OCCASION

This publication has been made available to the public on the occasion of the 50th anniversary of the United Nations Industrial Development Organisation.

DISCLAIMER

FAIR USE POLICY

CONTACT

Please contact publications@unido.org for further information concerning UNIDO publications.

For more information about UNIDO, please visit us at www.unido.org

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
Vienna International Centre, P.O. Box 300, 1400 Vienna, Austria
Tel: (+43-1) 26026-0 · www.unido.org · unido@unido.org

D00500

United Nations Industrial Development Organization

Distr.
LIMITED

ID/WG.37/15
16 January 1970

ORIGINAL: ENGLISH

Expert Working Group Meeting on the Establishment of Pharmaceutical Industries in Developing Countries

Budapest, 4 - 10 May 1969

ACTIVE PRINCIPLES, DRUGS, PHARMACEUTICAL INTERMEDIATES AND PHARMACEUTICAL PREPARATIONS EXTRACTED OR PREPARED FROM BOTANICALS, ANIMAL ORGANS, AND AGRICULTURAL RESIDUES 1/

by

Gyula Horváth
Union of the Hungarian
Pharmaceutical Industry
Budapest - Hungary

1/ The views and opinions expressed in this paper are those of the author and do not necessarily reflect the views of the secretariat of UNIDO. This document has been reproduced without formal editing.

Historical background

Since the earliest beginnings of human civilization, nature has been an inexhaustible source of medically valuable substances that provide useful additions to the weapons for the fight against pain and disease. As witnessed by a great many historical finds, observant and reasoning man has discovered ages ago that some plants, and animal organs can be usefully applied in the art of healing. Those who, in antiquity, practised medicine used quite a number of plants, and animal organs.

In the reign of the great pharaoh Djoser of the Ist Dynasty (2773 B.C.), Imhotep, the physician later raised to divine rank, used a variety of natural substances for medical purposes. In the time of the IVth Dynasty (2723 - 2563 B.C.), the court physician Iry gained great fame. Several medical schools flourished in Egypt; the clergy cultivated gardens full of medicinal herbs; medicine as well as the science of embalmment were raised to rare perfection.

The Ebers papyri (1555 B.C.) list 900 prescriptions in which radish, onion, garlic, saffron, pepper, cardamom, ginger, aniseed, caraway, fennel, pomegranate, linseed, senna-leaf, lotus, castor oil plant, thyme, [illegible], and [illegible]poppy figure as healing ingredients. Leeches, mandrake, hyosciamus, brewer's yeast were known; the excrements of pelicans, gazelles, crocodiles, and children were used in medicaments.

Among others, also Flavius Clemens of Alexandria (A.D.200) makes mention of the high level of medical sciences in Egypt;

and points to the six of the forty-two sacred and secret books of Egyptian priests as dealing with medical knowledge and the science of healing.

Around 2100 - 2200 B. C., an unknown sumerian doctor in Babylon has recorded in cuneiform script upon clay tablets more than a dozen prescriptions in which thyme, and asa foetida, among others, are the active substances.

Later Assyrian tablets mention reed, onions, garlic, mandrake, lotus, saffron, thyme, caraway, deadly nightshade, Indian hemp, linseed, human faeces, excrements of gazelles, urine of she-asses, testicles of dogs as medicinal substances of vegetable, or animal, origin.

In India, Vedic medical science has prescribed medical herbs since time immemorial. The Susruta-Samhita, collected between 800 B.C. and A.D. 400, contain 760 prescriptions mostly with ingredients of vegetable origin. Tsharaka-Samhita, dated at around A.D. 100, describes 500 plants with healing properties, rauwolfia among them which it designates "the moon".

Shen-nung Pen Tsao is held to be the earliest written remains of a very highly developed Chines medical science. Ancient medical knowledge of the Chinese is contained in the 52 tomes of the Pen Tsao Kang Mu, published A.D. 1597; there 1892 medicaments are described. Among others, Ephedra sinica, ginseng, chaulmoogra oil are mentioned, the last as a medicine for leprosy. As far as history goes back, Chinese physicians prescribed pig's blood or pig's liver as a treatment of anaemias.

In Mexico, the medicinal men of the Aztec and Maya peoples widely used sarsaparilla as a diuretic, peyotl cactus that contains mescaline, powdered tobacco, cocoa beans, the fungus Nanacatl, and the red beans of the Colorines plant as an aphrodisiac.

Peruvian Inca medical science applied peruvian balsam i. e. the oil of Myroxylon peruiferum; for malaria it prescribed the bark of the Quina-quina plant which is not the Cinchona tree: as a laxative the fruit of Uill-Cautari plants used to be given, for diarrhoea Ratantici bark was taken, and the leaves of the coca plant were also used.

The pharmakopeles, or herb-collector, used to be an honoured person in ancient Greece; Aristoteles (born 384 B. C.) was about to become one. Hyppokrates who lived in the IVth century B. C, has left us a valuable scientific treatise on vegetable drugs. Theophrastus, born in 371 B. C., the founder of botany, was also a Greek. In the IInd century B. C., toxicology has been carried to scientific pertection by the Greek.

Dioscorides (Ist century B. C.), of Greek extraction, was one of the famous doctors of the Roman Empire. Pliny the Elder (A. D. 23) has reported the preparation of a number of medicaments, among them that of plasters, and ointments, and mentions aconite as a notable poison. In these times the use of strophantus as an arrow poison was well known. Galenus, who lived in the IInd century, acquired great fame, and has become the eponym of a particular branch of dispensing and medicaments, viz. of the galenical preparations.

In the VIIIth century, the Greek Hellodoros, and the Arab Djafar became famous. Basilius Valentinus (XVth - XVIth century) used

to study experimentally the effects of the medicines he prepared by administering them to his patients and thus can be regarded, no doubt with some exaggeration, as the founder of the science of clinical pharmacology. Paracelsus (born A. D. 1493) has provided some part of the chemical foundations of medical science.

Research, justly claimed to be scientific, in the domain of natural substances began to flourish in the XIXth century. A number of active substances of vegetable, and of animal, origin were then isolated; the fermentation industries that have progressed enormously since were then given their scientific foundations by Pasteur. A long list can be made of the alkaloids then discovered: morphine, by Seetürner, in 1806; xanthine, by Marcet, in 1817; strychnine, by Pelletier and Caventou, in 1818; brucine, by Örstedt, in 1819; solanine, by Defosses, in 1820; caffeine, by Runge, in 1820; nicotine, by Posselt and Reimann, in 1828; atropine, by Mein, in 1831; codeine, by Robiquet, in 1832; theobromine, by Voskresensky, in 1842; cocaine, by Nieman, in 1860; pylocarpine, by Hardy, in 1875; hyoscine, by Ladenburg, in 1880; ephedrine, by Nagal in 1887; scopolamine, by E. Schmidt in 1888; mescaline, by Heffter, in 1896; lobeline, by Wieland, in 1921. Stoll's results in the domain of the foxglove glucosides and of the isolation of ergot alkaloids proved to be fundamentally important. The method of producing great quantities of ergot by artificial infestation is due to the Hungarian Békéssy. Kabay, also a Hungarian, worked out a method, in 1927, for the extraction of opium alkaloids from the dry poppy head. From the point of view of the manufacture of steroids, the scientific results concerning diosgenine, hecogenine, and solasodine, are of great moment.

Nor was the progress in the field of drugs of animal origin less spectacular. In the second half of the XIXth century the bile acids were isolated (Gmelin, Thenard, Berzelius, Liebig, Mylius, Diels, Wislicenus); adrenaline was discovered by Takamine in 1901; heparine by Howell and McLean, in 1918, and insuline by Banting, and Best, in 1921. By the discovery of the sexual hormones and the corticosteroids in the thirties and forties, some very valuable substances have been added to our stock of medicaments. The discovery, by Rickes et al. and by Smith, in 1948, of vitamin-B_{12} has been also of great moment.

This brief historical survey cannot be bit very sketchy and arbitrary indeed, since the scope and purpose of this paper would not allow a full treatment of the brilliant results of medical and chemical research.

Raw material basis for biologically active natural substances, its particular significance for developing countries.

Nature, notably its world of plants and animals, is an inexhaustible treasure-house of a variety of medically utilizable substances. When utilized to the purpose, this fund of primary substances offers specially advantageous possibilities in great parts of developing countries, first of all in those which are situated in tropical or sub-tropical zones. These regions, where at present 72 per cent of the human race lives and where by 1980 more than 80 per cent of it will live, proffer important advantages over countries in the temperate zones, for the procurement of medically useful natural primary substances. A significant number of the known medicinal herbs grows in these regions exclusively, and there are many which are to be found, or can be made to grow, also here. The following are the medically import-

ant plants peculier to these regions.

Asia Minor. Gall, opium, salep, tragacanth.

Arabian Peninsula. Coffee, myrrh, olibanum, senna.

Western Asia. Asa foetida, cinchona, opium, pyrethrum.

East India. Aloe, areca nut, Indian hemp, cassia, cardamom, catechu, cinchona, coca, croton, cotton, ipecacuanha, kamala, sacca, pepper, rauwolfia, senna, strychnos, zeodary, zingiber.

Ceylon. Cocoa, cardamom, china, cinnamon, coca, coffee, tea.

South-East India. Gum benzoin, catechu, pepper, strychnos.

Malaya. Gum benzoin, cocoa, clove, cluna, coffee, cubeb, myristica, pepper, vanilla.

North-Africa. Centaury, [illegible], coriander, euphorbia, [illegible], opium, sandarac, scilla maritima, senna.

East Africa. Aloe, clove, coca, coffee, myrrh, olibanum, strophantus, vanilla, zeodary, zingiber.

Western Africa. Coffee, cola, cotton, physostigma, strophantus.

Central America. Peruvian balsam, jalap, sabadilla, Jamaica smilax, vanilla, dioscorea.

West Indies. Aloe, cocoa, coca, coffee, quassia, zingiber.

South America. Copaiva, tolu, ipecacuanha, quassia, china, coca, condurango, quillaja, ratanhia, cocoa, herba mate.

The developing countries do not lack raw materials of animal origin either. These become available chiefly in the course of the processing of farm animals, but it should be possible to organize the production of medicaments specially from snake venom or from agricultural raw materials and agricultural residues. Organs mostly of mammals of higher order will be processed, but in maritime countries also organs of fish may yield valuable basic substances. Thus, for instance, from the liver of a number of species (Hippoglossus, Thymnus vulgaris, Sarda chiliensa,

Germo alalunga, Xiphias gladius, Stereolepis ishinagi, Thunnus thynnus) vitamin-A concentrate can be manufactured.

The various organs of farm animals (cattle, pig, sheep) are those most suitable for being processed by the pharmaceutical industry. The organs, or animal products, most often collected and processed are the following: liver, lung, [illegible] and intestines, pancreas, blood, urine, bone marrow, wool, thyroid gland, pituitary gland, testicle, heart.

Generally, in most of the developing countries in the tropic or subtropic zones the plants of medicinal importance grow wild. However, some of the more important ones are cultivated in plantations. A task of prime importance would be a scientific mapping of the stock of medicinal herbs to be found growing wild. In the course of such a mapping morphological identification and a rough estimate of available quantities are indispensable. For an evaluation of the availability of raw materials of animal origin, national data about quantity and quality of livestock, and the yearly number of commercially slaughtered animals ought to be known. From the point of view of processing, only organs expertly collected in up-to-date slaughter houses with a cold-storage plant can be taken into consideration.

Only a qualitative survey of agricultural residues needed for pharmaceutical manufacture is generally necessary since, as a rule those substances are available in quantities far greater than required.

After the assessing of raw material supplies, a preliminary analysis of the market situation and of economic efficiency must be carried out with respect to smallest profitable volume of manufacture, prospective home consumption and foreign sales. This analysis should include the costs, sometimes rather high costs, of the collection, transport, and storage of the starting materials.

Collection, and handling, of raw materials of natural origin are extremely

labour-intensive operations which can be tackled to great advantage by developing countries with a high proportion of redundant manpower.

Required organizatory measures for the collection, handling, and storage of starting materials.

Collection, handling, and storage of raw materials of vegetable origin on the one hand, and of animal origin on the other, require different methods or techniques, therefore these will be dealt with separately.

Most of the plants used in medicine, grow wild. Their collection is an additional source of income for the agricultural population. The organization of collecting requires careful and persevering work. Since the useful parts of the plants must be clean and of good quality else they cannot be processed, those charged with their collection the correct techniques must be learnt, and can be by demonstration. It is not enough that the plants should be correctly identified, that their useful parts be collected in a workmanlike manner, also the best ways of handling the material so collected, and how to dry and how to store it, must be fully understood. Quality depends also on the place of growth and the time of harvesting. Special care must be taken in the case of the collection, drying, and storage of toxic plants. Generally, not more of the raw parts of plant should be collected at one time than can be prepared for drying on the same day, because during storage in the raw state heat will generate in the plant heap and this will cause great damage in it.

As a rule, roots will be gathered either at the beginning or at the end of the growth season of the plant. Barks are collected usually

at the beginning of this season. Leaves are best picked before the efflorescence of the plant, and buds before their unfolding. Fruit, or seed, are collected when ripe.

A network of inspectorates or collection depots needed for the collection of medicinal herbs to be processed [illegible] or station supervisor must be in possession qualified to train and instruct the gatherers employed in his district.

Usually the people who collected also dry the plant material, this they do by natural means. Some parts of plant can be allowed to dry in direct sunlight, but there are others that must be dried in a shaded, covered and adequately ventilated place.

For the drying of plant delivered in great quantities collection stations could be provided with the necessary apparatus which will mostly consist of dryers operated by heating. Duty of the inspector is to check the identity and exterior of the plant material delivered, to procure adequate facilities for storage and transport. Pharmacists, nursing staff, teachers are especially fitted to act as inspectors or station supervisors. The collection of harmless, non-toxic plant material could be organized very usefully for school children under supervision by their teachers.

The demand for plant material usually processed in great quantities cannot be met by collecting plant that grow wild. Consequently these are then cultivated in plantations. The most important among these are the various species of cinchona, coca bush, [illegible], [illegible], castor oil plant, pennyroyal, capsicum, valerian, tea, coffee, cocoa, poppy, mustard, datura stramonium, hyoscyamus, lavender, chrysanthemum, etc. Cultivation in plantations must be directed by an expert since it involves the growing, handling, drying, and storage of plant material

on a commercial scale.

For the storage of collected herbs, both at the collection station and at the manufacturer's, air conditioned store rooms of great capacity should be available. Owing to their low weight per volume ratio, for the transport of collected plants a rather substantial rolling stock will be needed.

The collection of animal organs can be undertaken by slaughter-houses only. The treatment of the organs collected must be carried out according to certain specific measures in order to prevent as far as possible the enzymatic degradation of the active substances. After the animal is killed, the organ that provides the raw materials of a pharmaceutical preparation is cut out with appropriately fashioned tools, and separated from foreign tissues, by a skilled workman, then

- organs, e.g. pancreas, hypophysis, containing a very easily decomposed active substance, are put into deep-freeze at minus 40 to -50°C, and then stored at -10 to -20°C;
- organs less sensitive, e.g. liver, lungs, are put into refrigerators at -10 to -20°C,
- less frequently organs are put into organic solvents (in ethanol, or acetone) whereby they will be dehydrated and the lipoids removed from them;
- and in some cases organs are comminuted and dried (in spray-drying apparatus).

Organs kept under refrigeration cannot be stored but for a restricted time, whereas organs dehydrated with a solvent, or organs spray-dried, are much more stable. In any case it is desirable to process the organs to an intermediate stage i.e. to prepare an intermediate product which can be stored without incurring the risk of decomposition.

One case apart is the collection of snake venom carried out at snake farms; and another is the preparation of fish liver oil carried out by subjecting fresh or frozen fish liver to high pressure or to an extractive process.

Besides a well appointed system of slaughter-houses and refrigerator plant, a fundamental condition of the procurement of animal organs consists in the availability of refrigerator cars for their transport, and of cold storage facilities at the works for their preservation prior to processing.

Quality specifications for the medicinal herbs, and animal organs, to be processed must be precise and laid down in such a manner that it should be possible to check them. Prices for collected material must be adjusted so that after a fair reward for collecting and other work, the manufacture of pharmaceutical preparations should be possible at competitive conditions.

Nothing is said here of the collection of other agricultural products, or that of agricultural residues, since, in general, no specific measures or techniques are needed or employed in this.

General processes for galenical preparations, fermentation, extraction, and isolation of active ingredients.

Raw materials of natural origin intended for commercial processing should meet the fundamental requirement that the concentration of their active ingredient should be as high as possible. Successful processing is direct consequence also of the technologically correct execution of the collecting and storage operations, and also of the effective organization of these.

Comminution or milling is a very important preparatory operation. The active substance of a natural raw material is to be found within cells, therefore an efficient extraction of the active substance becomes possible only after the raw material has been comminuted, or milled. It is important that particle sizes should fall between definite limits because both too coarse and too fine milling hinder satisfactory extraction. Vegetable starting material will generally be milled in the dry state. In exceptional cases, viz. when seasonal demand requires the prompt processing of great bulks of fresh plant, preparatory work may begin with comminution.

Raw material of animal origin are generally delivered in a frozen state at the processing factory where too preparatory work starts with the milling or the comminution of frozen or defrosted organs. Organs dehydrated in an organic solvent are first milled and then processed.

Quite often, preliminary to processing the raw material must be homogenized in order to assure the uniform quality.

Extraction of the active principle from the comminuted or milled raw material is usually the first step of processing. A departure from this practice is the case of fresh plant from which, after comminution, its juice is removed by pressure and only the fibrous residue is subjected to extraction later on.

The preparation of vegetable extracts has traditions many thousand years old. The most ancient method is the preparation of decoctions, this, however, does not form part of industrial practice. Maceration, i.e. soaking of plant material in water, more seldom in spirits, at

room temperature is another ancient method very rarely resorted to by industry. But percolation is still an operation widely practised in the preparation of galenical medicaments. In essence, percolation is a co-current extraction with water, or with aqueous alcohol. With several percolators suitably combined in series, a battery with which to carry out counter-current extraction can be realized. For extractions in commercial [illegible] usually extractor units rotating around their horizontally or vertically arranged axes are operated. For the extraction of very great quantities, diffusion batteries, U-shaped, U-sloped, or mobile-plate (Bollmann-type) extractors are used. Soxhlet type extractors are rare in use. As a rule, continuous counter-current extraction is practised by the [illegible] operations. The extracts are filtered, perhaps also clarified. These liquid extracts themselves may be marketed as galenical preparations, or in more cases, they are evaporated and the syrupy, or still more concentrated or dry residue is sold.

If the isolation of active vegetable substances from the extract is the aim, various methods are available, e.g. evaporation, precipitation, adsorption chromatography, ion-exchange, liquid-liquid extraction, crystallization, lyophilization or useful combinations of these.

Isolation of active substances from animal organs also begins with extraction of the comminuted, or milled, substrate. Extraction with water, or an organic solvent, or a mixture of these, is most frequent. For the processing of extracts combinations of the separation methods mentioned are resorted to, besides these re-precipitation and salting-out are important, sometimes dialysis is used. Lipoids present in great quantities compared to that of the active substances encumber the processe of extracting the latter from animal organs, but this situation is further aggravated by the perishable nature of raw materials and intermediates, and this renders particular care and accuracy in technological work indispensable. Through satisfactory preventive measures the absence of pathogenic micro-organisms and of pyrogenic matter in the final product must be ensured.

Operations, and apparatus for the processing of natural substances, whether of vegetable or of animal origin, are practically the same, yet in industrial practice it is better to prepare these products separately.

Processing of raw materials of agricultural origin makes extensive use

of fermentation as a basic process, this consisting either of the production of an active substance or of the execution of a chemical conversion, through the utilization of the biological activity of micro-organisms. The production of medicaments is carried out mainly by sterile, aerobic fermentation. Special care must be taken with pathogenic microorganisms of which the incubation and processing must be carried out in the course of the manufacture of vaccines. For the processing of fermentation broths, generally, extraction, adsorption, and precipitation are used or combined. Since fermentation will be dealt with by a special working group of UNIDO, more detailed discussion of this process can here be dispensed with.

The final purification of many an active substance produced from natural sources is carried out according to laboratory methods scaled up, the execution of these operations requires great care in view of the value of the substances handled.

Rigorous observance of instructions that refer to technology, work-hygiene and work-safety is absolutely imperative.

Commercial extraction of the active ingredients of natural substances involves the circulation of great amounts of organic solvent. Therefore the recuperation e.g. by distillation, of solvents is an important complementary activity within this manufacture. Solvents thus purified may be used again. However, solvents, or solvent mixtures, so heavily contaminated may result that their purification will be discouraged on economic grounds; these solvents can be destroyed by burning up at a place well away from the factory premises.

In many cases the residues of extraction of vegetable or animal raw material can be utilized in agriculture either as manure (e.g. compost from extracted poppy head) or as fodder (e.g. liver after extraction).

Examples of processing the most usual raw materials

We shall refrain here from a discussion of the preparation of galenical products since the methods used for this purpose are described in detail in pharmacopoeias, or in national formularies. However, some characteristic examples of the preparation of medicinal substances from natural sources might be instructive.

Preparation of opium alkaloids

Dry poppy head, after the seed has been removed, is extracted with water in a multiple, Kurci-type extractor. The solution, after its acidity has been buffered, is evaporated till a concentrate of about 1°5 specific gravity is produced. Heroin, codeine, etc. are extracted with alcohol, or some other organic solvent. This organic solvent is evaporated and the residue is diluted with benzene and the pH of this liquid is adjusted to 9°1. Crude morphine base separates and is filtered off to be purified by re-precipitation and clarification. Secondary alkaloids are recovered from the benzene phase.

Preparation of ergot alkaloids

Ground ergot is de-fatted with a low-boiling petroleum fraction, then the ergot powder is digested with the aqueous solution of an alkaline earth hydroxide. The digested mass is extracted in a counter-current apparatus with an organic solvent. From the organic solvent extract the active substances are reextracted into an aqueous solution of tartaric acid, wherefrom a mixture of the alkaloids is precipitated by alkalification. Ergotamine, and ergotoxine are separated by adsorption chromatography, and then purified. Water-soluble ergometrine is recovered from the extracted residues.

Preparation of quinine

The ground Quina bark is admixed with slaked lime and moistened with a solution of sodium hydroxide, and allowed to swell. Then this mass is extracted with benzene at 60 to 65° C, and the benzene solution is

extracted with dilute sulphuric acid at 60° C. The acid solution is heated to boiling point and its acidity buffered with a solution of sodium hydroxide. The crude quinine sulphate that separates after cooling is purified by clarification and re-crystallization.

Preparation of theobromine

The finely ground shells of cocoa beans are soaked in water, digested in calcium hydroxide, and extracted at 40 to 50° C with water. From the comparatively concentrated extract which can be produced in the diffusion batteries theobromine is precipitated by acidification.

Preparation of the glucosides of Digitalis lanata

The milled herb is digested with magnesium oxide, and extracted with ethyl acetate. The extract is evaporated under mild conditions in a film-evaporator. The aqueous residue is dissolved in alcohol and this solution is shaken with ether several times. From the aqueous solution the mixture of lanatosides A, B, and C separates in crystals.

In order to produce lanatoside-C, the mixture is dissolved in a mixture of methanol and chloroform and this solution is shaken with water. The supernatant aqueous methanolic phase is collected and evaporated to yield mainly lanatoside-C; upon evaporation of the heavier methanol-chloroform phase mainly lanatoside-A, and -B are recovered. The crude products are taken up in methanol and chloroform several times and shaken with water. Five repetitions of this process yield pure lanatoside-C recovered from the substance of the original aqueous methanolic phase. The separation process here outlined can be carried out, more simply and with a minimum of loss, according to a modified Craig method, by fixing the watery phase.

From lanatoside-A acetyl digitoxine can be prepared with an enzyme isolated from Digitalis. An aqueous-alcoholic solution of lanatoside-A

is allowed to stand for 3 days at 20 to 25° C admixed with the enzyme preparation. The mixture is agitated occasionally. Filtration follows, the filtrate is shaken with chloroform. The chloroform extract is washed with a solution of sodium chloride, evaporated, the residue is taken up in ethanol and agitated with a freshly prepared aqueous suspension of lead hydroxide. After filtration, methanol is removed from the filtrate by evaporation and the residual aqueous solution is extracted several times with chloroform. The combined extracts are evaporated and the crude acetyl digitoxine is purified by repeated recrystallization.

Preparation of betaine hydrochloride

Molasses are passed on an ion-exchange column, then betaine will be adsorbed together with inorganic cations. Elution with dilute hydrochloric acid is followed by evaporation to dryness of the solution thus obtained, the residue is extracted with hot ethanol and from this extract betaine hydrochloride is recovered by crystallization.

Preparation of insuline

Pancreas in deep-freeze is comminuted without defrosting in a suitable apparatus and extracted with acetone or with acidified ethanol of 60 to 70 per cent strength. The extract is evaporated so that its acid pH is maintained. Salting-out the residue produces crude insuline which is then de-fatted with an organic solvent, and carried into solution by acidification. The pH of this solution is adjusted to 5.3 to 5.4 (the iso-electric point) and insuline precipitates. It is crystallized from solvents in the presence of a zinc salt.

Preparation of pepsine

The peeled off mucous membrane of pig's stomach is milled, then subjected to autolysis in the presence of hydrochloric acid. From the viscous solution thus obtained pepsine is separated by salting out, or by precipitation with alcohol, or acetone.

Preparation of ACTH

The acetone-dry powder of the anterior pituitary of pig is extracted with glacial acetic acid at 70°C. When acetone is added to the extract, impurities precipitate. After filtration ethyl ether is added to the filtrate and ACTH precipitates. Further purification of the product is carried out by adsorption and counter-current distribution methods.

Production of dry preparations from organs

The organ, e.g. pancreas, testicles, thyroid gland, etc. is dehydrated in an organic solvent, then dried, and ground to powder; or the raw organ is milled to a fine pulp and dried in a spray-dryer.

Preparation of heparine

Finely ground lungs of cattle are autolysed, and extracted in the presence of sodium chloride at pH 9.5 and 60° C, then boiled. After filtration, the protein content of the solution is adjusted to the required value by the addition of calcium ions. After repeated filtration, protein is removed by the addition of sodium chloride, and heparine is precipitated with alcohol. Proteins in the precipitate are removed with the help of proteolytic enzymes, then crude heparin is obtained by precipitation with alcohol. Crude heparine is separated from calcium ions, fats, and pigments, then it is purified by repeated precipitation with alcohol, and by chemical treatment, finally the pyrogenic impurities are removed.

The examples briefly described are but illustrations without aiming either at complete assortment or at technological details. As illustrations, those want to show the variety of operations and processes on the one hand, and the similarities on the other, which are involved in the processing of natural substances.

Besides the production of the pure active substances, an especially profitable business consists in the preparation of medicaments that contain as active ingredient various extracts, of vegetable or animal origin e.g. the preparation of laxative tablets, anti-cough syrups, ointments.

General lay-out of a plant for manufacturing galenical preparations, phytochemicals, and biochemicals

A suitable lay-out for such a manufacturing plant is shown in Drawing I.

Owing to the great bulk of raw materials to be processed, it is advisable to choose the site of the factory in the vicinity of the most important collection-centre of the vegetable or animal raw materials in question. An advantageous site, if available, would be one at an industrial area able to supply the connection possibilities of basic energies. Lacking such a junction, another advantageous choice would be a site on a river, mainly to serve as a water supply and a receiver of effluents. When choosing and procuring a site, space for later expansion must be provided for. Location should take account of the features of the surrounding countryside and prevailing wind in order to minimize noxious or disagreeable consequences of air pollution. Inner roads and those running alongside, should regularly be made dust-free by spraying with waste oil, for instance.

Supply of fundamental forms of energy must be assured else failure of water-, steam- or electricity supplies will cause considerable financial losses.

Transport may be by road or rail, in the latter case factory sidings should be built. When drafting up, allowance of floor space for storage should be ample indeed since the main raw materials are very bulky and since refrigeration of animal organs is indispensable. To reduce carriage, store-houses and workshops should be near each other. For

the great masses of solvents in use, or awaiting recuperation, a separate tank park not far from the workshops will have to be installed.

Plants designed for the production of basic chemicals will be -- besides their division into rooms according to the needs of a process - divided into two storeys, advantageously by iron supports. Buildings for finishing too are divided into two storeys by stable building elements.

Also upon two storeys, and in a separate building of their own, the control and the research laboratories should be accomodated, as well as the managing offices for which, however, a separate entrance from outside might be provided. Very advantageously, managerial offices, laboratories, plants and storehouses may be connected with covered passages both for traffic and haulage.

A properly equipped mechanical workshop fit to cope with repair and maintenance is indispensable.

It is advisable to provide concrete surfacing for the courtyards between storehouses, service shops, and repair shops, while building intended for production, control, research and managerial work should be surrounded by gardens or lawn. However, this conversion onto park-like arrangement must not be such as to obstruct free access to buildings in case of fire.

It is expedient to accomodate dressing-rooms and baths for the people that work in that building. If a cafeteria and kitchen is necessary, it is best to put these on the third storey of the managerial building, or to build separately for this service.

The whole site, and all the buildings, inside and out, must be kept in perfect order and state of cleanliness all the time, this should be a fundamental principle of manufacturing pharmaceutical preparations.

Proper ventilation of the buildings is very important; suitable temperature and moisture content of the air must be monitored - with a few exceptions - by air-conditioning.

Should the plant site be a certain distance away from workers' dwellings or housing estate, adequate conveyance for them should be made available, and it is well to have a certain number of personnel live in official residence near the factory site.

Besides considerations imposed by climate, and besides those dictated by economic design, the aesthetical impression made by the whole lay-out should not be forgotten. Arrangements within buildings will be dictated mostly by considerations of technological serviceableness.

A short review on special manufacturing methods for finished pharmaceutical preparations of natural origin

The finishing operations used in the manufacture of pharmaceutical preparations containing an active ingredient of natural origin are practically the same as those used for other pharmaceutical preparations. Generally the following forms are applied in therapeutical practice.

Injections (aqueous, or oily: powder ampoule)
solutions,
syrups,
tablets, coated tablets,
capsules,
ointments,
plasters,
suppositories,
powders or granules.

Active substances of natural origin are very often coloured, and smelling. In such cases finishing should be carried out in separation from that of other substances.

Several of the active ingredients of animal origin are sensitive to heat and, in consequence, cannot be sterilized by heating. Therefore a solution or a powder containing such a substance must be manufactured and packed under absolutely aseptic conditions. In such workshops employees must have had a disinfectant bath, must have changed into aseptic clothing, and must have put on a surgical mask covering nose and mouth before allowed to enter the sterile rooms for work. Thus a system of so called white-black dressing rooms and baths must be installed to cope with this requirement.

Very many of the natural active substances have strong physiological, not seldom dangerously toxic effects, consequently employees handling such drugs must be provided with adequate protective equipment.

Many natural active substances, especially those of animal origin, tend to decompose when in an aqueous medium. Therefore these are marketed in powder form, sealed into glass ampoules their solvent being filled into separate ampoules. Ampoules may be filled by weighing the powder, or by lophilization into the ampoule of the solution that contains the pure active substances. Lophilization allows more accurate dosage and ensures such a consistence of the substance in which it is very easily soluble.

Considering that in tropical regions syrups will often start fermenting, in order to make them adapted for longer storage, their solid ingredients are filled into wide necked bottles, and this mixture of solids is converted into a syrup by adding water to it before use.

For tropical regions film-coated tablets are more suitable than those coated with sugar, the former being more advantageous also by imparting a more uniform and pleasing exterior to the tablets. With film-coatings resorption in the stomach, or resorption in the intestines, or retarded resorption may be easily effected.

In the choice of the carrier substances used in ointments or suppositories, the high ambient temperatures of the tropical climate should be taken into account.

In the course of finishing - except in the case of injections where this is given - perfect closure of the container or bottle must be ensured as a protection against the deleterious effects of the warm and humid air. In the packages of substances particularly sensitive to moisture, hygroscopic material, e.g. silica gel, is included in small porous bags.

On the labels, or directions of use of medicaments delivered to patients it is advisable to illustrate the method of application by pictures should illiteracy be still prevalent in that region.

In plants where various preparations are finished, work must be rigorously programmed and supervised lest confusion produce a mix-up of the drugs. No compromise should be allowed concerning strict discipline, cleanliness, and order.

In all the work-phases of finishing, care must be taken that operators do not touch the substances by hand. With up-to-date machinery and appliances this is comaparatively easy to prevent.

Since most of the natural active substances are hygroscopic, temperature and humidity of the air in plants should be controlled and monitored all the time.

Analytical and biological control methods, and laboratories

A principal characteristic of pharmaceutical manufacture is quality control of raw materials, intermediaries, and finished preparations according to rigorous prescriptions. Quality specifications are regulated by pharmacopoeias and by similar official or semi-official prescriptions, and by criteria set down in the technological directions of the manufacturing firms.

Control tests are carried out according to physical, physico-chemical, pharmacological, and clinical methods. Quality specifications prescribe the physico-chemical constants of the substances, the methods for the determination of their chemical identity and purity, the tolerable limits of impurities, their biological activity, the limits of their unpleasant secondary effects, and the outward appearance and quality of packaging materials and of the finished product.

The most varied methods are employed in quality control. Conventional methods for fundamental tests are generally to be found in the pharmacopoeias. Quality requirements, however, become more stringent and more sophisticated year by year. Besides former physical, or chemical, or biological tests now become classical, analytical practice is amplified by instrumental physico-chemical tests, further by biological assay methods. Spectroscopy, gas-chromatography, paper- and thin-layer chromatography, ion-exchange, isotope techniques, etc., recently the tools of scientific research only, have by now become routine work in quality control laboratories.

Preparations for parenteral administration must be checked in respect to sterility, pyrogenic effect, and, sometimes, toxicity. For several substances made from animal organs a requirement stated a few years ago is their microbiological analysis in order to check the absence of pathogenic organisms.

Most often the determination of the active substance content of material to be processed in commercial plant is not carried out there with scientific accuracy, but by a preparative reproduction in the laboratory of the process realized in the factory. The yields achieved in production are generally determined through a comparison with such laboratory results. Especially important from the point of view of these determinations is the strict adherence to prescriptions concerning sampling in order to ensure a representative and authentic sample.

Also intermediates produced in the course of manufacture will be rigorously controlled, likewise any auxiliary substances and those that are recirculated after recuperation, will be subjected to quality tests.

This control needs good organization, expediency, and accuracy, else rate and efficiency of manufacture will suffer, production and selling alike will slow down.

Results of tests must be recorded in documentary form, also reference samples must be stored for a long time in a system that keeps them easily accessible.

For pronouncements on quality the head of the quality control department must be held responsible in person, therefore only an expert with the best qualifications available, with adequate experience and judgement, ought to be appointed to this post.

For the equipment of control laboratories appliances, apparatus, and instruments of proven worth are available. It is advisable to have separate departments each for chemical analysis, physico-chemical tests, and biological- pharmacological tests. To the latter a breeding house of the test animals is usually attached.

It is important indeed to have up-to-date instrumentation in control laboratories in order to ensure quick and accurate work. Besides the usual classical items, the standard stock of instruments in a quality control laboratory will have to include a spectrophotometer, a spectrograph, a polarograph, a gas chromatograph, an amino-acid analyser, etc.

Recently it seems to have become a customary arrangement that rare and special analyses which require special instruments and skill,

are performed on order, either occasionally or on a permanent basis, by some scientific institute. However, primary responsibility for the accuracy and correctness of such results still rests with the firm which sells the product involved.

There are countries where the quality of pharmaceutical preparations is checked by a national institute, and not only at the time of its registration but, on random samples, during the whole time the preparation is on sale. Should unsatisfactory samples be found, an order is issued for the withdrawal from circulation of the product.

Other papers to be given in the course of this symposium will deal with the question of official supervision.

Organization scheme of the enterprise

Manufacture, and sale, at a high standard of excellence of pharmaceutical products require professional competence and up-to-date organization.

Drawing 2 is a scheme of the organization of a pharmaceutical manufacturing enterprise. Its general principle follows from the requirement that the general manager as the chief executive, should be enabled through his deputies entrusted each with one group of activities to grasp and to co-ordinate their work so that the most efficient utilization of all the resources be ensured.

Activities connected with research, quality control, production, energy supplies, maintenance and investment, should be co-ordinated by a chemist or a pharmacist as the technical manager.

The business manager will direct sales, home and foreign, will provide and supervise scientific medical information according to the strictest rules of professional ethics. On him it devolves to direct and supervise the procurement of raw- and auxiliary material and the activities in connexion with storage and transport.

The financial manager will direct and supervise financial transactions, accountancy, labour questions, wages accounting, and the caretaker's office.

In a comparison with a usual industrial undertaking, the well provided scientific library of the pharmaceutical firm and its department for scientific medical information composed of highly trained professional employees, will be noted as conspicuous features.

An advantageous plan of work will provide one shift for administrative, and research staff, two shifts for finishing plants, control laboratories, storehouses, and maintenance shops(the last three keeping some persons on duty during the third shift) and three shifts for basic manufacturing plants and energy suppliers.

The organization scheme shown is intended to serve as an illustration; local and personal circumstances should be flexibly taken account of within this scheme.

No compromise, however, is allowed concerning the management of the production, control, and research units, these positions require university graduates of good qualification. Pharmaceutical production is characterized by the high, not less than 10 to 15 per cent, concentration of university graduates in its total staff. Similarly indispensable is a proportionally numerous force of technicians, laboratory assistants, foremen, and skilled workers. Lack of proper training and practice is apt to cause in the pharmaceutical industry damages, both moral and financial, much above the average and may lead, ultimately, to the complete disablement of the undertaking.

Training of the required staff

It would be a rare occurrence indeed if a newly established pharmaceutical undertaking in a developing country could hire all of a properly trained staff on the local labour market. As a rule, the realization of the establishment of the firm, or the level of perfection of this realization, depend on advance training activities well thought out and accurately performed.

Similarly, as a quite rare occurrence it happens that young people are sent to foreign universities and are placed, after graduation, with foreign manufacturing houses to gain the necessary professional experience.

However, in most of the cases a pharmaceutical undertaking, in a developing country, either about to be established or about to expand, seeks the acquisition of the necessary know-how through co-operation with a foreign pharmaceutical manufacturer. In this case the training of the personnel needed may take place in the plants of the foreign partner. In order to ensure the starting-up of the new plant without a hitch, and its steady operation once put on stream, not less than 10 to 20 per cent of the higher technical, and not less than 5 to 10 per cent of the labour force to be employed by the new company should be so trained. Duration, and time, of this training should be arranged so that the recipients of it should return when the manufacturing plant is about to be assembled and installed, in order that they may take part in this work and thus gain thorough knowledge of the plant they shall have to operate. The assembly and installations finished, the participation of the experts of the foreign partner in starting-up operations is advisable. These experts, together with the local personnel trained abroad, will put the plant on stream and help the training of the local labour force. The period of this start-up and training may be anything between 3 to 12 months, depending - among other factors - on the abilities of the labour force locally hired. This process may be significantly shortened and facilitated if, after their returning home, the foreign trainees offer theoretical and

practical courses of some weeks' duration according to a well thought out program to their fellow workers to be.

Considering the value of special training and skill, no matter whether acquired abroad or at home, attractive terms of employment should be offered to personnel really possessing these, in order to induce their loyalty to the firm. Even when rather attractive terms are granted, 20 to 25 per cent of the trainees are apt to leave in search of better employment and this must be reckoned with when the number of those to be trained is established.

If new manufacturing plant is realized with foreign cooperation, the possibility occasionally to resort to the counsel and help of the experts of the foreign partner, or to have local people trained at and by the foreign partner, should be secured by contract.

In order to ensure smooth operation of the new plant it is indispensable, first, that technological operational instructions should be written in the language most used on the premises, or be made clear by drawings or pictures, and that these be affixed at proper points in the plant; second, that employees entrusted with the comparatively more delicate operations or activities should be given systematic theoretical and practical instruction. This needs time and costs money, yet is an investment recovered many times over in the prevention of damage and loss due to ignorance.

The most suitable steps to establish and to develop a pharmaceutical indrustry

Establishing and developing a pharmaceutical industry with a minimum of risk is best accopmlished stepwise. Study of the pharmaceutical industry of any developed country will show that the laying the foundation of this always began with dispensing and packaging, i.e. with the finishing operations. The underlying reason of this is twofold, namely

- finishing is a rather profitable business which requires but small investments,
- finishing is mainly repetitive work which is much more easily learnt than operations of basic production.

If gradual unfolding of demand allows the stepwise realization then it is advisable to begin with finishing operations. Even within this frame a certain staggering might be necessary. In the first instalment, the manufacture of powders, syrups, ointments, plasters, suppositories, tablets, coated tablets, and capsules could be introduced, then, by gradual progress, the production of solutions and of injections could be tackled, to leave for the last stage the aseptic production of parenteral medicaments.

Following this, the preparation of basic substances of natural origin, and the manufacture of the more simple fermentation products may be introduced. The final stage of development - should demand and intention prevail - comprises the establishment of manufacture by syntheses and the more sophisticated fermentation techniques.

For the establishment of a greater pharmaceutical factory unit this graduation can be realized through the suitable timing of the different steps. An undertaking with ample capital resources at its disposal can venture upon the simultaneous realization of these several stages, but the augmented risk hereby involved should not be left out of consideration.

No doubt, the most difficult task is the pioneer creation of a nucleus of pharmaceutical production. However, this once achieved, difficulties met on the road of further development and expansion can be negotiated with less effort. The partial recompense for heavy costs and great risks involved with the introduction of a pharmaceutical industry, various benefices, e.g. the gift of the site, temporary exemption from taxation, a favourable system of duties, preferential dealing in state purchases, should be asked from and be granted by state administration, considering that similar help seems to be willingly granted in several developing countries which have the interests of public health and industrial progress in mind.

The following are the two fundamental pre-requisites of pharmaceutical manufacture which utilizes natural raw materials:
- a thorough survey of the supply of medicinal herbs which can be collected in the country, and an organization for the collection operations;
- an extensive network of slaughterhouses and refrigeration plants, and an organization for the collecting and storage operations.

Provided these facilities are reliably available, prior to decision
- a market survey, and
- a feasibility report
must be procured. For the latter, help may be asked from an UNIDO expert, or from a foreign partner willing to co-operate.

Decision, arrived at after due analysis of the necessary data, will be followed by its carrying into effect. The most important steps in this are the following:

Preparation of projects

Calling for tenders, and evaluation of them

Drawing-up of contracts for deliveries and services on the basis of the most favourable tender received,

Erection of buildings

Training of personnel abroad

Installation work

Commencement of home training of operators

Technical inspection and taking over of the plant

Starting-up operations

Occasional consultation with experts

Regular vocational training of employees

Realization of further developments based on proper results or on those acquired by purchase.

This enumeration is very sketchy indeed, and only the expending of quite a considerable amount of further efforts not named in this list, will see the project through.

The necessary efforts in research and development

Pharmaceutical industry is one of those that consume any amount of research, the progress, even the continuance of this industry depends on its research activities.

In the beginning, and for a short time after, a smaller company may stay alive, even progress a little, by the purchase of the results and technological experience of others, but at a certain stage of its development it cannot but establish a research organization of its own.

The necessary R.D. activities can be provided for by an organization within the firm, by a scientific establishment or institute, on a contractual basis, but most expediently by the combination of these two arrangements. It may be mentioned at this juncture that the internal research organization will not be able to work effectively unless it works with a suitable concentration of efforts, and to ensure this it will always be necessary to rely also on the well considered acquisition of results from other sources, with special regard to the developing international division of labour.

In the first step, and prior to everything else, the introduction and progress of research in the field of pharmaceutical technology should be fostered. This is indispensable not only because no new compositions or forms of medicaments can be elaborated without it, but also because without it the eventual difficulties in manufacture cannot be obviated, the uniformity and stability of the product cannot be ensured, and progress in the domain of finishing operations will stop.

A further step consists in the organization of research in the field of phytochemistry. and biochemistry. In the beginning the relevant departments will endeavour to optimize the processes actually practised, later on the elaborating of new or the adapting of foreign processes will become their main task. If grown strong enough, these departments will do research for the more efficacious utilization of specific raw materials found in the country through a search for new active substances in them, and an

elaboration of production methods suitable for the best recovery, etc., of such substances. At this, the highest stage of development, an efficient pharmacological research department will have to be created.

At the beginning, suitable staff of research departments might be 3 to 5 per cent of the total number of employees, at a higher stage of development about 8 to 10 per cent will suffice. Within the research staff the suitable proportion of university graduates to laboratory assistants is 1 : 2, or rather 1 : 3 if possible.

At the beginning, allocation of funds for research may amount to 2 or 3 per cent of the turnover, later 4 to 5 per cent may be justified.

When R.D. activities have attained a certain level of proficiency, the erection of pilot plant will be necessary. When pilot plants are not yet available, experiments on larger than laboratory scale will have to be carried out in manufacturing apparatus, with a proper programming of activities.

Full expansion of R.D. activities will necessitate, acoording to results habitually obtained, the use of the services of a patent agency, or the recruiting of a patent agent into the staff.

Lively, and world-wide, competition is a prominent feature of pharmaceutical industry, consequently the prices of pharmaceutical chemicals in bulk drop generally 3 to 5 per cent every year. Thus, in order to maintain a competitive position an incessant struggle is imposed wherein intensive R.D.work is called to lower production costs.

Some economic aspects

The economic success of a manufacture of a medical preparation from a natural raw material largely depends upon the purchase prices of the plant matter, or the animal organs, used. Since the collection of these fundamental raw materials is a labour intensive process, it can be carried out at relatively lower expense in the developing countries where employment rate is low.

As mentioned earlier, there is a great difference, from the point of view of possible profits, between the basic substance and the finished preparation made of it. To illustrate this, the following examples may not be out of place.

Ergotamine tartrate

Selling price of the substance		2.75	US$ /gr.
Production costs of the substance			
materials	2.2o		
wages	o.o6		
overhead	o.15	2.41	US$ /gr.
Selling price of Ergotamine Tartrate o.5 mg Injection, 1 ml., in packages of 100		1.26	US$
Production costs			
materials	o.2o		
wages	o.1o		
overhead	o.5o	o.8o	US$
Selling price of a combination, 12 coated tablets each composed of		o.3o	US$
o.2 mg Ergotamine tartrate			
o.3 mg Phenacetine			
o.15 mg Amidazophene			
Production costs			
materials	o.o2		
wages	o.oo5		
overhead	o.o25	o.o5	US$

Theobrominum purum

Selling price of the substance		3.1o	US$ /kg.
Production costs of the substance			
materials	o.6o		

wages	o.o5	
overhead	1.45	2.1o US$/kg.

Selling price of a combination
30 coated tablets 0.2o US$

each composed of

o.o2 gr Dienoestrol
o.o8 gr Theobromine
o.o2 gr Phenobarbital
o.25 mg Extr. Strychn. sicc.
o.o2 gr Papaverine
o.2o mg Extr. Belladonna sicc.
1.oo mg Aloin
o.15 mg diacetylo-dioxy phenylisatine

Production costs of the combination

materials	o.o5	
wages	o.o1	
overhead	o.o4	o.1o US$

Lanatoside-C

Selling price of the substance 3.56 US$/gr.

Production costs of the substance

materials	1.6o	
wages	o.2o	
overhead	1.2o	3.oo US$/gr.

Selling price of Lanatoside-C tablets
4o x o.25 mg o.4o US$

Production costs of the tablets

materials	o.o3	
wages	o.o1	
overhead	o.o9	o.13 US$

Betaine hydrochloride

Selling price of the substance		1.4o US$
Production costs of the substance		
materials	o.7o	
wages	o.o3	
overhead	o.65	1.38 US$

Pepsin 1 : 3000

Selling price of the substance		4.3o US$
Production costs of the substance		
materials	2.oo	
wages	o.4o	
overhead	1.5o	3.9o US$

Selling price of a combination		
lo tablets, each of		
o.1 gr pepsine		
o.4 gr betaine hydrochloride		o.2o US$
Production costs of the combination		
materials	o.o15	
wages	o.o55	
overhead	o.o15	o.o35 US$

As these few examples show there is a difference of about one order of magnitude between profits that accrue from the sale of the substance and from the sale of the preparation made from it.

Bulk sale of active substances from vegetable or animal origins yields a net profit of about 5 to 6 per cent ; amortization of investment takes from 8 to 12 years.

When the company can effect, in about 50 per cent, the sale of its products in the form of finished preparations besides sales in bulk, its profit will rise to not less than 15 to 25 per cent, and its investments will be amortized within 3 to 5 years.

Only companies which manufacture finished preparations in a significant proportion of their output, and sell these through their own sales organization, can expect to operate profitably.

Conclusions and proposals

It can be stated that developing countries are in a favourable position as far as availability of vegetable, and animal, raw materials, and as far as possibilities of the establishment of a pharmaceutical industry on this basis are considered. The introduction of this industrial activity, and its gradual expansion will, no doubt, favourably affect the foreing trade balance of the country, and seems to warrant that also the investing company will gain the profits due to it.

In a technical and technological respect, and in respect of the special training of the staff, laying the foundation of pharmaceutical production will need co-operation with a country that has well developed such an industry, or with a pharmaceutical company in possession of extensive experience. Further progress in the period after proper experience has been gained may rely mainly on their own efforts, nevertheless to stand aloof from the ever increasing international give-and-take of scientific and technical information would be very bad policy indeed.

The pioneering introduction of pharmaceutical industry, and its further progress, can be significantly supported by preferential treatment granted to it by state authorities.

The preparation with utmost circumspection of market survey and feasibility report is very important and not less important is the speedy realization of

decisions arrived at on their basis. It is very useful when the principle of gradual realization can be followed since this gives a better foundation of future progress and is, at the same time, less risky. Besides the organized and well serviced production side, a successful sales organization and an honestly convincing scientific information service are indispensable.

Very important also is the special training of personnel at various levels before, and their systematic instruction after operations have started.

Should the realization of a pharmaceutical manufacture which will use vegetable or animal raw material be decided, then the most important agenda will be
- surveying the home resources of raw material with respect to quantity, quality, and availability;
- preparation of a market survey with special regard to demand in near-by countries, or in those within the same economic group;
- elucidation of the extent and nature of preferences to be expected from state authorities;
- preparation of a feasibility report;
- deciding, in principle, upon the establishment of the manufacture;
- selecting the partner with whom to co-operate and contracting with him;
- selecting the factory site and obtaining it;
- designing;
- asking for tenders and contracting with the most advantageous tenderer;
- constructing the buildings;
- training of personnel abroad;
- assembly work;
- preliminary training of local labour;
- inspection of the plant in view of take-over;
- putting the plant on stream with the co-operation of partner's experts;
- regular technical instruction of personnel in charge of the more important jobs;
- expansion of the activities on the basis of suggestions coming from the research staff or on the basis of know-how acquired elsewhere.

A smaller plant may be constructed in one step. Medium, or bigger plants require gradual realization in order to raise economic returns and to minimize risks to be incurred. A corresponding scheme may be the following.

Stage 1. Erection of buildings and assembly of facilities of energy supply, maintenance, finishing operations, storage, and laboratory control of qualities.

Stage 2. Building of workshops for the production of galenicals, phytochemicals, and biochemicals; establishing the research laboratories.

Stage 3. Expansion of existing facilities.

Should this scheme be realized, the production units of Stage 1 can already start operation with substances purchased while items of Stage 2 are still being constructed or assembled.

In no respect can this survey claim completeness; its aim has been to draw a general picture with which to awaken interest. As suggested in this study when the intention to realize has become definitive, further broad and detailed technical and economical analyses become indispensable.

The particular domain here treated of the pharmaceutical industry merits special reflection whenever the industrial expansion of a developing country is deliberated upon.

Production of medicaments is not simply a technical-economical activity since through its beneficial effect upon public health it touches and is touched by moral and humanitarian principles. Production of medicaments, when practised within the boundaries of both sound morality and reasonable economics, is a useful means with which to further the interests of the community as well as those of the individuals concerned.

References:

Thorwald,J.: Might and Secrets of Early Medical Men /in German/. Munich, and Zurich, 1962

Fülöp, Zs.: The Philosopher's Stone /in Hungarian/ Budapest, 1957

Römpp,H.: Chemical Encyclopedia /in German/. Stuttgart, 1958.

Bayer,L.,et al.: Pharmaceuticals and their Production /in Hungarian/ Budapest, 1957

Tolnay P.: Industrial Enzymology /in Hungarian/ Budapest, 1963

Kosszán,B.: Production of Basic Pharmaceutical Substances /in Hungarian/ Budapest, 1965

Halmai,L. and Novák,I.: Pharmacognosy /in Hungarian/Budapest 1963

Mosig,A.: Short System of Medicinal Herbs /in German/ Dresden and Leipzig, 1961

Vincke,E. Production of Hormone Preparations /in German/ Leipzig, 1955

Bersin, Th.: Biochemistry of Hormones /in German/ Leipzig, 1959

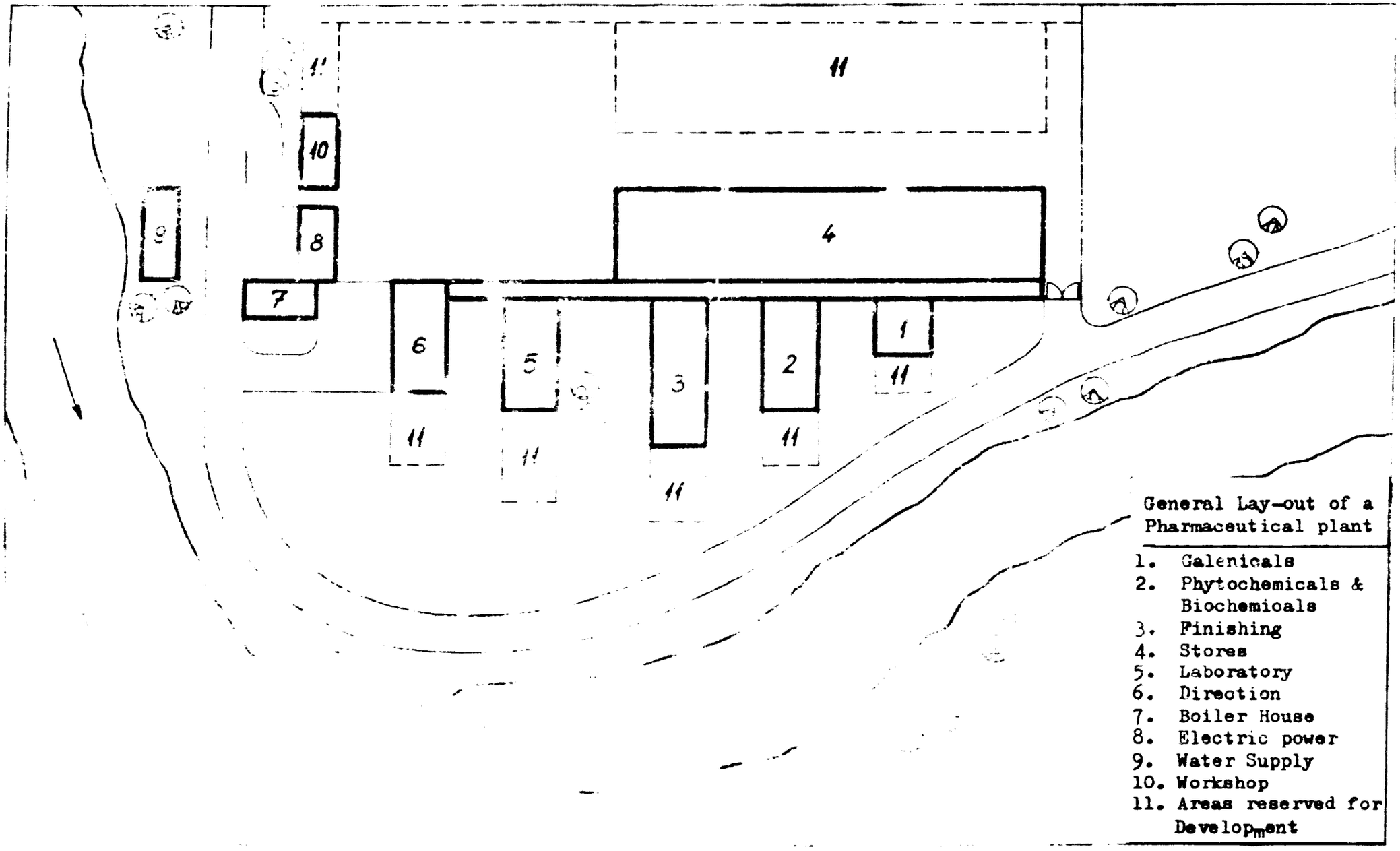
Webb,F.C.: Biochemical Engineering. London, 1964

Blakeborough, N.: Biochemical and Biological Engineering Science; 2. Bond London, and New York, 1968

Strong,F.M.: Biochemical Techniques. Minneapolis, 1957

Ehrhart,G., and Ruschig,H.: Pharmaceutical Products; 2 Vols. /in German/ Weinheim, 1968.

1. DRAWING

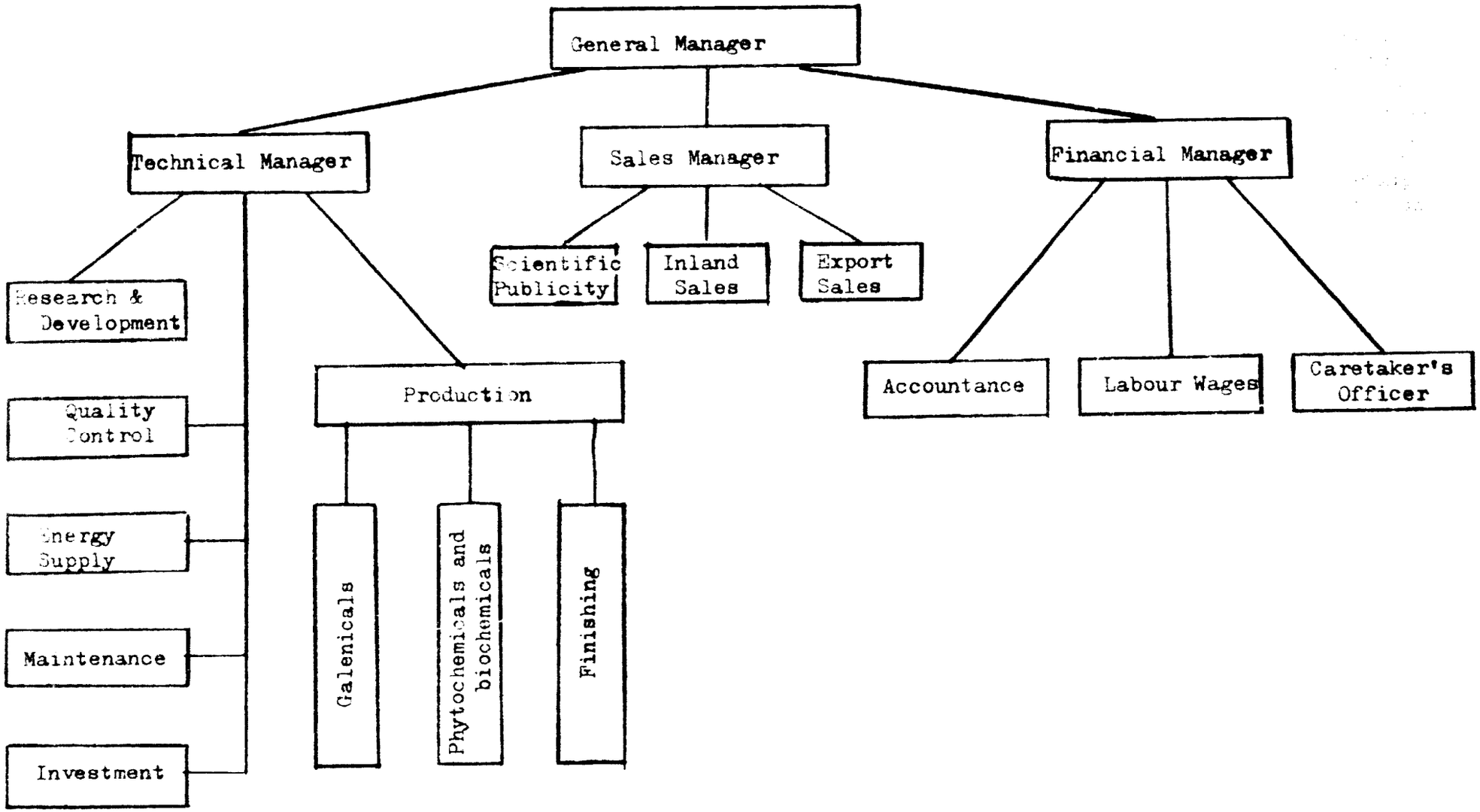


General Lay-out of a Pharmaceutical plant

1. Galenicals
2. Phytochemicals & Biochemicals
3. Finishing
4. Stores
5. Laboratory
6. Direction
7. Boiler House
8. Electric power
9. Water Supply
10. Workshop
11. Areas reserved for Development

ORGANIZATION OF A PHARMACEUTICAL COMPANY

2 DRAWING




11.8.72