III.

Summary and Discussion of Each Workshop Paper

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TOBACCO LEAF PROTEIN

The concept of using leaf protein as a food is not new. Over the last 60 years, scientists from several countries have researched the extractability of proteins from leaves and preparation of leaf protein concentrate (LPC). The greatest impetus for leaf protein research came in the early 1940's when Norman Pirie of England examined the potential of producing LPC as a source of protein for human consumption to alleviate wartime food shortages. After World War II the interest in leaf proteins for human use waned because their green color and slightly grassy taste hindered consumer acceptance of them as human foods. Since that time, the Pirie process for leaf protein extraction has been modified for commercial production of LPC for livestock feed. Recently, a new technique has been developed and tested at the pilot-plant stage that can extract a high-quality, purified protein from immature tobacco plants. It has been proposed that tobacco be used as a dual- or multi-product crop for proteins and smoking and chewing tobacco,

The extraction process yields six products. They are:

Crystalline Fraction 1 Protein

Fraction 1 protein is a water-soluble, tasteless, and odorless white powder. It is nutritious; when fed to rats, crystalline Fraction 1 protein exhibited a higher protein efficiency ratio (PER) than casein, the common standard for comparing the nutritional quality of proteins. Because it is tasteless and odorless, Fraction 1 protein can be added to foods to improve their protein content and qualit y without changing their taste or smell. This product can be added to foods for its albumin-like functional properties such as heat set and gelling. It has been suggested that if crystalline Fraction 1 is washed free of sodium and potassium, it might be useful for kidney patients as a source of high-quality protein, although this has not been substantiated by research.

Fraction 2 Protein

This product also is water-soluble and nutritious and might be used as a protein supplement for food products such as cereals. Its functional properties are not so desirable as those of Fraction 1 protein, however.

Green Sludge

Green sludge consists of water-insoluble proteins and starch. It possibly could be marketed as a feed for poultry and other nonruminant animals. Green sludge can be converted by solvent extraction to a material similar to soybean meal in properties and amino acid composition.

Green Residue

This product represents the fibrous material left after protein extraction. The solids are composed of more than 50 percent cellulose and hemicellulose and about 13 percent protein. It is similar to alfalfa hay in nutritional value, The green residue can be converted through organic solvent extraction to white fibers suitable for cigarette manufacturing. The resultant deproteinized cigarettes would be lower in tar and nicotine than commercial cigarettes today.

Pigments and Other Bio-Organic Compounds

Organic solvent extraction of the green residue and green sludge produces pigments and other organic compounds. Carotenoids can be separated out and possibly marketed as poultry feed supplements.

Low-Molecular Weight Compounds

This product, composed of water-soluble sugars, amino acids, vitamins, salts, and other compounds, might be used as a fermentation liquor after it is concentrated by evaporation.

The extraction procedure for tobacco protein is fairly simple. First, the aboveground portions of the tobacco plants are crushed. The liquid is pressed out, leaving behind the solids (green residue). The green juice is heated rapidly to 1250 F (520 C) then quickly cooled to room temperature, causing green particulate matter (green sludge) to settle out of the now brown liquid. The brown juice is pumped to a storage tank where within 6 to 10 hours Fraction 1 protein crystallizes out of solution. The crystals are collected and washed. The remaining liquid is acidified, causing Fraction 2 proteins to precipitate out of solution. They, too, are collected and washed.

The process has the following advantages: providing a high-quality protein from a plant already grown on a total of 2.5 million hectares over a wide geographical range, and providing a smoking product that is lower in the constituents believed to be health hazards. Although the results of pilot-scale research seem promising, several technical, economic, social, and environmental problems would have to be solved before tobacco protein extraction could be viable on a commercial scale.

This procedure was developed by Leaf Protein, Inc. (LPI), a small venture capital corporation. To investigate the potential of this process on a commercial scale, LPI formed a joint venture with the North Carolina Farm Bureau Federation. The Federation, together with General Foods Corp., helped finance a pilot plant in the tobacco growing region of North Carolina, a small plant able to process about a ton of fresh plants every 9 to 10 hours. The plant was operated first in August 1980. Each experiment required a minimum of 600 lbs of fresh plants. Climatic and technical problems were encountered, and it was not until July 1982 that the pilot plant was consistently able to produce Fraction 1 protein of high purity. Although the pilot-scale operations appeared promising, at the end of the tobacco growing season the research facility was closed and the equipment was sent to the University of Florida which is using it experimentally to produce pig feed. The research was discontinued because of lack of industry interest in investing in commercial scale-up of the LPI process. This lack of interest was not caused by predicted scaling-up problems but by fears that the products would have limited marketability because of the social stigma attached to tobacco and the changed character of cigarettes and chewing tobacco would not gain consumer acceptance. The risk involved in investment was perceived to be too high.

Consumer attitude is perhaps the most serious deterrent to using tobacco as a source for protein. Given tobacco's negative image in the eyes of many American consumers, the appeal for foods containing tobacco leaf protein could be questionable. Tobacco protein would have to compete with the already abundant sources of protein in the United States—ranging from vegetable oilseed proteins to animal proteins—which are well-established and probably more readily acceptable to the public. The potential retail value of the extracted protein alone would not economically justify growing tobacco since all three proteins together account for only about *20* percent of the total estimated value of the finished products from tobacco. As much as 55 percent of the crop's estimated value would come from sale of the fibrous portion for cigarette manufacture. Unless the deproteinized fiber is acceptable to manufacturers **and** consumers, the process would not be profitable. No commercial firm has been willing to invest in commercial scaling-up of the LPI system. Whether the changed character of a cigarette would appeal to consumer taste is in question but will be a major factor in the economic success of tobacco protein extraction.

There are many technical constraints facing the LPI process, both at the agronomic and the processing level. The time at which the tobacco is harvested is critical because the leaf protein is surprisingly variable on a daily basis. Because the proteins and other leaf constituents deteriorate rapidly after harvesting, the harvested material must be processed almost immediately. At the processing level, the leaf pulp is difficult to work with when using conventional conveying machinery because it is viscous and is corrosive to metal. Another problem which is not so apparent at the pilot level as on the commercial level is disposal of wastes. Since about *90* percent of the plant material is water, handling and disposal of large amounts of fluid must be arranged. The brown juice left after extraction of the proteins and fiber has a high biological oxygen demand (BOD) so would be a source of pollution if released unaltered into an aquatic system. Evaporation processes to condense the liquids, however, are expensive. Solvent recovery is another problem. Because they are expensive, a certain proportion of the solvents used in processing green residue and green sludge must be recovered. This may be a problem encountered with commercial scale-up.

The environmental impacts of tobacco as a crop should be examined. Tobacco needs large inputs of energy, biocides (insecticides, herbicides, fungicides, nematicides), and fertilizers for cultivation. When grown in the conventional manner, tobacco is "hard on the soil." It readily extracts soil nutrients, particularly nitrogen, so unless large amounts of fertilizer are applied to tobacco fields, the crops over time will tend to decrease soil fertility. When grown for protein extraction, tobacco plants could be harvested four times per growing season. This faster rotation probably would lead to even faster nutrient depletion and would require greater fertilizer inputs than even conventional tobacco crops. Cultivation of tobacco, an annual planted at relatively wide spacing, presents an erosion hazard. The denser spacing used for protein tobacco compared with conventional tobacco might help reduce erosion rates. However, more frequent harvests, repeatedly exposing the soil to wind and rainfall, probably would increase erosion.

Conventional tobacco production requires large inputs of biocides. Pesticide inputs may decrease because the "cosmetic" appearance required of the cigarette tobacco leaf is not necessary for protein extraction. Seedlings either would be raised in seedbeds that have been fumigated to kill micro-organisms and then transplanted in the field or would be raised directly in newly cleared land. The latter obviously is not desirable or possible in many places. The need for herbicide application would be greater if tobacco were grown for protein extraction because repeated harvests provide increased opportunity for weed encroachment. It seems that growing tobacco for protein extraction would be equally, if not more, ecologically disruptive than conventional tobacco, a crop widely recognized as a resource-demanding crop.

A great deal more economic information is needed to assess the commercial viability of the process. No processing costs at the pilot level or projected commercial processing costs are available. In addition, the ability of the products to enter the marketplace must be assessed. The products would have to be able to compete on the market with alternative products in price, availability, ease of use, and consumer taste preference (with products for human consumption). For example, Fraction 1 protein would have to compete with egg albumin as a functional food additive and the bio-organic compounds from the green residence and green sludge with alfalfa as a source of carotenoids for poultry feed. Both egg-whites and alfalfa are well-established in these markets and tobacco might have difficulty attracting a portion of these markets away from them. Most important, the deproteinized tobacco fibers would have to be able to compete with mature, cured tobacco leaves. Not only would a different taste have to be acceptable to the consumer, but the processor would have to be willing to make processing changes for the new product, An important factor in market entrance is the amount of product available. If only limited quantities of a product in a large-volume market (e.g., fibers for tobacco or for livestock feed) are available, industry may be unwilling to go to the trouble and expense of using small and/or intermittent amounts of the products.

Although the LPI process appears promising at the pilot-level scale, a great number of technical, ecological, social, and economic barriers stand in the way of commercial feasibility. The cost of taking this process from the pilot-plant scale to commerical production scale could be high. Although the pilot-plant operation was supported by private capital, the private sector is showing reluctance to work with a tobacco-related product. Despite potential advantages of the products, financial backing for further research on agronomic, extraction, and product testing and marketing has not been forthcoming. It seems that tobacco processors are not interested in altering an already profitable manufacturing system to incorporate processing of tobacco proteins of uncertain marketability, and that the food industry is unwilling to invest in a crop carrying such a social stigma. In addition, tobacco proteins have not undergone mandatory Food and Drug Administration (FDA) testing on animals to assess their safety for human consumption. Until this happens food processors may be leery of the possible presence of toxic compounds in the proteins.

There is some evidence that the protein extraction process might be used successfully on soybeans, clover, alfalfa, tomato, spinach, and other crops which are less ecologically disruptive and more socially acceptable. These plants would face many of the same problems with research and commercial scale-up that tobacco faces, but could be more acceptable to producers and consumers. Perhaps further research should investigate these alternative crops for LPI processing.

PROTEIN FROM TROPICAL PLANTS

At the present growth rate, world population will double within the next 30 to 40 years. This population increase will be most rapid in the less developed countries of the humid lowland Tropics, where annual increase in food production remains low. LPC extracted from tropical plants is being investigated as a possible source of protein. LPC is prepared from alfalfa on a large commercial scale in Europe and the United States. Because alfalfa has not been grown successfully in the humid Tropics, suitable tropical replacements are needed for leaf protein extraction.

Leaf protein fractionation is based on the principle that nitrogen-fixing plants contain higher levels of protein than can be used by ruminant animals and that nonruminants, able to assimilate only a portion of total plant protein, cannot consume the volume of leaves necessary to meet their protein needs. The high protein content of these plants allows for partial removal of protein for nonruminant use and subsequent use of the remainder of the plant by ruminants.

USDA's Tropical Agriculture Research Station in Mayaguez, Puerto Rico, has tested at least 500 introductions of tropical plants as possible sources of LPC. Desirable characteristics of plants as sources of leaf protein concentrate include high protein content, high dry-matter content, readily extractable protein from freshly cut plants, good regrowth potential, ability to fix nitrogen, erect growth for easy mechanical harvesting, nontoxicity, and low concentration of antinutritional substances.

The extraction procedure used was a relatively simple process in which the liquid pressed out of the leaves was subjected to successively higher temperatures, thus causing the proteins to precipitate out of solution. At 55° C, a green coagulum formed and was separated by centrifugation, washed several times, and spread in thin layers on glass plates to dry. The supernatant from the centrifugation was heated carefully to 640° C. The white curd coagulum that formed was separated by centrifugation, washed with acetone, and dried in a rotary evaporator. The liquid was heated further to *820* C. After cooling, a light tan precipitate formed and was processed in the same way as the 64° C fraction.

The spontaneous coagulation of protein in the juice extracted from some plants (subsequently called Type I plants), including cassava ***(Manihot esculenta),*** leucaena ***(Leucaena leucocephala),*** and many other tree legumes, was observed during the survey of tropical plants. Another group of plants (Type II) yielded a green protein coagulum after the extracted green plant juice was heated to 55° C and yielded a very small quantity of a light tan precipitate at 820 C. This first was observed with leaf protein extract of sorghum-sudan grass hybrids and other grasses. Careful heat fractionation of aqueous leaf extracts of other plants (Type III) yielded three distinct protein fractions: a greencoagulumat550 C, a copious white protein precipitate at640 C, and a small amount of light tan precipitate at 820 C. These are the most promising plants for leaf protein extraction; species selected for further study were chosen from this group. A final group (Type IV) includes plants in which the proteins in the aqueous extracts do not precipitate either spontaneously or after heat treatment.

Leaf protein concentrates subsequently were prepared from seven Type III plants ***(Vigna unguiculata, Clitoria ternatea, Desmodium distortum, Psophocarpus tetragonolobus, Macroptilium lathyroides, Phaseolus calcaratus, Brassica napus)*** and leucaena and cassava, both Type I plants. The protein quality of the LPC extracted from these plants was evaluated using rats. The tropical legumes cowpea ***(Vigna unguiculate), Desmodium distortum,*** rice bean ***(Phaseolus calcaratus),*** and winged bean ***(Psophocarpus tetragonolobus)*** gave excellent results, comparable to those obtainable from alfalfa LPC. The LPC from these plants had amino acid contents similar to each other and to reported values for alfalfa LPC and soybean meal. The tests supported the suspicion that the spontaneously precipitated protein concentrate from Type I plants would have less nutritional value; rats fed LPC from cassava and leucaena grew poorly. USDA investigations indicated that with current methods, good quality leaf protein concentrates for nonruminants could not be prepared from many of the leguminous tree leaves because the presence of phenolic substances negatively affects the nutritional value of the extracted proteins. The leaves of some of these species, however, could be used as feed for ruminants.

Investigations of tropical grasses as sources for leaf protein extraction showed them to be low in extractable protein. Nitrogen fertilizer could be applied to fields to increase the protein content in grasses, but the increased value probably would not offset the cost of the fertilizer. Tropical grasses were considered poor sources of LPC because they have higher production and processing costs and lower quality and quantity of extractionable proteins.

The following conclusions were drawn from this relatively short investigation of possible tropical plant sources for leaf protein extraction:

- Some tropical plants are sources of LPC that are equivalent to alfalfa LPC in yield, extractability, and nutritional quality.
- A single crop in the Tropics cannot be used for year-round production; a pattern of different plants has to be formulated for rainy and dry seasons.
- Cassava, leucaena, other tropical trees, and tropical grasses seem to be unpromising as potential sources of LPC.
- The type and number of protein fractions obtained by heat fractionation can be used as a rapid preliminary method to screen plants for protein extraction potential.

Machinery has been developed in England and the United States for LPC processing. Some are used for large-scale commercial LPC operations in Europe and the United States, and others have been used to assess its viability for on-farm and village-level LPC production. Research on village-level LPC production has been carried out in India, Pakistan, and Sri Lanka. Work in Aurangabad, India, is the most relevant to practical application of the LPC production systems on the village level. Establishment of a commercially viable, locally operated LPC production unit at a village farm was attempted. The green protein concentrate from alfalfa was used as a milk replacement for calves (thus making the cow milk available for human consumption), as poultry feed, and as human food. The pressed crop was fed immediately to cows. The cost of equipment and a dairy unit of five to six cows was assessed at $4,450, which is prohibitively expensive for a small-farm operator but probably affordable for village cooperatives. Concurrent research in India on LPC production concluded that on a nutritional basis, leaf protein would be much less expensive than most protein from grain legumes consumed in the area and that a LPC-containing product made for human consumption could provide half the daily protein requirements of a child at a price affordable to the majority of Indian poor ($0.025 to $0.03 per day).

On-farm leaf protein fractionation has been researched in Britain, Australia, and the United States. The on-farm system is that after harvesting, the crop is processed to produce pressed forage for ruminants and a juice with soluble proteins for nonruminants. Processing takes place on a farm and at least one of the products is used at the production site. The ideal situation would be a combined dairy and hog farm where the crop is grown and extraction products used onsite, thus reducing transportation expenses, storage costs, and spoilage. Research at the University of Wisconsin at Madison has concentrated on development of a weather-independent, on-farm forage-harvesting system using a protein fractionation process. After harvesting, the main produce is pressed forage that can be preserved directly as silage. Field losses from harvesting and baling are reduced and a higher percentage of the protein content can be retained in pressed residue than in sun-dried hays. Research results indicate that ruminants respond to being fed pressed residue as they do nonfractionated plants. The juice extracted from the plant material could be fed directly to hogs to minimize storage and preservation expenses. The proteins in the juice degrade rapidly and the carbohydrates ferment within a day, so the processing must be geared to the feeding time of the animals. Proteins could be isolated from the juice by fermentation, but the product is not acceptable yet to hogs.

Commercial LPC production was initiated in 1967 at the USDA Western Regional Research Center in Berkeley, Calif. A highly mechanized process, the Pro-Xan process, was developed for obtaining LPC from alfalfa. The first commercial application of this process took place in France in association with a commercial alfalfa dehydrators plant. (Dehydration is carried out immediately after harvesting to avoid losses from haymaking and ensiling and to produce a product higher in protein content than hay or silage.) Leaf protein concentrate from alfalfa now is prepared on a large commercial scale in Europe and the United States for livestock feed. There are plans to open a plant in New Zealand, and two pilot plants have been set up in Japan.

Attempts to process LPC to obtain an acceptable good-grade product have been unsuccessful. Green LPC from the 550 C fraction can be produced economically, but its green color, grassy flavor, and low volubility have prevented acceptance by consumers and food producers. Purifying this protein concentrate by solvent extraction is technically feasible but costly and only partially effective. The white protein fractions separated at 64° and 820 C are nutritious but are practically insoluble. If soluble, they would be of greater use to the food industry. Producing a water-soluble, bland-tasting white protein using various filtration techniques including diafiltration, ultrafiltration, and gel filtration has been attempted. Although gel filtration seems to be the most effective system, it is very expensive. Another method has been developed that produces a pure, water-soluble protein at a lower price than gel filtration. This is a crystallization process used to extract Fraction 1 protein from tobacco. * Although this process seems to be technically feasible at the pilot-plant level, its economic feasibility has not been proven and has encountered constraints to commercial scale-up.

*See paper by Wildman in the appendix.

Use of LPC technology in developing countries is most promising as applied to medium-sized production systems such as cooperatives, organized communities, and large farms. On-farm production of LPC is too expensive and labor-intensive to be feasible for most farmers who own or lease small plots of agricultural land. The system is probably most adaptable to cooperative farming operations, such as a combined dairy-hog operation. Onsite use of the products offers many advantages including lower transportation and storage costs, reduced waste because leaf production can be coordinated with demand for LPC and pressed fodder, and ability to use excess pressed juice for irrigation water.

Large-scale LPC production might be possible in developing countries if incorporated into an integrated production system, such as an operation combining dairy or beef cattle with hogs or poultry. The high degree of coordination and planning of such an enterprise probably would restrict it to public ownership or to capital- and management-intensive private firms, such as beef exporters. While this would benefit foreign exchange earnings, it would fail to provide an inexpensive, efficient protein source for those in developing countries who need it most.

Screening of tropical plants for extractable protein has produced several good candidates for LPC production in tropical and subtropical countries. Processing machinery has been developed for alfalfa LPC production, but it might be adapted for use on tropical plants to meet developing country needs. Before LPC production using tropical plants is feasible, however, comprehensive studies should be conducted on agronomic of plants chosen for protein extraction, economic feasibility, farmers' acceptance of LPC extraction and use, and production technologies. A variety of agricultural, economic, and social factors and impacts must also be considered.

ENDOD IN COMBATING SCHISTOSOMIASIS

Rural people in Ethiopia and certain other countries traditionally have washed their clothes with a detergent solution made from dried and ground ended berries. Ended (*Phytolacca dodecandra),* the soapberry plant, is a shrub that is closely related to the American pokeweed plant. In 1964, researchers studying the distribution of disease-carrying snails in streams found large numbers of dead snails immediately downstream from people washing clothes using ended as a detergent. Subsequent phytochemical studies indicated that ended contains effective biocidal compounds. Ended is being studied as a potential molluscicide for use against snails that carry schistosomiasis.

Schistosomiasis is a debilitating snail-borne disease common throughout the Tropics and subtropics. It is one of the most serious and rapidly spreading parasitic diseases of humankind, affecting an estimated 200 million to 300 million people and potentially infecting an additional 400 million. The disease is spread when uninfected people work and bathe in the same water as infected people. New shallow-water habitats for snails, the intermediate hosts, have been created by irrigation, hydroelectric power, and other water-related projects, many of which have been funded by international agencies.

No single method to control schistosomiasis effectively has been found. Ideally the most effective treatment for the disease is site-specific and repeated molluscicide applications combined with mass treatment of all infected people, improved environmental sanitation, and health education. However, no safe, effective, and affordable drug suitable for mass treatment has been found, and available molluscicides are inadequate or expensive. Environmental sanitation and health education are long-range measures. For now the most practical and effective method to control schistosomiasis is through a combination of selective treatment of infected individuals and control of new transmission by killing the host snails at each proven site of infection.

Although several chemical molluscicides have been used within the last few decades to control schistosomiasis and other snail-borne diseases (e.g., copper sulphate, Frescon, sodium pentachlorophenate, Yurimin), several of them are no longer produced either because they are ineffective or cannot be marketed. The only molluscicide recommended by the World Health Organization is Bayluscide, an expensive chemical used only in a few developing countries with the help of external financial assistance. The lack of a market as a result of developing countries' limited foreign exchange has discouraged the private sector from developing other molluscicides. The discovery of endod and the lack of adequate and affordable chemical molluscicides have stimulated the testing of plants as potential molluscicides. Croton (Croton tiglium, C. macrostachys), ambrosia ***(Ambrosia maratima),*** and jatropha ***Jatropha curcas)*** show some promising molluscicidal activity, but a great deal more work must be done to evaluate their potential as commercial molluscicides. As recognized by a workshop on plant molluscicides convened by the United Nations Development Programme, World Bank, and World Health Organization in January 1983, ended seems to be the most promising plant molluscicide evaluated to date. whereas several other chemical molluscicides are unstable in intense sunlight or under different water pHs and concentrations of organic or inorganic matter in the water, ended remains stable in sunlight and under a wide range of water conditions. It is a potent molluscicide, killing snails within hours. Tests showed ended to have no mutagenic properties, indicating that widespread use of it as a molluscicide might not pose a safety hazard to humans.

A 5-year pilot study investigating the effect of ended on schistosomiasis was carried out in northern Ethiopia between 1969 and 1974. Systematic application of locally collected endod berries over the 5 years reduced the prevalence of schistosomiasis in children aged 1 to 6 from 50 to 7 percent, and in the entire population (17,000) from 63 to 34 percent. The incidence of disease in an untreated nearby village was almost constant over the course of the study, indicating that the reduction in the treated village was as a result of ended applications. The cost of the treatment amounted to only US $0.10 per person per year. A critical element in the success of this control study was local political support and community participation. The local political officials and municipal council were involved in the planning and execution of the study, and the council provided finances, manpower, and facilities.

In addition to its value as a molluscicide, the ended berry may have commercial potential as a detergent; an insecticide for the control of mosquitoes, the black fly that carries river blindness, and other water-breeding insects; a fungicide against certain human skin diseases; a spermaticide or an abortifacient. Ended berries have been used in Ethiopia and many other tropical countries for centuries to control an aquatic leach that is a major pest of livestock. The berries are also effective against snails that spread fascioliasis, a serious cattle and sheep disease.

Most chemical studies done on ended to date have focused on saponins, the biocidal compounds in the berries. Saponins account for only 25 percent of the dry weight of ended berries, and the berries in turn represent only a small proportion of the total plant biomass. The berries, leaves, stems, and roots could be potential sources of other useful products including pectins, thickening agents, starches, sugars, animal feed, and fuels. As research on ended progresses, these and other uses for the byproducts might be developed. Ended is a potential multipurpose crop that could provide products for local use or support local industries.

The active chemical in ended berries has been isolated, identified, and named Lemmatoxin. Three extraction procedures have been developed, two of which are based on solvent extraction and the third on fermentation. The fermentation method is simple; berries are ground, soaked in water, and left in a warm place to ferment by means of the yeast cells normally found on ended berries. This is perhaps the most practical extraction method for developing countries to use. Processing equipment is affordable, it can be supplied and operated locally, and no extraction solvents have to be imported. The fermentation extract can be applied in a variety of ways. It can be dusted on the surface of the water as a powder, sprayed on the water as an emulsion, or compressed into briquettes to allow for slow release of the active chemical.

If high-potency ended varieties could be grown locally, the dried and ground berries could be applied directly to rivers, streams, and irrigation channels. This would avoid the processing costs involved in preparing an extract. A study carried out between *1976* and *1981* tested *65* different strains of ended and chose three on the basis of molluscicidal potency, berry yields, and resistance to insect pests and drought. These three strains subsequently were used in cloning experiments using tissue culture. Plantlets developed through mass propagation have been distributed to Brazil and three African countries for field trials. Additional research is using tissue-culturing for in vitro biosynthesis of the active molluscicidal principle.

Although research on chemistry, extraction application, and toxicity of ended has progressed rapidly since *1964,* a great deal more toxicological, agronomic, and economic research is necessary before large-scale application of ended for control of schistosomiasis and other snail-borne diseases could be possible. Toxicity studies on sheep and dogs showed that while intravenous injection of ended can be fatal, oral intake of small to moderate amounts can be tolerated by animals and large amounts induce vomiting. This emetic property acts to protect people and animals from possible overdoses. Ended berries, leaves, and roots have been taken orally for centuries in several African countries for various medical purposes, including birth control and ridding the body of internal parasites. Had ended shown negative effects, it probably would have been discarded long ago. Mutagenic tests on ended berries carried out in vitro have been negative. However, more comprehensive mutagenic and toxicity tests should be carried out on a variety of different animal species to provide more complete evidence of ended's safety.

Because ended has never been grown commercially on a large scale, it will have to be subjected to a range of agronomic studies. Agronomic research on ended during the last decade has concentrated on selection and breeding of plants for good growth and berry productivity and potency. Some studies have recently been carried out in Ethiopia on its plant ecology and susceptibility to pests, particularly to a stem-boring fly that kills young shoots. Data have also been collected on plant nutrition, germination, spacing, and irrigation. This preliminary work will have to be expanded; field trials are needed to determine both the agronomic needs of ended and the ecological effects of cultivating the plant, including impacts on soil, water availability, and pest outbreaks.

Although no comprehensive ecological studies to determine the effects of ended application on streams have been conducted, observations indicate that local animal populations are largely unaffected. Any localized effects of ended application are unlikely to be long-lasting because the active chemical biodegrades rapidly. Within *24* to *48* hours ended's potency declines. Extensive research is needed to provide comprehensive data on ecological impacts.

In summary, ended appears to be a promising potential as a molluscicide for controlling schistosomiasis. Research on endod, however, is still at an early stage. Before ended can be used as a molluscicide, far more research is needed on its toxicity, agronomy, ecology, economics, extraction, and application techniques, cost effectiveness compared to other molluscicides, and the distribution and marketing of berries or the extracted molluscicide. In addition, its potential as a multiproduct crop should be examined.

Ended could be a community-controlled solution in developing countries to the widespread problem of schistosomiasis. Because the plant can be grown locally and the biocidal compound extracted simply using a low-technology fermentation method, inexpensive local production of the molluscicide is possible. The alternative of importing expensive Bayluscide or another chemical molluscicide is not a viable option for most developing countries with limited foreign exchange. Ended could be cultivated and extracted either publicly or privately and then applied to infection sites by the community. The public sector would have to bear the startup research costs for such a community-based public health project, but financial assistance might be sought from development assistance agencies such as the U.S. Agency for International Development. Once started, a project could be sustained by local revenues and paid or volunteer community labor.

Ended use need not be restricted to schistosomiasis control in developing countries. Further research may develop endod's potential as a source of larvicides, insecticides, spermatocides, or other products. A similar community-based project based on the use of ended as a larvicide for the control of malaria perhaps is another future application. Ended might also be investigated as a biocide for pest control in the United States.

MILKWEED: A POTENTIAL NEW CROP FOR THE WESTERN UNITED STATES

Arid/semiarid-land plants in the United States represent relatively untapped sources of valuable oils, waxes, natural rubbers, insecticides, medicines, and important chemical feedstocks. These chemicals, produced by plants as defenses against predators, pests, and climatic stresses such as temperature extremes and drought, could be extracted to provide a variety of commercial products. Interest in arid/semiarid-land plants as sources of insect repellents, attractants, and toxicants; * fossil fuel substitutes; and chemical feedstocks** is growing. The showy milkweed ***(Asclepias speciosa),*** discussed in greater detail later, is an example of an arid/semiarid-land plant being investigated as a potential multipurpose crop for chemical feedstocks and fiber products. Arid and semiarid lands, often considered agriculturally unproductive in relation to traditional U.S. food and fiber crops, could become important for the production of a variety of commercial chemical extracts.

Despite the general lack of attention to the commercial potential of arid/semiarid-land plants, some of these plants already provide a variety of commercial products. Some arid/semiarid-land-plant extracts used in the United States are jojoba oil, gum arabic, tragacanth gum, candelilla wax, and natural rubber from guayule. Jojoba oil is a valuable lubricant able to withstand high temperatures. The first commercial harvest of cultivated jojoba plants in the Southwest United States occurred in ***1982;*** until then only wild plants had been harvested. The market value of imports of gum arabic, used in the food industry for its functional properties, was about *$8* million in *1982.* Gum arabic is obtained from an ***Acacia*** species native to Africa and the Middle East, but a related species could be grown in the United States to supply an equivalent gum and provide savings in foreign exchange. Tragacanth gum is used in pharmaceuticals and cosmetics and as a thickening agent in some prepared foods. Although the plant could be grown in the United States, gum is imported from Iran. As a result of political instability in the area, imports recently have been erratic. The United States has had similar problems with procuring candelilla wax which is imported from Mexico. Imports dropped by over 50 percent between *1978* and ***1982*** as a result of harvesting problems. Guayule, a desert shrub that contains natural rubber, could be grown in the United States to provide a substitute for ***Hevea***

*See paper by Jacobson in the appendix.

**See paper by Tankersley and Wheaton in the appendix.

rubber imported from Southeast Asia. During World War II when the supply of imported rubber was cut off, guayule was produced in the Southwestern United States as an alternative source of natural rubber. Production was discontinued after the war when synthetic rubber became available and importation of natural rubber resumed. Interest in domestic production of guayule has again arisen with increasing demand for rubber and higher prices for hydrocarbons and petroleum-based industrial feedstocks. Semicommercial production is being carried out in the Southwest United States. *

A major constraint to developing new arid/semiarid-land plants and plant products is lack of adequate field-screening procedures. The availability of good field-screening technologies could help identify promising species for research and locate good sources of germ plasm (e.g., for high oil content, high biomass productivity) for potential and existing crops. Chemical screening generally has been done in the laboratory by solvent extraction. Fairly recently, two laboratory techniques, wide-line nuclear magnetic resonance (NMR) and near-infrared reflectance (NIR), have been developed for more rapid screening, All three methods require that plants be brought in from the field for laboratory analysis. Solvent extraction must be done in the laboratory; NMR is not portable enough for field screening; and even though portable NIR units are available, plant material still has to be brought to the lab. Collecting, preparing, and documenting field samples are time-consuming activities, and because most of the material will be unpromising and therefore discarded, they are not cost effective. The plants yielding good laboratory results have to be relocated in the field, a task that is often difficult. It would be far more time- and cost-efficient if plants could be screened rapidly in the field and seeds or cuttings from the promising plants collected then. Lack of adequate field-screening techniques poses a serious deterrent to the search for potential new crops and plant products.

A plant should be screened for a range of chemical compounds to investigate its potential as a multiproduct crop. Once the plant material has been collected and transported to the processing site, additional costs for extracting more than one product may be relatively small but can add significantly to the total commercial value of the plant. Multiple-product development can justify the costs of growing, harvesting, and transporting the crop and extracting the chemicals. In addition, the development of many products helps buffer the market risk of the crop; if one product fails, the other products can help offset the economic loss,

Different techniques are used to extract particular chemicals. In general, polar solvents extract biologically active compounds and other reactive chemicals, including dyes, antioxidants, and adhesives. Nonpolar solvents yield compounds that are useful as lubricants, waxes, and elastomers. The water or acidic aqueous fraction may provide polysaccharides such as gum or pectin and some water-soluble protein. The residue from extraction is comprised of cellulose, hemicellulose, protein, and lignin (if present). This material maybe burned as fuel, used as livestock feed, fermented to produce industrial chemicals, or the fiber maybe removed and used for pulp, paper, or fabric.

Native Plants, Inc. (NPI) has been studying the showy milkweed ***(Asclepias speciosa)*** as part of a program to investigate plants as new sources of commercial chemicals. This species was chosen for study because it is distributed over a wide range of climates and soil types. It is an herbaceous perennial found throughout the Western United States, from the Mississippi River to the Pacific Ocean, and from central Alberta and Saskatchewan to central Oklahoma. Milkweed is a potential crop for areas of low rainfall. For example, ***A. speciosa*** can be grown easily in the western Great Plains, where overuse of the ground water stored in the Ogallala aquifer is requiring a shift from irrigated to dryland agriculture. Milkweed eventually may provide farmers with a substi-

*See OTA background paper entitled ***Water-Related Technologies for Sustainable Agriculture in Arid/Semiarid Lands: Selected Foreign Experience,*** ch. V, for more information on guayule.

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tute for irrigated crops or an alternative to other dryland crops (e.g., dryland wheat, grain, sunflowers, and sorghum) grown there. Most of NPI's work has been on milkweed's photochemistry and extraction procedures. Although some research has been done on agronomy and crop storage, a great deal more is needed. In addition, the economic viability and ecological and social impacts of developing milkweed as a crop need to be examined carefully.

Fractionation of milkweed produces the following extracts with commercial potential: pigments, rubber, and triterpenoids from nonpolar solvent extraction; inositol and sucrose from polar extraction; and pectin from the acidic aqueous extract. The residue left after extraction consists of fibers that can be marketed for various commercial uses and fibrous material that is suitable for livestock feed. The material that can be used for feed represents 70 percent of the original plant biomass. It is equivalent to alfalfa in protein content and quality and in digestibility for sheep, but must undergo exhaustive solvent extraction or heat or acid treatment before it is rendered nontoxic.

Before commercialization of milkweed can be successful, much additional research on agronomy, harvesting, and crop storage is needed. Small test plots have been established by NPI in Utah, New Mexico, Texas, and Kansas. Attempts to establish stands elsewhere were unsuccessful and problems with controlling weeds and obtaining uniform stands were encountered. Developing effective methods of weed control, especially when the milkweed plants are still seedlings, is critical. Harvesting research indicates that plants can be harvested with standard farm equipment such as that used for alfalfa. Test plots gave yields of about 4.3 tonne/ha, but denser planting might be expected to yield between 6.7 and 9.0 tonne/ha. Storage tests indicated that although the nonpolar extractable remain stable, the polar extractable deteriorate over time when harvested material is stored. Covering the stored material alleviates the problem considerably. Storing the crop so that commercial processing could take place throughout the year would provide considerable financial savings in plant capacity.

Several environmental constraints must be considered before this crop is grown widely as a commercial crop. A major concern is that the arid and semiarid areas where milkweed cultivation has been tested are highly susceptible to erosion, especially by wind. The effectiveness of zero till, crop overseeding, sod culture, narrow stripcropping, and various other options should be evaluated. Another problem to be considered is loss of soil nutrients caused by removal of plant material. Nitrogen will have to be replaced by commercial fertilizer and possibly organic manure from cattle feedlots. Some pest problems should also be anticipated. Aphids are serious pests of milkweed and may become an economic liability in milkweed plantations. Pest control using natural predators and both natural and synthetic insecticides should be investigated. The danger of milkweed itself becoming a pest is an important consideration. Milkweed could cause considerable problems by spreading to neighboring fields planted in other crops. Wild populations of milkweed cause significant problems as weeds in some agricultural fields of Minnesota.

Major technical constraints will affect the profitability and competitiveness of milkweed compared with other crops. First, commercial extraction and purification of inositol and pectin (sweeteners), which together represent 58 to 73 percent of the total estimated value of milkweed products, are not yet commercially viable. Proto-commercial processing has uncovered other processing problems that must be resolved, and development of more efficient methods for detoxifying the residue for livestock feed is needed.

NPI calculated milkweed production costs using a 2-hectare research plot. The costs were found to be greater for milkweed than for dryland wheat or grain sorghum. Weed control accounted for more than half of total production costs. If weed control and harvesting techniques were improved, production costs could be reduced significantly. The milkweed seeds used in the research were collected from wild plants. Seed improvement through breeding, selection, and denser spacing of the plants could be expected to increase yields and improve the profitability of milkweed. The costs of erosion-control practices, not considered in the NPI analysis, should be factored in.

The total value of milkweed products ranges from $511 to $645 per tonne. These figures represent only the market value of the processed goods. Because no figures are available on processing costs to extract these materials from milkweed, market values indicate little about crop profitability. Processing costs may be considerable. For one thing, the costs of recovering extraction chemicals might be very high. As already mentioned, extraction and purification of inositol and pectin are difficult and expensive; economically viable techniques have not yet been developed. The other high-value products are triterpenoids, sucrose, fibers, and livestock feed. It is questionable how effectively sucrose and fibers from milkweed could move into the high-volume, well-established markets for these products. Livestock feed may prove to be competitive with other feed crops, especially on lands where these crops are unproductive such as areas of the western Great Plains. The potential of milkweed to substitute for fossil fuels as sources of hydrocarbons and chemical feedstocks can not be assessed from the information given. Before the economic feasibility of milkweed production can be predicted with any accuracy, more data on the costs of these products and the costs of producing alternatives from milkweed are needed. If milkweed products were to be moved into fossil-fuel related markets or other large-demand markets, large acreages of semiarid land might be converted to milkweed production. Ultimately, however, the competitiveness of milkweed as either a small-demand "specialty" crop or a large-demand crop is contingent on the marketability of the products. A great deal more marketing research must be done to assess milkweed's economic feasibility.

The scale of production is a vital consideration to the economic viability of milkweed. Large-scale production probably is needed to make it a profitable enterprise. Both the "specialty" or high-cost products (e.g., inositol, pectin) and the low-cost products (e.g., livestock feed, fiber) require large-scale production. Large amounts of milkweed are necessary to produce even small amounts of the more valuable products, and enough of the large-volume products must be available to capture a portion of their markets. If the economic viability of milkweed were dependent on inositol and pectin, care would have to be taken to avoid flooding the markets. A balance that could satisfy the demands of the low- and high-volume products would have to be reached. As will all new crops, scaling-up from pilot studies to commercial production would be the most difficult step and would be contingent on milkweed's attractiveness to investors.

If milkweed were to become commercially viable, it could provide many benefits. Although dryland wheat, grain, sorghum, and sunflowers are grown on the western Great Plains, the productivity of this area is not high in its contribution to total U.S. crop production. Substituting milkweed for these crops, therefore, would not reduce seriously the total production of traditional U.S. food and fiber crops. The western Great Plains is a cattle-feeding center. If milkweed were to replace some of the crops grown there for livestock feed, it could continue to supply feed necessary to support this industry. Milkweed could provide farmers with an alternative crop, thus freeing them from their dependence on commodity goods. Grain prices have remained stable, but operating costs have risen, so that the region's farming economy is severely depressed, If proven to be profitable, milkweed would provide an alternative that could facilitate the region's economic recovery. Another potential benefit would be import substitution. If the extraction problems were solved, milkweed could fulfill the U.S. demand for inositol, all of which is imported. Milkweed triterpenoids could substitute for some imported oils or waxes and for all domestically produced and imported pectin.

Although development of milkweed as a crop would have many benefits and at this stage has some promise, many economic, technological, agronomic, and ecologic problems must be resolved before it could be a commercially viable crop. Its potential will have to be examined in relation to present crops as well as new arid- and semiarid-land crops being studied.

INSECT REPELLANTS, ATTRACTANTS, AND TOXICANTS FROM ARID/SEMIARID LAND PLANTS

From the time of the early Remans until 1900 only three efficient plant-derived insecticides—pyrethrum, hellebore, and nicotine—have had widespread use. Advances in chemistry and improved screening techniques, however, have led to the discovery of many plant-derived insect toxicants, repellents, attractants, feeding deterrents, growth inhibitors, and sterilants since the turn of the century. Some of these active compounds may be developed commercially and would expand the range of available products for insect pest control. New plant-derived insecticides might provide substitutes for some synthetic insecticides that are ecologically disruptive and for others to which insects have developed a resistance.

Arid- and semiarid-land plants are good sources of insect toxicants and related compounds. Some of these biologically active chemicals are produced by the plants as defenses against pests and pathogens. In environments of climatic stress where plant growth is slow, insect attack can be particularly debilitating to a plant. A strong defense system may be critical to survival and probably has been an important factor in the evolution of arid/semiarid-land plants. Not only are these plants good sources of insecticides and related chemicals but they are adapted to areas that are marginal for production of traditional food and fiber crops. Arid/semiarid-land plants with commercial potential offer the opportunity to expand agriculture on land that is unproductive for established crops. In addition, perennials such as the neem tree or mamey apple may be ecologically preferable to other crops on arid and semiarid lands which commonly are highly susceptible to erosion.

The USDA Biologically Active Natural Products Laboratory in Beltsville, Md., has been studying plants as potential commerical sources of insect toxicants, deterrents, and attractants. Seven plants appear to be particularly promising. Most of these plants have been used locally in different countries for various purposes including insect control. The plants represent potential multiproduct crops for the United States and developing countries. Most of the work done by USDA has been on extraction and application of the chemicals. A great deal of applied research on agronomy, commercial processing, and marketing is needed before commercial production of most of these species would be possible.

Calamus

Calamus, ***Acorus calamus*** is a semiaquatic perennial that can grow on dry land. The roots have been used from ancient times in India and Japan for the treatment of a variety of ailments and as an insect repellant and toxicant. The different varieties—American, Indian, Japanese, and European—have different insecticidal characteristics. Commercially available oils from the Indian and European varieties are obtained either by steam distillation or solvent extraction. They are repellent or toxic to clothes moths, house flies, fleas, lice, mosquitoes, and many stored-grain insects. The Japanese variety causes sterility in male house flies. Oil from the Indian variety is highly attractive to Mediterranean fruit flies, melon flies, and oriental fruit flies. The roots are used in China as an insecticide and vermifuge. The component primarily responsible for sweetflag's repellency and sterility is B-asarone which can be synthesized more cheaply than it can be extracted from plants. It is effective against the rice weevil, probably the most damaging insect pest of stored grains. Another active component, asarylaldehyde, is commercially extracted from the plant material. These two compounds probably would be useful as fumigants for protecting stored grain from insects because they permeate grain-filled storage areas without leaving residues on the grain after the areas are ventilated. Other potential uses of Calamus compounds are for tuberculosis treatment, as a germicide, and in perfumery. One constraint to using ***Calamus*** chemicals is that B-asarone has a depressant effect on the central nervous systems of mice, rats, and monkeys. Although these pharmacological properties may limit use of ***Calamus*** oil to certain applications, they should not prevent use of the oil for agricultural insect control and possibly for medical purposes.

Big Sagebrush

Big sagebrush, ***Artemisia tridentata,*** is a multibranched perennial that is the dominant plant of the Great American Desert. It has been cultivated in the West since 1881 as a fodder plant for range cattle. The brittle branches sometimes are used for thatch by Indians, the seeds are ground into a meal by the California Indians, and a pollen extract is used against hay fever. In the past, ***Artemisia*** has had various insecticidal uses. For example, sagebrush leaves and shoots were placed in granaries to protect stored cereals from weevils and other pests, and the water in which they were steeped was used to kill or repel insect larvae, fleas, and locusts. An extract from sagebrush is effective as a feeding deterrent against the Colorado potato beetle, a pest of growing economic importance. This pest's resistance to insecticides applied in potato-growing areas is an increasingly serious problem in several areas of the world, and this resistance probably will become more common. Only one of the compounds responsible for the feeding deterrent activity has been identified. It has not been synthesized and it is unlikely that synthesis would be economically feasible. However, the crude, unpurified extract could be sprayed directly on crops, although the potential ecological effects of doing so must be assessed first.

Neem

Neem, ***Azadirachta indica,*** a common tree of dry scrub forests in India and Burma, grows on poor soils in hot, dry areas. Although all parts of the tree are repellent to insects, extracts of the seeds are outstanding as repellents and feeding deterrents for a broad spectrum of economic agricultural and household insects (e.g., Colorado potato beetles, Japanese beetles, scale insects, cotton bollworms). Seed extracts deter at least 25 species of crop pests in the United States from feeding, inhibit the growth and development of others, and render others sterile. These compounds seem to be nontoxic to man, animals, and plants. Because they are absorbed by the plant tissue, they offer relatively long-lasting protection to crops even after rain showers of high intensity. Three antifeedants have been isolated from neem. The most potent is effective against a variety of insect pests native to the United States. This chemical cannot be economically synthesized because its structure is so complex, but it can be extracted in pure form.

Neem is a source of many potential products in addition to insect antifeedants and repellants. Almost every part of the neem tree is used medicinally in India. Oil can be extracted from the seeds for soap, wax, lubricants, and lighting and heating fuel, and the residue can be used as an organic fertilizer. Other parts of the tree are used in various countries for commercial products, including timber and cabinetry wood, tannins, a toothpaste ingredient, and livestock fodder. Neem production could sustain cottage industries in Asia and Africa and provide a base for large commercial operations in the United States and Central and South America.

Neem plantations have been established in northern Cameroon, Nigeria, Gambia, India, Honduras, and some Caribbean islands. The U.S. Peace Corps is encouraging neem cultivation in Cameroon and Gambia, and USDA has started a program to develop neem commercially in Puerto Rico and the U.S. Virgin Islands. Constraints to commercial development include short-term seed viability, rapid photodegradation by sunlight of the major active principle after field application, unpleasant smell of the seed oil, frost susceptibility, poor growth on poorly drained soils, and poor agroforestry potential because of interference with other crops and vice versa. Despite these constraints, cultivating and processing neem seem promising. USDA is carrying out the major basic research on extraction and application of the chemicals. Universities and government agricultural institutes in India are focusing on applied aspects (i.e., agronomy, product uses, marketing) of commercially developing neem.

Heliopsis Longipes

Heliopsis longipes, a perennial herb in the aster family, is native to Mexico. ***Heliopsis*** roots have been used locally in Mexico as a spice, medicine, anesthetic, painkiller, and an insecticide against warble larvae found in cattle wounds. Root extracts have also been effective against houseflies, mosquitoes, body lice, bean weavils, and other household and agricultural pests. The active ingredient has been isolated, identified, and prepared synthetically, but extraction is more economical than is synthesis. Some transplanting and cultivating experiments using wild plants have improved plant biomass yields. However, in spite of the succulent character of the roots, they dry out when exposed to air and will not grow when transplanted. Therefore, care must be taken when transplanting wild plants that the roots are kept moist or plants are replaced immediately.

Mamey

Mammea americana is an edible fruit-bearing tree found in Latin America and the Caribbean. The flowers, fruits, seeds, and leaves are effective against a wide variety of insect pests including melonworms, fleas, ticks, lice, fall armyworms, mosquitoes, and cockroaches. Two major insecticidal compounds have been isolated and identified, and methods to extract them have been developed. People have used the plant for many other uses, but no serious attempt has been made at export or commercial production. The wood is used in construction and cabinetmaking; the flowers are used to make a liqueur in the French Antilles; the fruit is eaten raw or is stewed and made into a drink or candles; and gum from the bark extracts chiggers from the feet, The tree is cultivated on Caribbean islands, and in Mexico and Central and South America for the edible fruit. ***Mammea's*** potential as a commercial crop in southern Florida, Puerto Rico, and the U.S. Virgin Islands should be investigated.

Basil

In addition to its widespread use as a spice, ***Ocimum basilicum,*** or sweet basil, is recommended for use against gastric disorders, malarial fevers and skin diseases, and for insect control. The oil from basil is an effective repellant and larvicide for mites, aphids, and most species of mosquitoes; a growth inhibitor for milkweed bugs; and an attractant for fruit flies. Most repellant compounds in the oil have been identified. The oil content of plants varies depending on soil fertility and weather immediately preceding harvesting. Because extraction is simple and inexpensive, synthesis is not commercially practical. The plant is cultivated easily and can be grown and its oil produced in many places in the United States.

Mexican Marigold

Tagetes minuta is an annual that is native to Central and South America but also grows in parts of East Africa, India, Eastern United States, South Africa, and Spain. The oil produced by the seed, leaves, and flowers is strongly repellent to blowflies and is useful in the Tropics as a blowfly dressing for livestock. The leaves are used locally in Africa and India to repel mosquitoes and safari ants. The oil is more toxic to mosquito larvae than DDT. The plant also has potential medical uses and the roots exhibit fungicidal and nematocidal activity. An extraction method for the essential oil has been developed. Although two larvicidal compounds and the growth deterrent can be synthesized, laboratory synthesis of several of the pesticidal compounds gives low yields and unreliable results. Because large-scale cultivation of the plant should be feasible, extraction of the essential oil seems to have the greatest commercial potential.

COMMERCIAL PRODUCTS FROM MARINE PLANTS

Marine plants are represented both by seaweeds, macroscopic forms that mainly live in shallow coastal waters, and by phytoplankton, free-floating, widely distributed unicellular plants. Although a few flowering plants (angiosperms) are abundant in shallow waters, the majority of marine plants are algae, typified by their lack of a vascular system. Taxonomically, algae are highly diverse. Their highly specific coloration has served as a basis of classification; marine algae are divided into at least 12 distinct groups based on color (e.g., red seaweeds, brown seaweeds, blue-green algae, etc.). While no precise estimate has been made, it is thought that well over 100,000 species of marine algae exist. Biogeographically, marine algae live in all parts of the ocean and frequently are found in extremely high concentrations. Although precise figures are difficult to substantiate, the primary productivity of 1 acre of the marine environment may be twice that of a Midwest cornfield.

Marine plants have evolved unique and highly specialized biochemical pathways to adapt to their unique seawater medium and survival pressures. The marine environment is rich in chloride and bromide salts and other chemical entities such as sulfate. Marine plants use these elements in biosynthetic processes to produce compounds that are unique to the marine environment. Many marine plants have evolved toxins and deterrents as protection against abundant and freely migrating predators. Even though the same evolutionary pressures have produced similar responses in terrestrial plants, the defensive chemicals from marine plants are novel and represent interesting new chemical species that are unprecedented in terrestrial sources. Other chemicals represent adaptations to the physical environment such as wave shock and motion. For example, complex polysaccharides (complex sugars) act to reduce the surface tension of seawater. These constituents, too, are highly specific to marine algae.

Marine algae have been used in different countries for a long time as sources of foods, food thickeners and flavorings, animal fodder, soil manure, potash, and herbal medicines. For example, “Nori” and “Wakami” have become integral parts of Japanese diets, and over 18,000 tonnes of Nori are commercially produced each year. Numerous species of marine algae are used in China as herbal medicines to treat many maladies ranging from intestinal problems to sunstroke.

A classical use for seaweeds has been the extraction of halogens and potash. Brown algae were used for several decades as the major source of iodine, and the red seaweeds were used occasionally for deriving bromine. The U.S. Pacific coast between 1910 and 1930 was the site of a flourishing potash industry based on the high potassium concentrations found in local brown algae. The uses of marine algae as sources for elemental halogens, potash, and crude food-thickeners largely were curtailed by the mid-1900’s as other, more cost-efficient sources were developed. But also during this period, many currently used algal products, particularly algal polysaccharides, became established.

A well-established industry in the United States now harvests marine seaweeds and extracts agar, carrageenan, and alginate. Agar is found in many species of red algae and is used mainly as a gelling agent and thickener *in* foods but also as a biochemical adsorbent, culture and nutrient medium for bacteriological research, and major nutrient medium for the industrial production of antibiotics. Carrageenan, which is also extracted from red algae, has widespread use within the food industry. The total annual market value of polysaccharides derived from red algae is about $200 million. Alginate, extracted from brown seaweeds, is particularly valuable for incorporation into industrial products and processes. It is used for its thickening, emulsion stabilization, and gelling properties.

Even though the majority of marine algal products come from the readily collected macroscopic forms, several products are being produced by the culture of unicellular forms. The green alga ***Dunaliella,*** for example, recently has been established in mass culture as a commercial source for glycerol (glycerine) and the orange pigment beta-carotene. Glycerol is used in the manufacture of many products (e.g., printing ink, antifreeze) and beta-carotene is used to impart color and provide vitamin A in animal feeds and human foods such as margarine and is also used as a sunscreen agent.

Several algal species have been used consistently in the biomedical sciences. In particular, active components of red algae ***Digenia simplex*** and various ***Chondria*** species are extracted, purified, and marketed as drugs in Asia. No other examples of successfully algae-derived pharmaceuticals exist, but there certainly is a great potential for further development in this area.

Even though relatively little ***basic*** chemical research has been performed on marine algae, mass culture techniques, both in the ocean itself and in controlled coastal facilities, have great potential to provide industrially significant quantities of marine algae. Funding from the Department of Energy (DOE) through the Solar Energy Research Institute (SERI) and several other agencies has supported work on requirements for effective algal growth. Marine algae probably will be a focus of considerable attention over the next decade as we investigate new resources for both energy and industrial product development.

Although relatively few algal products have been developed successfully by industry, the potential for the discovery and development of a plethora of unique new products seems unlimited. A few of the most notable areas for exploitation in the near future are summarized below.

Biomass Conversion

Work already has begun on assessing algae as sources of biomass for conversion to methane gas, ethanol, and other useful chemicals. Algae are efficient photosynthetically and are cultured conveniently in the open ocean, ponds, or controlled culture vessels. However, problems with fertilization of cultured seaweeds must be solved. Biomass conversion processes are not cost efficient, but continuing research is needed so that the technology will be available when required in the future.

Pharmaceutical Development

Although numerous biomedical uses for algal polysaccharides have been established, the majority of applications involve use of their physical properties rather than their physiological activities. A surprising percentage of algal polysaccharides, however, show antiviral activity. For example, a red seaweed extract contains an antiviral compound that is effective against ***Herpes simplex,*** a virus responsible for a disease that has reached epidemic proportions in the United States. Several substances with antibiotic and antitumor activity have been isolated from macroscopic seaweeds. Although few comprehensive studies of microscopic algae have been reported, some of these algae exhibit antimicrobial activities and are known to produce powerful toxins. However, almost no information exists on the pharmacological potentials of the tens of thousands of microscopic marine algae mainly because of the difficulty in purifying a single species of unicellular algae and growing it for biomedical studies. Much could be learned from such research.

The slow rate of developing new marine pharmaceuticals clearly can be linked to the limited involvement of the major pharmaceutical companies. Pharmaceutical firms do not have in-house expertise and marine biological laboratories in the past have not employed scientists with biomedical expertise. This is changing, however. Major programs have developed under the Department of Commerce's Sea Grant Program. The Sea Grant effort in biomedical development is an effective blend of academic and industrial (basic and applied) research that is yielding fruitful results. The Sea Grant project, "Marine Chemistry and Pharmacology Program, " at the University of California, for example, has discovered more than 75 pure compounds with potential biomedical use and the project has emphasized collaboration with the pharmaceutical industry. This collaboration is the vital link to ensure that basic marine research finds its way to the industry that is **capable** and **interested** in developing new products.

Other governmental agencies have had more limited involvement in marine biomedical development. For example, the National Cancer Institute has dedicated significant resources toward the isolation of new antitumor drugs. Here again, the need to involve basic marine scientists to locate, identify, and quantitate suitable marine species for study was underemphasized, and considerable difficulties were encountered.

Agricultural Chemicals

Many synthetic pesticides are halogenated compounds. Since halogenation is a natural process in marine plants, the compounds produced are likely to possess agrichemical activity. Initial collaborative investigations indicate considerable promise. Of 12 algal compounds assessed in herbicidal and insecticidal bioassays, 9 showed some activity, and 1 was nearly equivalent to DDT in insecticide activity.

Here again, the success in developing marine algal agrichemicals lies in developing a close relationship between academic and industrial research. A limitation on commercial development of marine extracts is that little Government funding is available outside of USDA. Agricultural research funding should be expanded in the United States to include a greater component of academic research.

Food and Food Products

In addition to agar, carrageenan, and alginate, marine algae are recognized sources of numerous useful food products, including cooking oils. Although the seaweeds usually are low in protein, many phytoplankton are rich protein resources. The blue-green algae are potential protein resources, and one blue-green algae, ***Spirulina,*** has already been marketed as a health food.

Enzymes

Marine enzymes, while almost completely unknown, could be used beneficially in industrial processes.

Industrial Chemical Feedstocks

Both macroscopic and microscopic marine algae could be cultured to yield hydrocarbon mixtures that could be used as diesel fuel without further purification. Other compounds found in most marine algae could be used in the plastics industry. Notwithstanding the work on agar, carrageenan, and alginate, phytoplankton, in general, have been virtually unexplored for their polysaccharide components even though it is highly conceivable that they could yield new and important products.

Needs for Developing Marine Algal Resources

Small-volume products, such as a specialty pharmaceutical, could be developed from naturally occurring populations but, in general, effective use of marine algal resources, especially unicellular algae which cannot be collected in pure form, must be coupled with mass culture technology. Mass algal culture and product derivation should be developed keeping in mind multiple-product development. The algal resources that should be considered for development are those that produce more than one marketable product to offset the relatively high production costs.

A basic problem in considering development of marine algal resources is that there has been insufficient research on potential products from algae. Although a significant number of chemical investigations have been conducted on seaweeds, there have been few on unicellular algae. Considerable resources are being devoted to developing algal-culture technologies, but generally these studies are not predicated on a solid knowledge of algal chemistry, genetics, nutrition, and reproduction. In addition, mass culture techniques must be refined.

Biotechnological advances, particularly in the field of marine genetics, can be expected to have sizable impacts on use of marine resources. Marine products and biochemical processes are unique, and this unique gene pool could be highly useful in future product development.

A significant problem lies in the poorly developed working relationships between Government, universities, and appropriate industries. Government funding agencies have difficulty supporting applied research, particularly as it may benefit a single private enterprise. The university system finds its relations with industry strained by patent and proprietary information problems. Close cooperation between these entities will be necessary, such as has been developed by the Sea Grant Program. As this tripartite collaboration develops, it seems likely that marine algal species will become major sources of future products.

ANTICANCER DRUGS FROM THE MADAGASCAR PERIWINKLE

Although literature sources cite 3,000 plant species used or recommended for cancer treatment in different parts of the world, only one species has been used to produce a commercial cancer-chemotherapy drug. This plant is the Madagascar periwinkle, ***Catharanthus roseus.*** It is an herb or subshrub found throughout the Tropics and cultivated as a garden plant worldwide. The development of the periwinkle anticancer drugs from isolation and purification of several ***Catharanthus*** alkaloids to laboratory and clinical testing and subsequent marketing of two of them represents a tremendous success story in the field of plant-derived pharmaceuticals. In the short time since first clinical use, these alkaloids have become two of the most valuable cancer chemotherapy treatments available.

The Madagascar periwinkle was one of 440 plants selected for study in an Eli Lilly plant-screening program for plant-derived drugs. The plants were chosen on the basis of carefully assessed reports of folklore use and reported alkaloid contents. Alkaloids, complex nitrogen-containing plant compounds, are often physiologically active. They are the most common active ingredients in many plant-derived medicinals. C. ***roseus*** was reported to contain alkaloids and folklore uses indicated that it contained biologically active compounds. Past use of the plant had been based on its blood-sugar-lowering properties, suggesting to Eli Lilly researchers that it might provide a substitute for oral insulin. When tested at Eli Lilly, however, the plant initially did not exhibit hypoglycemic activity but did show strong and repeated antitumor activity when subjected to an antileukemia model. Ironically, the periwinkle had not been one of the 3,000 plants cited as cancer treatments in reports of folklore use.

Standard isolation and purification techniques were not successful in extracting the antitumor agents from the plant, so new extraction methods were devised. Using these new techniques (selective extraction followed by column chromatography and gradient pH technique), Eli Lilly isolated 55 alkaloids from C. ***roseus.*** A total of 74 alkaloids, 3 of which were previously unknown, have been isolated from mature periwinkle plants, and 21 additional compounds have been isolated from immature plants. This extraction work and subsequent sterochemical research to determine the alkaloids’ chemical structures represent significant advances in the field of photochemistry.

Two of the periwinkle alkaloids that showed potential as antitumor drugs have reached the marketplace. These are leurocristine (LC)-whose generic name is vincristine and is marketed by Eli Lilly as ONCOVIN-and vincaleukoblastine (VLB)-known generically as vinblastine. Although LC and VLB are closely related chemically, they have different potencies against tumors because of minor differences in their molecular structure. Leurocristine, called a “miracle drug” because it was placed on the market only 4 years after initial discovery and is extremely valuable in cancer chemotherapy, was responsible for a resurgence of interest in plants as sources of antitumor compounds. LC is most effective in treating childhood leukemia of the lymph system; alone it can induce a 50-percent response rate in children with acute lymphocytic leukemia, and in combination therapy gives a 90-percent response rate. It is also effective against a variety of human cancer, including Hodgkin’s disease, breast cancer, and primary brain tumors. VLB is used mainly in treating lymph tumors, especially in Hodgkin’s disease patients. It shows a 70- to 80-percent response rate in patients with lymphoma, is highly effective against testicular tumors, and shows activity against various other cancers.

These two compounds and other dimeric ***Catharanthus*** alkaloids showing similar antitumor activity represent a new class of antitumor agents. Although their mechanism of action still is not completely understood, it seems to be based on disrupting cell division, thus arresting tumor growth.

Chemotherapy treatments have improved over the last two decades so that they are effective alternatives for or additions to radiation and surgery as cancer therapies. Much of the improvement in chemotherapy is the result of combination drug treatments in which various drugs with different mechanisms of action are used together. The periwinkle alkaloids are important in these multidrug therapies and have been key elements in the increasing sophistication of cancer treatments.

The potential of ***Catharanthus roseus*** alkaloids as medicines is by no means exhausted. A great deal of chemical work has yet to be done both on LC and VLB and on the other periwinkle alkaloids showing antitumor activity. One alkaloid that seems particularly promising and needs more research is leurosidine. Clinical tests for an experimental leukemia model in mice indicate that leurosidine is the most experimentally active ***Catharanthus*** antitumor alkaloid. However, the yields from periwinkle plants are low and high doses are needed for testing, so sufficient amounts of leurosidine for comprehensive clinical trials have never been stockpiled. Another compound that has not been fully investigated is an unidentified chemical called “super leurocristine” which displays 300 times more antitumor activity than leurocristine/leurosidine fractions. This was never clinically tested and the high cost to stockpile the active fraction for testing now is considered prohibitive.

Chemical derivatives of ***Catharanthus*** alkaloids also deserve additional research. Since slight chemical alteration may produce dramatic changes in dose-limiting toxicity of a compound, work on chemical derivatives may uncover potentially marketable compounds with more benign side effects than the original compound.

Another area that should be explored further is the conversion of leurocristine to vincaleucoblastine. The yield of leurocristine from periwinkle plants is 0.0003 percent, the lowest yield of any commercially used medicinal alkaloid. The yields of VLB are considerably higher, and since the chemical structures of the two are closely related, it maybe possible and economically beneficial to convert VLB into leurocristine. This conversion has been done successfully in the laboratory, but a great deal more work must be done before it can become a commercially viable operation.

Attempts to synthesize VLB and LC have been unsuccessful. This should continue to be a research priority. Until synthetic equivalents can be produced, the active compounds will have to be extracted from periwinkle plants. ***Catharanthus roseus*** plants were initially collected from the wild. As it became apparent that there would be a demand for thousands of tons of plant material, periwinkle cultivation began on farms in India and Madagascar. To avoid the risk that the supply of raw material might be cut off and to guarantee an uninterrupted supply of plants, cultivation was started in Texas.

The success of the work on the Madagascar periwinkle was dependent on two major factors: careful plant selection and the availability of an appropriate test system (an experimental mouse tumor) to monitor the effectiveness of purified active compounds. Plant selection was based on alkaloid content reported from folkloric use. Folkloric use can be a valuable indicator of the desired chemical activity if care is taken in interpreting the reports. If not, such reports can be misleading. Another method by which to choose plants for screening is random selection. The success of random selection could be improved by considering botanical and chemotaxonomic relationships between the plant to be tested and plants of known photochemistry and biological activity. An experiment mouse tumor served as an appropriate biological test system to monitor the purified alkaloids for the desired activity.

Perhaps the major lessons to be learned from the research and development (R&D) of ***Catharanthus*** alkaloids as anticancer drugs are that pharmaceutical drugs can be obtained from renewable resources rather than petroleum-derived synthetics and the developing new plant-derived drugs can be profitable. Despite the potential of plants for providing valuable new drugs and high profits to the companies developing them, U.S. pharmaceutical firms have eliminated their plant-screening programs and the Federal Government has discontinued its program for plant-derived anticancer drugs. * This disinterest is not because the potential for finding valuable drugs in plants has been exhausted. Only a tiny proportion of the Earth's higher plant species has been phytochemically screened, and these species represent a bank of potentially important drugs. As already mentioned, more than 3,000 plants have been cited as possible anticancer treatments, not to mention known activity of numerous other plants that could be valuable for other medical uses. This disinterest in plant screening for pharmaceuticals is not universal. The Germans, Japanese, Russians, and Chinese have major investments in exploring potential plant sources for pharmaceuticals and other chemicals. Perhaps the reasons for the neglect of this research in the United States should be examined and decisions to discontinue work reconsidered.

*See the paper by Farnsworth and Loub in the appendix,

STRATEGIC AND ESSENTIAL INDUSTRIAL MATERIALS FROM PLANTS

The United States depends on other nations for many materials and manufactured products important to U.S. industry, including agriculturally produced plant substances and mined materials. Some of these products are or could be agriculturally produced in the United States and used as industrial materials or as renewable replacements for petroleum as sources of feedstock in the chemicals industry.

Some industrial materials are classified as "strategic, " or critical to national defense. Three "strategic" industrial materials are castor oil and sperm whale oil, * which are high-quality lubricants, and natural rubber. Law requires that sufficient supplies of these materials be acquired and stored in the United States to meet national defense needs in case of war. "Essential" materials are those required

*The Endangered Species Act of 1970 prohibits production or importation of sperm whale oil so it is not stockpiled in the United States. A substitute for this high-quality lubricant must be provided. Jojoba is a promising substitute.

by industry to manufacture products depended on daily. Essential materials include items manufactured or extracted from plants (e.g., **waxes,** oils) and replacements for petroleum used as feedstock in manufacturing synthetic materials (e.g., plastics,. chemicals).

The United States imported an estimated $23 billion worth of agriculturally produced industrial materials and petroleum for feedstock during 1979. Average annual growth in imports for 1975-79 was 10 percent. The manufacture of synthetic organic chemicals consumed about 470 million barrels of petroleum as feedstock in 1978, valued at $15.1 billion. U.S. industry purchased nearly $2 billion worth of agricultural imports, $3.5 billion worth of newsprint and other paper products, and $2 billion worth of chemicals extracted from plants and petroleum.

Technologically, it seems possible to produce domestically nearly all the aforementioned imported agricultural products and materials and to substitute domestically produced agricultural products for the 470 million barrels of imported petroleum feedstock, with a net savings of about 270 million barrels of imported oil per year. Table 1 lists some of the potential domestic crops and what they might replace. Sufficient research indicates that their domestic production and use in the chemicals industry are chemically feasible, agronomically possible, and economically viable, although more agronomic and economic research must be undertaken before definitive conclusions can be drawn about their ***substitution*** feasibility. Production of only one-third the annual domestic demand for strategic materials would eliminate the need to stockpile them, could save at least $1 billion of public money over the next 18 years (otherwise spent in acquiring and maintaining strategic stockpiles of natural rubber and castor oil), and could provide replacements for sperm whale oil. Producing 100 percent of the strategic and essential industrial materials or their replacements might reduce U.S. foreign outlays by about $16.5 billion annually at constant 1979 dollars and demand levels.

Table 1 .—Potential Domestic Crops and Uses

Guayule
Cram be
Jojoba
Lesquerella
Veronia-Stokesia
Kenaf
Assorted oilseeds
Hevea natural rubber, resins
High erucic rape oil and petroleum feedstocks
Sperm whale oil and imported waxes
Castor oil
Epoxy oils
Imported newsprint and paper
Petrochemicals for coatings and other industrial products

SOURCE: Office of Technology Assessment.

Production of substitutes for one-third to one-half the industrial materials purchased abroad would demand about 60 million acres of cropland. The United States has about 413 million acres of cropland and about 36 million acres of pasture and other land in farms that easily and inexpensively could be converted to crop production. Another 96 million acres of land could be converted to crop production with more difficulty and expense. The Nation's total cropland base (land capable of sustained crop production under intensive cultivation by known methods) is therefore about 540 million acres. According to USDA, about 462 million acres of cropland will be needed in 2030 to meet domestic and foreign trade demands for food and fiber. This would leave 78 million acres of the cropland base to meet other production needs. If 60 million acres were used for industrial and strategic materials production, 96.8 percent of the Nation's cropland would be used.

The question of land availability must be examined carefully. The land resource base that will be needed or available for food, fiber, and industrial chemical crops over the long term will depend on certain unpredictable circumstances including international trade (e.g., level of export sales, price of petroleum); changes in land productivity; and quantity and quality of agricultural land being lost to urban development, water impoundments, etc. Another issue is the feasibility of converting farmland and land in other uses to the production of industrial crops. Lands currently in agricultural production could be converted to industrial crops more easily than uncultivated lands and lands owned or operated by nonfarmers. It would be largely a question of the economic tradeoffs of one crop against another. If a new crop is sufficiently more profitable than an old one, it probably would be planted. However, the scant amount of information on motivations of persons owning farmland that is not farmed indicates that much of this land is owned for esthetic, recreational, or speculative purposes and could not be shifted into agricultural production easily. In this case, putting these lands into industrial crops is not a straightforward economic issue. The land would have to be leased or sold to farmers, and this transferal of landownership or control could be a constraint to new-crop development.

Another land-related question that should be raised is whether a 100-percent" utilization rate of the agricultural land base is optimal. Serious thought should be given to possible land quality degradation, especially from cultivating marginal lands. Clearly, some agricultural lands could benefit from substituting a more ecologically suited crop for a traditional crop (e.g., crambe in areas marginal for corn or wheat), but care must be taken that increased use of the Nation's agricultural land base does not outpace development of appropriate cropping systems that minimize ecological degradation. In addition, the need for a land reserve that could be tapped in the event of unforeseen circumstances should be considered.

Current research on new crops is extremely limited. Only guayule, jojoba, and crambe are being grown on semicommercial scale acreages. Federal funding for research is greatest for guayule because of its importance to the military. However, the total *1981* public expenditures for guayule research totaled only $3 million. Research commitments to all other potential substitute commodities discussed here were considerably less.

Little additional basic chemical research is needed for these commodities. Chemical engineering to develop efficient, economical extraction and processing systems, however, is needed. Because of the present lack of risk capital in the private sector, public support of such research probably would be necessary if these plant materials are to be commercialized. However, in *1982,* the Office of Management and Budget imposed rigid guidelines governing Federal research and directed USDA to terminate any ongoing research of a commercial nature. Byproduct-use research also will be needed to assess commercialization potential. The value of byproducts is unknown because information on their potential uses is limited.

The greatest need for research on these potential commodities in the immediate future is in the areas of plant breeding and agronomy. Most of these new crop materials being grown in research projects are from wild or nearly wild plants. Genetic improvements are needed to increase seed and oil yields and predictability of the plant under cultivation. Little agronomic research has been done for potential new commodities other than crambe and guayule.

The economic benefits of using domestic production to replace agricultural imports and to substitute renewable agricultural materials for petroleum as feedstock in the chemicals industry depend on:

- the relative costs of substitutes and current sources of these materials,
- the degree of profitability in producing new agricultural raw material, and
- the level of subsidization required by the agricultural industry to meet national strategic and essential materials needs.

One study of the commercial feasibility of establishing a domestic rubber industry based on guayule estimated that the price for imported rubber and the costs of domestic production will converge in the late *1980's,* making it equally as attractive to produce the material domestically as to import it.

The primary consideration in substituting agricultural commodities for petroleum as feedstock in the chemicals industry is the price of petroleum. In industrial uses, seed oils could sell at a higher price per pound than petroleum without increasing the price of the final chemicals produced because these plants yield relatively pure chemicals that could be used with little processing. Extraction of the same chemicals from petroleum is complex and expensive. The economic viability of substituting agricultural commodities for petroleum cannot be assessed until semicommercial production and prototype-scale extraction are undertaken so that the values of the chemicals produced can be compared. Genetic improvement could make these substitutes more economically competitive.

During recent years, the Federal Government has spent between $7 billion and $14 billion annually to subsidize production of commodities that are already in surplus. If this subsidy were spent instead to encourage the domestic production of imported plant materials or to provide substitutes for petroleum feedstocks in the chemicals industry, the average subsidy on the 60 million acres required to reduce imports by half would fall between $116 and $233 per acre per year. If 60 million acres are used to produce such commodities, on-farm employment could increase by about 155,000 jobs. This also would generate indirect income and employment benefits to agriculturally related enterprises.

Evidence suggests that oil-conservation efforts in the United States and other importing countries already have had major dampening effects on world production and pricing. In the event the world oil price decreased as the United States switched to agricultural alternatives, the United States would have increased leverage with oil suppliers as long as its option to substitute agricultural commodities were kept open.

Domestic production of imported agricultural materials and petroleum substitutes would have foreign policy implications. Exporting nations would react unfavorably to U.S. import substitution, whereas other nations importing these materials would benefit from resulting lower prices. It would be important for U.S. domestic agricultural policy and U.S. foreign policy on import substitution to be consistent, and Federal policy makers would have to be cautious about geopolitical problems that might arise from Government support of import substitution efforts.

The key short-run issue for farmers, agricultural firms, and the Federal Government would be whether to subsidize production of new agricultural commodities instead of continuing to subsidize surplus production or support agreements to take land in surplus commodities out of production. Incentives for consumers of intermediate industrial materials and end-products to support substitution of domestically grown commodities would be lower cost, assurance of continued supply, and decreased price fluctuations.

Four domestic policy shifts would be needed to move toward domestic control and production of strategic and essential industrial materials:

1. from dependence on foreign nations for agriculturally based strategic materials to domestic supply of them;
2. to a national policy of encouraging agricultural research that has foreseeable commercial application, including participation with the private sector in commercialization activities, partly research and partly commercial in nature;
3. to spend Federal funds to support production of useful agricultural commodities rather than supporting production of surplus commodities or pay for farmers to discontinue production; and
4. to look at domestic production of agriculturally produced materials as a way of using our farm-production potential rather than depending on foreign trade.

Sufficient resources should be committed to the kinds of activities suggested hereto use or discard, with just cause, the many development options that exist for domestic production of imported strategic and essential industrial materials.

INFORMATION USEFUL TO PLANT-DERIVED DRUG PR0GRAMS

Higher plants are essential ingredients of a large proportion of U.S. prescription and over-the-counter drugs. From 1959 to 1973, new and refilled prescriptions containing plant products represented 25 percent of all prescriptions dispensed from community pharmacies in the United States. The dollar cost to the consumer for prescriptions containing active ingredients from higher plants was $1.6 billion in 1973. Adding an almost equal amount to this figure for plant-derived drugs dispensed from other outlets (e.g., out-patient hospital pharmacies, extended care facilities, Government hospitals), an estimated total cost to the consumer was $3 billion in 1973. The current annual cost to the consumer for plant-derived drugs is estimated to be at least $8 billion. In addition to the prescription drugs, the sale of herbal teas in the United States is estimated at about $200 million annually, and the sale of over-the-counter (OTC) drugs obtained from plants is probably at least $1 billion.

National Prescription Audit (NPA) data show that 41 species of higher plants yield all of the plant-derived prescription drugs. An additional 62 species of plants entered the prescription market in the form of crude extracts with active principles. Less than 50 pure compounds from plants were represented in the prescriptions analyzed. Virtually all of these compounds are produced commercially by extraction of plant material or by chemical modification of extracted plant compounds. Although most of these drugs have been synthesized, synthesis is not commercially feasible, with few exceptions.

Although much has been written in scientific journals of this country and abroad that should spark industrial interest to invest in research on plant extracts, interest in this country has declined. In 1974, the American pharmaceutical industry's total research and development budget for pharmaceuticals for human use was $722.7 million, Only one firm was involved in direct research to explore plants for new drugs with an annual program budget less than $150,000. Today, there are no U.S. pharmaceutical manufacturers involved in a research program designed to discover new drugs from higher plants.

Of the developed countries, only West Germany and Japan pursue development of new plant-derived drugs. West German studies are supported by many small firms but have not captured the interest of large pharmaceutical companies. Japanese academicians receive government and industrial support for research on plant drugs, and Japanese pharmaceutical firms have major research departments dedicated to the same goal. Scientific papers from Japanese research laboratories relating to drug-plant development outnumber those from the United States by at least tenfold, and Japanese patents for plant-derived biologically active substances outnumber those from the United States by a factor of at least 50.

Plant sciences have not had a voice in U.S. corporate or high-level governmental decision-making, except in the area of basic agriculture. Important decisionmakers connected with drug development apparently are unaware of the extent to which plants contribute to our source of drugs. During the past three or four decades, research administrators rarely have been trained in plant sciences. Further, science has advanced to a point where interest has not been on the intact organism—plant, animal, or microbe—but rather on the cell, cell contents, and cell biochemistry. Typical industrial drug development increasingly has involved synthesis of molecules based on structure-activity relationships, and natural product drug development has been restricted to antibiotic production by micro-organisms.

Most useful drugs derived from higher plants have been "discovered" through scientific inquiry into alleged folkloric claims of therapeutic effects, although in recent years the random collection of plants followed by pharmacologic evaluation has been pursued. A major program of the National Cancer Institute (NCI) involving the "screening" of plants randomly collected worldwide ended in late *1981*. This program, which was started in about 1956, tested some 35,000 species of plants for antitumor activity in laboratory animals. Although a large number of highly active agents were discovered by the NCI program, some remain to be studied in humans and as yet none have been approved for use in humans by FDA.

Industry's development of useful drugs from higher plants during the past 30 years has not been more productive than Government efforts. Since 1950, pharmaceutical companies have produced only three plant-derived drugs that have reached the U.S. prescription market: reserpine, vincaleukoblastine, and leurocristine. * The total number of industry research dollars required to discover these drugs has been miniscule compared with the cost of placing synthetic drugs on the market. One reason for this might be that much of the unexplored flora in the world is found in tropical or semitropical developing countries that may be regarded as unstable supply sources for an international market. However, another country might serve as a source of wild plants or plant supplies may be obtained through cultivation or other techniques (e.g., tissue culturing). A second reason industry cites for lack of screening and plant-drug development is that patent protection is less secure with natural products than with synthetics. There is little evidence to back up this claim.

Data of value in organizing and implementing an effective plant-derived drug development program are difficult to obtain through available online drug data bases or from published reports. In addition, much of the useful pharmacological data on plant extracts were published prior to the earliest data covered by all available online data bases. Pharmaceutical companies are reluctant to share data derived from testing plant extracts, even if the data are negative and are of no commercial interest to the firms. Negative data are as important as positive data in a broad plant-based development program; knowledge of past negative research can help other researchers in selecting new plants for study without duplicating past work. NCI published negative data regularly at the beginning of the plant screening program, but this soon ended.

If plants to be screened for a plant-derived drug program are not to be screened randomly, they should be chosen on the basis of best available information (table z). Information sources will vary, but probably would include:

1. *Ethnomedical* data—anthropological writings, folkloric writings, popular books, pharmacopoeias, etc.;
2. *Experimental data on* plants—abstracting services (e.g., *Chemical Abstracts),* bibliographic online data bases, review articles.

After collection of available pertinent data, drug development programs proceed through:

- plant collection,
- bioassay for evaluation of crude plant extracts,
- isolation and identification of biologically active chemicals from plants, and
- clinical evaluation and marketing.

Few pharmacologists are experienced in evaluating crude plant extracts or are interested in developing bioassay systems outside their own area of interest. Even though a program is designed to identify only one or two types of

*See paper by Svoboda in the appendix.

Table 2.—information To Be Included in a Data Base for Drug Development From Plants

Plant characteristics: Latin binomial effects claimed; common names; place of collection; geographic range; parts of the plant studied.
Ethnomedical uses: Crude plant material or type of extract used to prepare the dose; dose employed, administration, and dosage regimen; beneficial effects claimed; side effects reported.
Chemical constituents: Part of plant in which specific constituent is present; range of percentage yield of the chemical; data on seasonal or other variations in chemical quality or quantity.
Experimental testing: Type of solvent used to prepare extract; type of test (in vitro, in vivo, human study); test species (e.g., rodent, primate) and status; dose and route of administration.
Other information: References to compounds that have been partially or completely synthesized; studies of cultivation; effects of cultivation, processing, and storage on yield of useful active constituents.

SOURCE: Office of Technology Assessment.

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biological activity, it would be cost-ineffective not to carry out as many bioassays as possible. Routine techniques are available for isolation and purification of active principles after bioassay-directed plant fractionation to enrich the biological activity; however, most existing compounds could not be separated economically from plants using the more sophisticated procedures. Efforts should be made to use simplified procedures so that high extraction costs do not prevent commercial development. Clinical evaluation is expensive and complicated, requiring evaluation at several stages by FDA. The estimated total cost for developing a new drug depends on the costs for clinical testing, but would fall between $5 million and $35 million.

Ten computerized online data bases have information useful to a plant-derived drug development program (table 3). All but one are unable to compare, correlate, or analyze research data analytically; they are solely bibliographic. Ideally, one would desire a nonbibliographic file that could list and, by computer, compare or correlate real data contained in pertinent citations, then present the data in a digestible tabular form providing the citation sources. In 1975, NAPRALERT (Natural Products Alert) was initiated to overcome the difficulties in using existing files for developing research projects associated with natural products and drug development.

Approximately one-third of the citations now computerized in NAPRALERT represent retrospective searches of literature from the early 1900's to the present. The remainder cover current information. In addition to bibliographic information, NAPRALERT records the chemical constituents and pharmacological bioassay information from plant, microbial, and animal extracts. The accepted and synonymous nomenclature of the organism, the parts of the organism used in the study, and the geographic source of the material are important elements of the data base. NAPRALERT also records ethnomedical or folkloric notes as they are encountered in the literature.

This data base can be used to systematize random screening of plants through organized computer search and analysis of data to pro-

Table 3.—Data Bases Pertinent to Drug Development

Name	Developer	Contents
Agricola	USDA	Agricultural chemistry and engineering, food and plant science, nutrition and related agricultural fields
BIOSIS PREVIEWS	Biosciences Information Services	Life science for microbiology, plant and animal sciences, experimental medicines, agriculture, ecology, pharmacology, biochemistry, biophysics
CAB	Commonwealth Agricultural Bureau of England	Compilation of 20 agricultural science data bases; includes plant and animal breeding abstracts, plant pathology, nutrition, entomology, related fields
FSTA	Food Sciences and Technology Abstract	Agricultural chemistry, food science, home economics, patents
CACON	Cacon Chemical Abstracts Condensate	Most life sciences and physical sciences
MEDLINE	National Library of Medicine	Life sciences and/or medical information
IMEPLAM	Mexican Institute for the Study of Medicinal Plants	Natural history and folkloric claims for Mexican plants
—	Chinese University of Hong Kong	Retrospective and current literature citations and brief abstracts of Chinese publications on traditional medical practices
NAPRALERT	University of Illinois	Bibliographic information; chemical constituents; pharmacological bioassay information; plant names, parts and geographic source; ethnomedical information

SOURCE: Office of Technology Assessment.

vide a ranked list of the more probable candidates for study. Such a method using NAPRALERT was tested for a WHO Task Force assembled to identify indigenous plants potentially useful for human fertility regulation, identifying approximately 4,500 plants based on folkloric claims or laboratory experiments. Three hundred were identified as most promising for study through folklore information, pharmacological, and geographic data. Fifty have received preliminary laboratory investigation, and eight have confirmed activity but have not undergone clinical testing yet.

NAPRALERT has the capability to present in one computerized report all published information on folklore uses, biological activities (in vitro, in animals or humans), and chemical constituents. Together these data may suggest areas for research on new uses or applications of a specified plant or group of plants. They can also be used effectively to assess potential dangers or to suggest safeguards that should be employed when using certain plants.

While plants already are important ingredients of U.S. pharmaceuticals, they could be potential sources of many new chemicals for the drug industry. Despite this potential, pharmaceutical companies have discontinued plant-drug development programs. One reason they give for their disinterest is the high cost of developing a new drug. Any means of systematizing plant selection for screening by making data on past research and folklore use readily available would decrease research time and improve the chances of discovering a marketable drug. Ten automated data bases exist that can provide such information useful to drug development programs. NAPRALERT is the only nonbibliographic file and represents a unique data retrieval system of great potential value to drug development work.

USDA'S DATA BASE ON MINOR ECONOMIC PLANTS

The world has thousands of minor economic plant species which potentially are as important ecologically and economically as the dozen major agricultural species. There is an overwhelming number of climatological, pedological, anthropological, latitudinal, and biological variables associated with these minor species. The Economic Botany Laboratory (EBL) of USDA is trying to gather such data on these potentially useful species.

Seven data base files and their subsets are or have been online, and three prototype files have been developed. The online files can be linked to each other through scientific names to provide more complete information of species' characteristics. But funding has declined for this service in recent years; some files have been taken offline and others have ceased to grow with increases in available information.

Data Base Files

Ecosystematic File incorporates data from over 1,000 questionnaires mailed worldwide to scientists and extension people, intentionally emphasizing developing countries. Within 2 years some 500 people responded, sending published and unpublished ecosystematic data (annual rainfall, annual temperature, soil type, soil pH, elevation, etc.) on 1,000 species of economic plants, weeds, and nitrogen-fixing species. Each species in the file is recorded with the name and address of the reporting scientist(s), thus providing opportunities for more specific followup.

Yield File includes data from the questionnaires and from publications of experiment stations. The entries probably account for less than 1 percent of the yield data published annually by experiment stations. With increased funding, the data in this file could be increased, thus providing a means to compare yields of exotic crops (with various inputs) in ecologically similar areas.

Climate File includes monthly temperature and rainfall means for about 20,000 stations worldwide and the elevation of most of these localities. This file is the computer tape of Wernstedt's World Climatic Data, supplemented by information from publications and the questionnaire sent out by USDA. A continentality variable that compensates for seasonal temperature extremes of continental sites has been added to the file. This helps differentiate among climates with similar mean annual temperatures but different vegetational potential. A species' ecological amplitude can be determined by using this file in conjunction with ecological data for geographical areas from which the species is reported.

Where no data on climate are available, the presence of weed or plants with known ecological amplitudes of temperatures and rainfall can help predict climate in remote areas. Data on weeds' climatic amplitudes were added to this file under the Ecological Amplitudes of Weeds program. Another use of the Ecological Amplitudes of Weeds program is in mapping the potential for an alien weed to spread in the United States. Climates favorable to the spread of a weed can be located by determining ecological amplitudes of a weed through consulting its distribution and extracting climatic data from the Climate File.

EBL has formulas for converting its 20,000 climatic data sites into Holdridge life-zone maps for countries not now mapped in the Holdridge system. Standing biomass, total carbon, and annual productivity of the zonal forests can be projected from this information, giving real or projected yield figures for high-biomass grasses, energy-tree plantations, or conventional crops. This could provide some guidelines for choosing the best crop-agroforestry combinations for agricultural development in Third World countries.

Nutrition File includes at least one credible entry for each plant species in Food Composition Tables for East Asia, Africa, and Latin America. The plant's nutritive contents (elements, vitamins, calorie, and fiber content) are ranked extremely low, low, high, or very high relative to USDA's recommended dietary allowance (RDA). The Nutrition File (as-purchased proximate analysis or zero-moisture analysis) can be linked through a species' scientific name to the Yield File to convert yields of grain per hectare to yields of protein per hectare, and to the Ecosystematic File to show which will yield the most leaf protein per hectare under any specified combination of annual temperature, annual precipitation, soil pH, etc.

Ethnomed File was compiled to encourage Third World countries to supply medicinal and poisonous plants for a collaborative screening program with the U.S. National Cancer Institute. With 88,000 entries, the Ethnomed File is probably the largest extant computerized data base for folk cancer remedies. The file also covers general folk remedies and pesticidal activities. Ethnomed no longer is online but survives as a much consulted printout.

Prototype Data Bases

Agroforestry File includes different subfiles containing information on ecological parameters, germination requirements, nutrition values, cultural requirements, yields, wood characteristics, use, and plant pathology for several species considered for agroforestry. Perhaps the prototype file's greatest impact was to show that almost no data were available on most nonconventional economic plants.

Pest file has only about 2,500 entries listing the scientific name of the host plant, the plant part affected by the disease of insect, and the name and type of pest. Although this information is useful for predicting pest problems if the pest is known to be in the area chosen for introduction, it does not help predict the possible presence of the pest on the site. If the file were expanded to provide data on the ecological amplitudes of pests and diseases, it could help avoid or reduce the risk from pathogens or pests. This could launch a new phase in biological control of pests' "biological evasion." For example, where the host tolerated more cold than the pests, planting in the colder area might be advantageous.

Intercropping lists major and minor crop combinations, all species in pasture mixes, yield data, yield differentials, and cultural and other variables. By using the scientific names to link this and other files one could find out which crops have been tried around the world as intercrops. In densely populated Third World areas, intercropping clearly promises more quality, quantity, and/or variety of crops per hectare than monocropping.

Limitations to the application of the EBL data compilation program exist. In intermediate ecotypes, the effects of factors such as slope, soil porosity, soil type, vegetation cover, cultural conditions, insolation, prevailing winds, etc., on plant characteristics maybe significant. Few data are available and some of these variables are entered for only a few places. The 20,000 sites for which there is climatic data are not classified under a single soil-classification system. This prevents correlation of plants' ecological tolerances based on soil properties.

A major program would be needed to collate the Food and Agriculture Organization and/or USDA soil units with the 20,000 climatic data sites, soil pH, weeds, crops, yields, diseases, insect pests, and native perennials. This could be done for a large number of the 20,000 sites. This "International Plant Utilization Data Base" would develop ecological amplitudes and means and determine optimal conditions for all the economic species of the world and their pests and pathogens. Ancillary to this could be the development of an economic data base that includes transportation costs, shelf life, world demand, trends in production, and current price of a species. Crops that make the most sense economically then could be chosen from the many crops ecologically adapted to the area. Experimental data resulting from trials would be used to select the right species for that particular area and to augment and refine the data base. This capability of matching crops to their most suitable environment would be extremely valuable for use in both the United States and in developing countries. It would assist significantly in agricultural planning programs sponsored by international development agencies by suggesting best crop options for target environments. Use of the EBL data base could minimize crop-development efforts in environments that are marginal or unsuited to the crop species and help avoid or reduce the use of costly or ecologically disruptive agricultural inputs (e.g., energy, water, agricultural chemicals). In addition, it could help reduce the risk of spread of disease and pests.

Such a data base could select species best adapted to a given climate for whole-plant utilization schemes in which food, oilseeds, leaf-proteins, chemurgics, drugs, etc., would be the main products and biomass would be an energy-producing or commercial fiber byproduct. Greater plant use becomes more important as petroleum supplies—for energy and for transportation of products—become more scarce and expensive.

Without renewed funding these data bases have a short life expectancy. The cost of maintaining the files online is at least $10,000 a year before any programs are run on the data. USDA is a constant user; daily, scientists consult the hard copy generated by the EBL data base to answer questions on agronomy, agroforestry, climate, ecology, ethnomedicine, nutrition, pathology, and utilization. Many other U.S. Government agencies have benefitted from the files and could reduce future costs by consulting them.