light

Exposure of postharvest potato tubers to light, whether incandescent, fluorescent, or natural, can dramatically increase glycoalkaloid synthesis (Jain et al., 1995). Zitnak (1981) exposed Sebago tubers to incandescent light of 15 W for 10 d, resulting in an increase in glycoalkaloid content from 48 to 190 mg/kg FW. Salunkhe et al. (1972) subjected Russet Burbank potato slices to fluorescent light of varying intensities at four temperatures for 48 h. For the highest intensity (200 ft-c) at 24°C, glycoalkaloids increased from 2 to 74 mg/kg FW. Percival et al. (1993, 1994) report similar findings. Kozukue and Mizuno (1990) found glycoalkaloids increased in May Queen tubers after light exposure at 10 and 15°C. Rises in α-solanine were especially high. Dao and Friedman (1994) reported increased glycoalkaloid (300%), chlorophyll, and chlorogenic acid concentrations after exposing White Rose potatoes to fluorescent light for 20 d. Baerug (1962) had negative results with exposure of Kerr's Pink tubers to incandescent light for 60 h. However, the light intensity they used was so low that it was less than exposing the tubers to 30 min of sunlight.

The usual indication that a potato may have increased glycoalkaloid levels due to light exposure is greening caused by chlorophyll production. However, there is a question whether increases in glycoalkaloid biosynthesis always parallel light-induced greening. In a series of related papers (Nair et al., 1981; Ramaswamy and Nair, 1984; Ramaswamy et al., 1976) it was reported that chlorophyll synthesis always preceded the synthesis of glycoalkaloids in cold-stored potatoes and that the formation of both appeared to be related. The authors postulated

that chloroplasts were responsible for the incorporation of labeled CO_2 fixation into the solanidine structure. Liljemark and Widoff (1960) and Dale et al. (1993) also reported that there was a connection between the two biochemical events, whereas Herbreteau-Lemonnier et al.(1989) stated that there was a positive correlation between solasonine and chlorophyll contents in callus cultures of *S. laciniatum.*

On the other hand, Gull and Isenberg (1960) found no relationship between chlorophyll and glycoalkaloid synthesis when evaluating different potato varieties. Katahdin tubers, which greened the least, showed the greatest alkaloid gain. The glycoalkaloid levels of Cherokee tubers, which greened most rapidly, rose slowly. Patil et al. (1971a) subjected 11 varieties to various intensities of fluorescent light for 5 d. Light intensity had a significant effect on chlorophyll production but did not cause similar changes in glycoalkaloid levels. De Maine et al. (1988) determined chlorophyll and glycoalkaloid concentrations in ten varieties after 42 h in light and dark. Glycoalkaloids increased markedly in illuminated samples for six varieties, increased less so in two varieties, and decreased slightly for two others. The researchers could find no correlation with the amount of greening that had occurred. Although Spoladore et al. (1983) found a correlation ($r = 0.62$, $n = 36$) between glycoalkaloid content and intensity of greening, they concluded that neither could be used with confidence in the indirect selection of the other. Dao and Friedman (1994) examined the effect of light on cut White Rose potatoes and found that tubers placed in contact with water did not green, whereas those in contact with air did. Glycoalkaloids increased equally in both samples. Jadhav and Salunkhe (1975) concluded that chlorophyll and glycoalkaloid synthesis were two separate events. Indeed, if chlorophyll and glycoalkaloid biosynthesis are linked, why does mechanical injury produce large increases of glycoalkaloids even in the dark with no evidence of higher chlorophyll production?

Part of the problem is due to genetic variability. Studies on different varieties (Dale et al., 1993; De Maine et al., 1988; Griffiths et al., 1994; Gull and Isenberg, 1960; Kaaber, 1993; Patil et al., 1971a,b) show that there are considerable differences in susceptibility to stress-induced production of chlorophyll and glycoalkaloid synthesis. Haard (1977) reported that cultivars of Newfoundland potatoes with red or blue anthocyanins were less susceptible to light-induced glycoalkaloid increases than cultivars without these pigments. Another factor to be considered is the light source. Many of the studies did not specify a light source. Of those that did, most used a full-spectrum source. Conner (1937) found that blue light increased glycoalkaloid formation and that red light increased chlorophyll production but had little effect on glycoalkaloid levels. Rosenfeld et al. (1995) found that tubers packaged in blue polyethylene bags were most susceptible to light-induced glycoalkaloid production. Jeppsen et al. (1974) found that red, green, or violet filtered light reduced glycoalkaloid production. Zitnak (1953) observed increased glycoalkaloid production in Netted Gem (Russet Burbank) potatoes after exposing them to infrared light. This was accompanied by significant greening. Ultraviolet light caused some increase in glycoalkaloid levels but no observed greening. Petermann and Morris (1985) concluded that each event was dependent on different wavelengths of light. This could explain much of the apparently contradictory data.

In an effort to reduce light-induced glycoalkaloid formation once the potatoes have reached the market, studies have also been conducted on various types and colors of packaging material (Gosselin and Mondy,

1989; Lutz et al., 1951; Rosenfeld et al., 1995).

b. Temperature

Several studies on the effects of light also evaluated the effects of different temperatures (Kozukue and Mizuno, 1990; Percival et al., 1993; Salunkhe et al., 1972; Zitnak, 1953). Increased temperature produced increased glycoalkaloid content, whether in whole tubers or slices. For example, Salunkhe et al. (1972) found that there was a slight increase at 0 and 8°C and a much larger increase at 15 and 24°C after 48 h in the dark. Hwang and Lee (1984) found that tubers stored at 1°C were lower in glycoalkaloids than those stored at 20°C. Linnemann et al. (1985) had similar results when comparing tubers stored for 12 weeks at 7, 16, and 28°C. Tubers stored at the lower temperature had the lowest amounts. Kaaber (1993) found higher storage temperatures caused an increase of glycoalkaloids in some varieties of tubers. Greening also occurred less at 6°C than at 18 and 24°C.

In contrast, other researchers have found that lower temperatures produced more glycoalkaloids than higher temperatures (Jadhav and Salunkhe, 1975; Liljemark and Widoff, 1960). For example, Bushway et al. (1981) found that tubers stored at 3.3°C had higher levels than those stored at 7.7°C. Is there a correlation between the formation of reducing sugars and glycoalkaloids, as both are produced in response to some type of stress?

The conflicting data can be partly reconciled if we consider that the potato tuber produces glycoalkaloids, not in response to a certain temperature, but rather in response to stress in general. Thus, stressful conditions for the tuber producing increased glycoalkaloid synthesis may include not only high (above 15°C) but also low temperatures (below 5°C). Although the higher temperatures may produce the more noticeable result due to increased metabolic function, the lower temperatures may still have a significant effect. Chungcharoen (1988) mentioned similar effects of heat and cold stress in potato plants. She found the optimal temperature for growing plants at around 16°C. For tubers after harvest, the optimal temperature for minimizing glycoalkaloid synthesis seems to be around 7 to 10°C.

Temperature influences other events that affect potatoes (Burton, 1989; Currier and Kuč, 1975; Stoddard, 1992). These factors, which often override concern for glycoalkaloid accumulation, include sweetening, respiratory rate, disease control, and sprouting. Low-temperature sweetening is caused by the accumulation of reducing sugars in potatoes stored at low temperatures. Sugars and starch exist together in the tuber and undergo continual enzyme-catalyzed transformations in the cells. Above 10°C, the sugars and starch remain in balance, with the sugars either reforming into starch or being used up in other reactions. Below 10°C, however, reducing sugars start to accumulate — the lower the temperature and the longer the storage time, the greater the amount of reducing sugars. This is undesirable because these reducing sugars can then participate in nonenzymatic Maillard browning reactions or at high cooking temperatures undergo caramelization, producing unsightly or off-flavored products. This process is, up to a point, reversible: holding the potatoes at a higher temperature (>15°C) for a time before processing will reduce the accumulated sugars. If the sugar levels become too high, however, the process is not completely reversible and higher-temperature curing is inadequate.

Lower temperatures (4 to 5°C) minimize losses due to respiration, susceptibility to disease, and sprouting. However, sugar ac-

cumulation is reduced and wound healing is promoted by higher temperatures (15 to 20°C). Thus, selecting an appropriate storage temperature becomes something of a balancing act. For long-term storage of table tubers, the lower temperatures are preferable. For short-term storage, especially for tubers to be used for chip or French fry production, the higher temperatures are recommended. Intermediate temperatures (7 to 10°C) may represent the best compromise for bulk storage of tubers. Research is still needed to evaluate the interaction of all the factors affecting potato storage.

c. Storage Time

Detailed discussions on potato storage can be found in Ahn et al. (1983), Brewer et al. (1990), Lisinska and Leszczynski (1989), Olsson and Roslund (1994), and Stoddard (1992). Love et al. (1994) in evaluating fertilization, storage temperature, and storage time on three varieties of potato, reported that storage time had the most effect on glycoalkaloid levels. Storage time is closely related to the effects of light and temperature, so that these factors must be considered in any comparative studies. Many of the cited references in the studies on light, temperature, and mechanical injury (see below) also include time studies. In general, the longer the storage time, the higher the glycoalkaloid levels, although there are indications that the levels reach a maximum and then begin to decline (Fitzpatrick et al., 1977), especially if sprouting occurs (Kozukue et al., 1989). Olsson and Roslund (1994) in a 9-month storage study of several clones kept at 4°C found that glycoalkaloid levels fluctuated over time, sometimes rising and sometimes dropping — in a few instances even falling below original levels. Wünsch and Munzert (1994) studied the effects of 6-month storage at 4°C on glycoalkaloid distribution in five different cultivars. Although there was some variation in the cultivars, the general trend was for a slight reduction in glycoalkaloids over time. The authors concluded that unless tubers are improperly handled, glycoalkaloid levels do not change until sprouting occurs.

d. Sprouting

After a period of dormancy, the potato tuber begins to sprout. Disregarding light or wounding effects, glycoalkaloid production at this point is focused at the eyes. When the sprout starts to grow, glycoalkaloid synthesis is concentrated at the growing portion of the sprout. The sprouts contain the highest glycoalkaloid levels in the potato plant. Glycoalkaloids in the tuber begin to decrease, presumably through enzymatic hydrolysis. Anything that will inhibit sprouting will reduce glycoalkaloids in stored potatoes. In addition to low temperatures, many physical and chemical treatments have been suggested to prevent or delay sprouting. γ-Radiation has been suggested as a sprouting inhibitor with mixed results (Bergers, 1981; Mondy and Seetharaman, 1990; Patil et al., 1971b; Schwimmer, 1981; Swallow, 1991; Wu and Salunkhe, 1977b). Such radiation may induce a reversible increase in glycoalkaloid content (Mondy and Seetharaman, 1990). Treatments with paraffin wax (Wu and Salunkhe, 1972a), corn oil (Wu and Salunkhe, 1972b, c), and mineral oil (Jadhav and Salunkhe, 1974) have had some success. Ahmed and Müller (1981) conducted extensive tests on the effects of storage time, light, and temperature on tubers with and without treatment of sprouting inhibitors. Specific chemical treatments include isopropyl-*N*-(3-chlorophenyl)carbamate (Mondy and Ponnampalam, 1985; Wu and Salunkhe, 1977a), the insecticides Alar, Ethrel, and Telone (Jadhav et al., 1973; Patil et al.,

1971a), lecithin (Wu and Salunkhe, 1977c, 1978b), maleic hydrazide (Mondy et al., 1978), and detergents (Sinden, 1971). All have been shown to reduce glycoalkaloid accumulation in tubers, but, due to added expense or consumer unease, none of these are in use today. A need exists to find new inhibitors derived from natural sources. Oxygenated monoterpenes derived from essential oils such as 1,4-cineole and limonene oxide appear to meet this need because they inhibit sprouting and fungal growth under practical conditions of storage (Vaughn and Spencer, 1991). Jasmonic acid also has been reported to block sprouting in potato tubers (Lulai, 1995). To facilitate commercial use of these compounds, further studies are needed on the composition, including glycoalkaloid levels, and nutritional values of tubers treated with monoterpenes and jasmonic acid.

e. Mechanical Damage

Early studies on potatoes (McKee, 1955; Sinden, 1972; and Salunkhe et al., 1972) indicated that damaged potatoes had a tendency to produce high levels of glycoalkaloids, especially at the point of injury. Injury-induced glycoalkaloid formation is often accompanied by blackspot formation, generally thought to be caused by the formation of chlorogenic acid and other polyphenolics (Boumann, 1995; Dao and Friedman, 1992; Leppack, 1995; Pavek et al., 1985, 1993; Stark et al., 1985). Wu and Salunkhe (1976) examined the effects of different types of damage on three different varieties of tubers. They found that cutting produced the highest glycoalkaloid levels. In general, injuries that affected the skin such as brushing and hammering caused higher levels of glycoalkaloid than puncturing or dropping. Storage time and temperature also had considerable effect. As expected, the higher the temperature or longer the storage time, the more glycoalkaloid concentrations increased. Fitzpatrick et al. (1977) showed that the glycoalkaloid content of potato slices increased from 55 to 994 mg/kg FW after 4 d of storage. Ahmed and Müller (1978) and Maga (1981) had very similar results with sliced potatoes.

Storing whole tubers and cutting them just before cooking is much preferred over cutting and then storing the slices in the open to await cooking. The time frame may be important, however. Bergenstråhle et al. (1992b) reported that the activity of the enzyme responsible for glycoalkaloid synthesis (UDP-glucose:solanidine glucosyltransferase) increased slowly over the first 11 h and reaches a maximum after 16 h. Therefore, short-term storage of peeled or sliced potatoes may not significantly enhance glycoalkaloid synthesis. Wu and Salunkhe (1976) also reported that most of the injury-stimulated glycoalkaloids were formed within 15 d of storage.

Fitzpatrick et al. (1978b), Olsson (1986), and Wu and Salunkhe (1978c) reported that susceptibility to mechanical damage varied with cultivar. Olsson (1986, 1989) further showed that although genotypes differed in their response to impact damage, the increased level of glycoalkaloids after damage correlated with original glycoalkaloid content, that is, a high initial level resulted in a greater increase than in a genotype with a low initial level, and that cultivars most susceptible to severe types of mechanical injury showed the greatest increase in glycoalkaloid content.

Finally, Mondy and Gosselin (1988) and Ramamurthy et al. (1992) showed that total phenolics increased dramatically after wounding. Mondy et al. (1987) found similar increases of glycoalkaloids and phenolics after bruising tubers. Friedman (1996b) reviewed the role of polyphenols in plant-host resistance of potatoes. Osman et al.

(1979) reported on the effects of damage on potatoes in terms of glycoalkaloid and phytoalexin production. They emphasized that concern with just the glycoalkaloids may not be justified. Depending on their history at the time of consumption, potatoes have a complex and variable mixture of compounds with unknown effects on quality and safety.

f. Humidity

Becuse part of the stress in tubers is attributed to dehydration, humidity may have an effect on glycoalkaloid levels in stored and sliced potatoes. Wu and Salunkhe (1977d, 1978a) found that immersion of potatoes in water reduced glycoalkaloid formation during soaking and also had a continuing effect after removal from the water, even in wounded potatoes. They attributed this lowered production of glycoalkaloids to a period of anoxia. Mondy and Chandra (1979) also found that water soaking reduced glycoalkaloid synthesis. More studies are needed to evaluate this aspect of storage. It is a common practice in many homes that after peeling and slicing, potatoes are placed in a pot of water to reduce browning if they are not to be cooked immediately. This practice could also lessen the glycoalkaloid production considerably. Most studies on wounded or sliced potatoes have left them exposed to air. Would high humidity, water soaking, or water spraying keep glycoalkaloid levels low?

Tubers react to stressful conditions by producing increased amounts of glycoalkaloids as well as other compounds such as phytoalexins and phenolics. These conditions include light, cold, heat, and mechanical injury. Why light induces glycoalkaloid production is not completely clear but may be due to the simple fact that potato tubers grow underground in the dark, thus light is stressful. Heat and prolonged storage probably induce a combination of dehydration and metabolic activity prior to sprouting, resulting in a dramatic increase in glycoalkaloid content. Potato slices stored at higher temperatures in the light contain 50 times more glycoalkaloids after 2 d than originally present. The response to stress seems to be genetically linked, because some varieties are especially sensitive to stress. If these have relatively high initial glycoalkaloid levels, the result may be tubers with glycoalkaloid contents far above the safe level.

Some varieties seem to be stress-resistant. For example, Bintje did not increase in glycoalkaloids as other varieties did after 12 weeks of storage at 28°C (Linnemann et al., 1985) or after 12 d of light (800 lx) (Kaaber, 1993). Other varieties can be bred for this decreased reaction to stress. How this would affect their resistance to pests is uncertain.

4. Processing

a. Glycoalkaloids and Taste

Experiments with human taste panels revealed that potato varieties with glycoalkaloid levels exceeding 140 mg/kg fresh weight tasted bitter (Gull and Isenberg, 1958; Ross et al., 1978; Sinden et al., 1976; Zitnak and Filadelfi, 1985). Those in excess of 220 mg/kg also induced mild to severe burning sensations in the mouth and throat. In a related study, Kaaber (1993) demonstrated that the Norwegian potato variety, Kerr's Pink, was quite susceptible to greening-related glycoalkaloid synthesis and accompanying increases in bitterness and burning sensations, whereas the Bintje variety was not. The study also described the burning sensation occurring in tubers with a glycoalkaloid content above 170 mg/kg FW. The Aymara Indians of Bolivia who are thought to be responsible for the early domestication and detoxification of potatoes and who are dependent on potatoes for their basic subsis-

tence can distinguish between concentrations of glycoalkaloids in solution only above 200 mg/l (Johns and Keen, 1986). This is right at the 200 mg/kg FW level considered toxic to humans. It is apparent that glycoalkaloids, at the very least, impart an unpleasant taste to potatoes and potato products at a level less than that of the accepted safe level of 200 mg/kg FW. Zitnak and Filadelfi-Keszi (1988) described the isolation of the diglycoside β_2-chaconine, also known as a potato bitterness factor. It is noteworthy that steroidal glycoalkaloids and saponins have also been found to affect the flavor of eggplants (Aubert et al., 1989a,b). Thus, it is in the interest of the processor to have potatoes low in glycoalkaloids to improve taste as well as safety.

b. Cooking and Processing

Table 2 lists the glycoalkaloid content of various commercial potato products. The high range for potato chips reported by Sizer et al. (1980) was attributed to one sample that contained a significant amount of peel. Little data are available on the variety from which these samples were derived.

Several studies have shown that baking, boiling, and frying does little to decrease glycoalkaloid content (Bushway and Ponnampalam, 1981; Bushway et al., 1983; Friedman and Levin, 1995; Gonmori and Shindo, 1985; Sizer et al., 1980; Zobel and Schilling, 1964). Most cooked samples had a glycoalkaloid content of about 95% that of the uncooked samples. Takagi et al. (1990) reported that microwaving potatoes reduced their glycoalkaloid content by 15%. Ponnampalam and Mondy (1983) found significant loss of glycoalkaloids after baking or frying, but this may have been due, at least in part, to incomplete extraction. As the authors and other researchers (Bushway et al., 1985) have mentioned, it is often more difficult to extract processed samples that have lost water than samples of fresh material. For this reason, the extraction procedure used in analyz-

TABLE 2
Glycoalkaloid Content of Various Potato Products (mg/kg)

Product	Total glycoalkaloids	Ref.
Commercial french fries, fresh	0.8–8.4	Friedman and Dao, 1992
	19–58	Davies and Blincow, 1984
Partially cooked fries, frozen	23–55	Jones and Fenwick, 1981
Precooked fries, frozen	19–35	Jones and Fenwick, 1981
Commercial wedges, fresh	44	Friedman and Dao, 1992
Commercial skins, baked	31	Friedman and Dao, 1992
	52–63	Bushway et al., 1983
Commercial skins, fried	55–203	Friedman and Dao, 1992
	120–242	Bushway et al., 1983
Commercial potato chips	24–109	Friedman and Dao, 1992
	95–720[a]	Sizer et al., 1980
	32–184	Davies and Blincow, 1984
	59–70	Jones and Fenwick, 1981
Potato pancake powder	45	Friedman and Dao, 1992
Peel wedges, frozen	76–120	Bushway et al., 1983
Peel slices, frozen	66–71	Bushway et al., 1983
Canned	29–99	Davies and Blincow, 1984
	24–34	Jones and Fenwick, 1981

[a] High value attributed to sample with large amount of peel.

ing processed potato products is of great importance. This has also been mentioned by Zhao et al. (1994), who used an *in vitro* method to determine glycoalkaloid solubilities in raw and extruded potato peels. They found that solubility was much higher for peels extruded at 110°C than for the raw peels or those extruded at 150°C.

Takagi et al. (1990) noted that the temperature of the oil in deep frying may have an effect on glycoalkaloids. They found that frying at 150°C caused little change, but frying at 210°C resulted in a 40% loss (170°C gave mixed results). Whether there is an actual degradation of glycoalkaloid needs further study, because glycoalkaloids will be extracted into the oil and increased dehydration of the potatoes may also affect the extraction. Chungcharoen (1988) showed that glycoalkaloids were stable in cooking oil at 180°C and that the effect of diffusion of glycoalkaloids into the oil continued as subsequent batches of potatoes, especially those with peels, were cooked in the same oil. Low-level glycoalkaloid potatoes cooked in this oil could actually increase in glycoalkaloid content due to absorption from the oil.

Bushway et al. (1980a, 1985) have evaluated the glycoalkaloid content of several potato-containing meals produced from potato by-products. They found that these meals contained high levels of protein and B vitamins but also averaged about 200 to 230 mg/kg total glycoalkaloids. They recommend that these meals be used in conjunction with other foods to reduce the intake of glycoalkaloids. In a related study, Bushway et al. (1984) found that cows fed diets of 10 and 20% tater meal showed no detectable solanidine in milk. Friedman (unpublished results) has also found high glycoalkaloid levels in potato protein isolates (200 mg/kg). These presumably coprecipitate during preparation of the concentrate. If potato protein isolates are to assume a greater role in animal/human nutrition, it will be necessary to reduce their glycoalkaloid content.

VI. PEST RESISTANCE

The exact role of glycoalkaloids in the resistance of potato tubers to attack from fungi, bacteria, insects, nematodes, and slugs is still undefined. Most researchers have concluded that glycoalkaloids play a minor role in protection against fungi. McKee (1959) found that although solanine exhibited toxic effects on *Fusarium* spp. and *Phytophthora infestans* in *in vitro* tests, he concluded that it would contribute little to protection in the plant. Tarlakovskii (1981) in a study of potato leaves reported that plants with a higher ratio of glycoalkaloids to sterols had increased resistance to *P. infestans*. Several other studies have concentrated on *P. infestans* but could find no relationship between resistance and glycoalkaloid content of tubers (Deahl et al., 1973; Frank et al., 1975) or leaves (Hazel et al., 1988). Corsini and Pavek (1980) could find no correlation between glycoalkaloid content and resistance to *Fusarium*. Morrow and Caruso (1983) reported that glycoalkaloid levels were unrelated to resistance against *Rhizoctonia solani*. Costa and Gaugler (1989) found that solanine had little effect *in vitro* on *Beauveria bassina*, an entomopathogen. Sinden et al. (1973) found that the potato alkaloids inhibited *A. solani* growth on agar and that older leaves with lower glycoalkaloid levels were more susceptible to attack from *A. solani*. It was concluded that glycoalkaloids impart some measure of resistance to fungal attack.

Olsson (1987, 1989) attempted to discover whether differences in susceptibilities to mechanical damage and initial glycoalkaloid content of different cultivars influenced their resistance to *Fusarium* and *Phoma* fungi. She reported that (1) although genotypes differed in their response to im-

pact damage, the damage correlated with original glycoalkaloid content, that is, a high initial level resulted in a greater increase than in a genotype with a low initial level; (2) cultivars most susceptible to severe types of mechanical injury showed the greatest increase in glycoalkaloid content; and (3) surprisingly, the initial content of glycoalkaloids in different cultivars, which ranged from 20 to 150 mg/kg fresh weight, did not affect resistance to fungal infection. In fact, some genotypes with higher glycoalkaloid levels were less resistant than others with lower levels.

Glycoalkaloid levels also seemed to have little if any effect in resistance to bacterial attack. McKee (1959) reported that cultures of *Bacillus subtilis, Micrococcus luteus, Erwinia* spp., *Pseudomonas* spp., and spores of *Streptomyces scabies* were unaffected by solanine in *in vitro* tests. Paquin and Lachance (1964) reported that α-chaconine and α-solanine had bacteriostatic properties with *Corynebacterium sepedonicum* (the cause of ring rot) *in vitro,* but a later study (Paquin, 1966) showed no correlation between glycoalkaloid levels and bacterial resistance in plants.

Studies have shown that different pathogens may cause different reactions in the potato plant. Subrtová et al. (1993) found that two varieties of potato tubers infected with soft rot (*Erwinia carotovora* bacterium) caused increased glycoalkaloid production. Tarlakovskii (1981) stated that attack by *P. infestans* zoospores induced glycoalkaloid accumulation in leaves. However, there have been several studies showing that *P. infestans* reduces glycoalkaloid production and induces production of the terpenoid phytoalexins, mainly rishitin and lubimin but also rishitinol, phytuberin, phytuberol, and solavetivone among others, in tubers and tuber discs (Holland and Taylor, 1979; Horikawa et al., 1976; Ishizaka and Tomiyama, 1972; Kuč, 1984; Kumar et al., 1991; Shih et al., 1973). A further complication is that there are two distinct races of *P. infestans*, compatible and incompatible. The incompatible reaction, where the damage to the tuber was contained, resulted in the decreased glycoalkaloid and increased phytoalexin levels as mentioned. The compatible reaction, where damage was extensive, did not seem to affect glycoalkaloid levels noticeably and there was little accumulation of phytoalexins. Other instances of glycoalkaloid induction or suppression have been reported by Fewell and Roddick, 1993; Fewell et al., 1994; Kusano et al., 1987; Li, 1985; Tjamos et al., 1986; Zacharius et al., 1975. What are the detailed mechanisms of these events? Mucharromah and Kuč (1995) state that the presence of arachidonic acid could induce resistance in tuber discs to compatible races of *P. infestans* and free sterols caused incompatible races to behave as compatible races. Also, do infested potatoes produce secondary metabolites such as the phytoalexins that might potentiate the biological action of glycoalkaloids (Griffin, 1994) or are some different mechanisms involved? It seems probable that, although most strains of fungi and bacteria are inhibited by glycoalkaloids, some strains of successful pathogens have developed a detoxifying mechanism and have become immune. Thus, it is important to determine if different pathogens induce greater or lower amounts of glycoalkaloids in potatoes and whether their enzymes can detoxify potato glycoalkaloids as they do saponins (Bowyer et al., 1995).

While the glycoalkaloids may or may not impart resistance against fungi and bacteria, the evidence for increased protection by glycoalkaloids from damage by insects is somewhat more compelling (Tingey, 1984). Several studies (Kuhn and Löw, 1955a; Levinson, 1976) have reported that foliar glycoalkaloids imparted resistance in potatoes to the Colorado potato beetle (*Leptinotarsa decemlineata,* Say. Sinden et al. (1980,

1986a,b, 1991) found that the nature of the glycoalkaloid was more important than the amount. They also found that commersonine and the leptines found in *S. chacoense* were more effective than α-chaconine or α-solanine against the potato beetle. Tingey et al. (1978) and Raman et al. (1979) determined that resistance to potato leafhopper (*Empoasca fabae*) was highly correlated with foliar glycoalkaloid content. Sanford et al. (1990, 1992, 1996) obtained similar findings in studying seven generations of leafhopper-resistant plants and the mortality of potato leafhopper adults on diets containing seven glycoalkaloids. However, Flanders et al. (1992) and Tingey and Sinden (1982) found no correlation in resistance to peach aphids (*Myzus persicae*), potato aphids (*Aulacorthum solani*), or potato flea beetles (*Epitrix aethiopica*).

Glycoalkaloids do not seem to impart much resistance to noninsect pests. Forrest and Coxon (1980), Grassert and Lellbach (1987), and Hoogendoorn et al. (1992) found that glycoalkaloid content had no effect on the resistance to potato cyst nematodes *Globodera rostochiensis* and *G. pallida*. Johnston et al. (1989) found that glycoalkaloids were only effective in providing protection against slugs (*Deroceras reticulatum*) at levels that would be toxic to humans. Johnston and Pearce (1994) describe a method using *D. reticulatum* as a bioassay for glycoalkaloids.

Jonasson and Olsson (1994) evaluated the influence of glycoalkaloids, chlorogenic acid, and sugars on the susceptibility of four potato cultivars to wireworm (*Agriotes obscurus* L.). The two cultivars that were most susceptible had the lowest glycoalkaloid content. In addition, glycoalkaloid content was the key factor in predicting larval feeding, accounting for about 65% of the total observed variation. Differences in fructose plus glucose levels accounted for another 13%, whereas differences in chlorogenic acid and sucrose levels among the cultivars did not affect the predicted larval feeding activity. This study implied that the apparent relationship between glycoalkaloid content and resistance to wireworm attack conflicted with requirements of a low glycoalkaloid level for reasons of safety. Keeping glycoalkaloid at low levels may decrease their resistance to pests, necessitating additional application of insecticides to protect the crop.

Olsson and Jonasson (1995) extended these studies by examining genotypic differences in susceptibility to wireworm attack in potatoes. They found that in 10 to 13 genotypes, susceptibility was negatively correlated with glycoalkaloid concentration and positively correlated with reducing sugar content in the outer 2 mm of the tubers. These observations suggested that (1) low glycoalkaloid content may not cause an increase in susceptibility to pests; (2) the concentration gradient across the tubers may be more important than the average glycoalkaloid content; (3) higher levels of glycoalkaloids at the periphery of the tuber can impart strong resistance (although the high content is compensated by low internal levels that do not exceed recommended safety levels for human consumption). They also discovered a clone with a glycoalkaloid content of 407 mg/kg FW in the periphery of the tuber and with an acceptable average content of 150 mg/kg. The development of new cultivars with localized high concentrations of glycoalkaloids at the periphery of the tubers may thus impart a double benefit: improved resistance to pests and low glycoalkaloid content after peeling.

In a relevant study of Colorado potato beetle antifeedants, Huang et al. (1995) postulated that biological activity did not depend on the chemical class of a compound, but rather on the compound's shape, lipophilicity, and electron density pattern favoring binding to a receptor site of a protein. Thus, glycoalkaloids, triterpenoids, etc.

could have similar effects in imparting resistance and might be specific for organisms with the same enzyme systems. If true, this hypothesis implies that it should be possible to design potent antifeedants by molecular modeling of antifeedant structure-protein receptor site interactions. This is analogous to the described modeling of glycoalkaloid-antibody affinities by Stanker et al. (1994).

Interestingly, plants with low initial levels of glycoalkaloids could produce higher levels if stressed by insect attack. The nature of the damage may also have an effect. For example, Hlywka et al. (1994) discovered that potato plants stressed by Colorado potato beetles produced tubers with a higher glycoalkaloid concentration than unstressed plants. Plants attacked by leafhoppers showed no increase in glycoalkaloids. The authors suggested that action potentials in plant tissues generated by wounding and other stresses may signal the transduction of glycoalkaloid-inducing signals from beetle-exposed leaves to tubers. The results imply that plants low in glycoalkaloids may need to be protected by other methods, such as safe pesticides, or the tubers may reach high levels of glycoalkaloids caused by insect damage-induced stress. This brings up the question of whether organically grown potatoes might have significantly higher levels of glycoalkaloids that would offset possible benefits of pesticide-free tubers. The effort to minimize conflict between food safety, requiring low glycoalkaloid content, and better resistance favored by high glycoalkaloid levels in the periphery of the tubers, is a challenging problem for plant science.

VII. MOLECULAR GENETICS

Identifying and eliminating toxic glycoalkaloids while retaining natural defenses against pests would allow modification of existing new cultivars with superior processing characteristics, currently unavailable commercially due to unacceptable alkaloid content (Norris, 1986; Stapleton et al., 1991). It is possible that suppressing one or more of the genes that encode enzymes involved in the biosynthesis of glycoalkaloids may lead to accumulation of biosynthetic intermediates shown in Figure 6 or may completely shut off the synthesis of glycoalkaloids via a biofeedback mechanism initiated by the presence of unnatural alkaloids.

The final step in the biosynthesis of glycoalkaloids is the attachment of sugar residues to position 3 of the alkaloid moiety (Figure 3). The literature suggests that alkaloids with less than three carbohydrate groups generally appear to be less toxic than the naturally occurring trisaccharides α-chaconine and α-solanine (Osman, 1983; Rayburn et al., 1994). Therefore, blocking glycosylation in the biosynthetic pathway should result in tubers with significantly lower toxicity.

The structure of the carbohydrate portion of a given glycoalkaloid plays a central role in the determination of its biological activity. The nature, number, and linkage of the monose residues, as well as their stereochemistry, can profoundly influence the biological properties that govern the relative toxicities of alkaloids *in vivo*. These properties include binding to receptor sites, absorption, transport, metabolism, and finally elimination of the alkaloids. A parallel can be drawn to the hemagglutinins (lectins), which are toxic glycoproteins. The toxic effects of these molecules appear to be due to the ability of the carbohydrate portion to bind to specific receptor sites on the surface of intestinal epithelial cells, resulting in cell damage and interference with the absorption of nutrients across the intestinal wall.

One approach (Moehs, 1996b, 1997; Stapleton et al., 1991, 1992, 1994) is to characterize and inactivate genes coding for glycosyl transferase enzymes such as solani-

dine glucosyl transferase (SGT) that catalyzes the last step in the biosynthesis of glycoalkaloids, that is, the glycosylation of the aglycones. The inactivation may be accomplished by generating antisense RNA specific for the target enzyme. This could permit the development of new potato varieties that produce alkaloids that are nontoxic or minimally toxic to humans, but would still protect the plants from insects and other pathogens.

Other possible approaches that may succeed in achieving the same objective include: (1) cloning and suppressing potato genes encoding aminotransferase enzymes that are postulated to catalyze the introduction of nitrogen during the biosynthesis of glycoalkaloids from cholesterol (Figure 6); (2) cloning and suppressing potato genes encoding enzymes that catalyze the introduction of galactose and rhamnose moieties into glycoalkaloids (Bergenstråhle et al., 1992a; Stapleton et al., 1991; Bushway et al., 1988, 1990); and (3) introduction of genes into potatoes that encode glycoalkaloid-degrading enzymes in tomatoes (Heftmann and Schwimmer, 1972) and fungi (Larini et al., 1996; Osbourne et al., 1996; Sandrock et al., 1996).

The molecular genetic studies need continuing guidance from safety evaluations in order to assure the safety of newly developed transgenic potatoes.

VIII. RESEARCH NEEDS

Although potato glycoalkaloids have been studied extensively, there are still many areas that are unclear. As can be seen, several studies have produced contradictory results. Kuč (1984) in his discussion on potato quality factors raised some relevant questions, including the following: (1) How does injury to the tuber trigger higher glycoalkaloid production? (2) Does injury to foliage cause an increase of glycoalkaloid synthesis in tubers? (3) What is the relationship between high levels of glycoalkaloids in the leaves and in the tubers? (4) Is there a relationship between high glycoalkaloid levels and the production of the sesquiterpenoid stress metabolites? (5) How would lowering glycoalkaloid production affect the concentrations of other compounds such as phytoalexins and what would be the consequences for pest resistance? None of these questions has been adequately addressed.

Needed studies in potato handling and sampling to benefit potato growers and consumers include the following:

1. Determine the *relative susceptibilities* to greening and mechanical damage of the present major commercial varieties and new cultivars. Measure accompanying changes in glycoalkaloids, calystegines, chlorogenic acid, tyrosine, and ascorbic acid content (Brown, 1993; Olsson, 1986).
2. Evaluate food-compatible enzyme inhibitors such as citric acid and sulfur amino acids and substrate inhibitors for their ability to inactivate SGT and other enzymes catalyzing glycoalkaloid biosynthesis.
3. Evaluate films made from safe agricultural products with built-in chromophores that absorb light for their ability to protect potatoes against greening, browning, and spoilage.
4. Investigate the effects that size and maturity (if this can be quantified) have on glycoalkaloid levels and make recommendations for a standard protocol to be adopted by the potato industry for measuring glycoalkaloid changes during sampling and handling of potatoes. Because tuber age makes a significant difference in glycoalkaloid levels, care must be taken to ensure all samples are on tubers at the same stage of maturity.

Mature tubers of the same size appear to be the best.

5. Because many factors, such as light, temperature, and mechanical injury, can induce glycoalkaloid production in postharvest tubers, it is essential to reduce these sources of variability when comparing the base levels of different varieties. Samples should either be analyzed as soon as possible after harvest or kept in carefully controlled environments to minimize changes in glycoalkaloid content. We have had good success with immediate flash-freezing and freeze-drying our samples to eliminate any further physiological changes due to storage and handling effects (Dao and Friedman, 1996). A detailed comparison of freeze-dried powders vs. fresh samples is needed. The information could form the basis for recommendations in establishing a standard protocol to minimize postharvest glycoalkaloid synthesis. Some effort should be made in the standardization of the analytical methods.
6. Determine whether changes in concentration of solanidine glucosyltransferase (SGT) can serve as an indicator of mechanical damage and other stress conditions.

In addition to the need to minimize postharvest glycoalkaloid production, complementary studies are needed to reduce preharvest glycoalkaloid formation by suppressing the enzymes and genes governing their biosynthesis. Such an approach provides a variety of benefits extending from the growing, processing, shipping, marketing, and consumption of potatoes and potato products. Perhaps the greatest benefit will be felt on the farm and in processing facilities. Reduction of toxicant levels in selected varieties will allow introduction of new potato cultivars that cannot currently be released due to their higher than acceptable levels of glycoalkaloids. Such an approach avoids problems of classic potato breeding programs because commercial potatoes are tetraploid and have an exceedingly complex genome structure, making it difficult for breeders to introduce a single genetic trait into an existing cultivar. A molecular genetic approach can create cultivars without altering existing genes. The following specific approaches merit exploration:

1. Develop toxicological profiles of known and newly identified *Solanum* glycoalkaloids and related metabolites, identifying those that exhibit major effects in mammals.
2. Identify the plant enzymes involved in the biosynthesis of the most toxic glycoalkaloids.
3. Use antisense RNA and related methods to develop potato cultivars with low levels of these glycoalkaloids while maintaining acceptable resistance to phytopathogens.
4. Determine relationships among three major resistance factors in potatoes: glycoalkaloids, polyphenols, and protease inhibitors.

The success of such an effort would enhance the value of potatoes as a high-quality food.

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