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PLANT REQUIREMENTS FOR MANUFACTURE OF ANTIBIOTICS

DEPARTMENT OF STATE

AGENCY FOR INTERNATIONAL DEVELOPMENT

COMMUNICATIONS RESOURCES DIVISION

Washington 25, D. C.

FOREWORD

This brochure is one of a series of reports resulting from overseas technical inquiries on factory or commercial establishments, operation, management, and engineering. The report is designed to provide only a general picture of the factors that must be considered in establishing and operating a factory of this type. In most cases, plans for actual installations will require expert engineering and financial advice in order to meet specific local conditions.

Mention of the name of any firm, product, or process in this report is not to be considered a recommendation or an endorsement by the Agency for International Development, but merely a citation that is typical in its field.

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For further information and assistance, contact should be made with the local Productivity Center, Industrial Institute, Servicio, or United States Aid Mission.

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INTRODUCTION

This report presents the establishment of a typical pharmaceutical plant, staffed and equipped to manufacture the antibiotics Penicillin, Streptomycin and Tetracycline.

Due to the nature of the products, parameters, and manufacturing processes, the operation is, of necessity, a large one.

In many cases, pharmaceutical plants have been established in foreign countries under the direction of one of the major United States pharmaceutical companies. This has been specialized assistance in plant design, equipment, chemical formulations, and production processes which have been developed over the years. In many cases, these industrial developments are considered proprietary to each manufacturer.

Antibiotics, as discussed in this report, refer to the chemical compounds derived from microorganisms which have the capacity of inhibiting the growth of, or even destroying other microorganisms. Penicillin, Streptomycin and Tetracycline are such chemical compounds, and though different in chemical composition, the methods of production are similar.

In the case of Streptomycin, a royalty agreement will have to be arranged with Rutgers University, Research and Educational Foundation, New Brunswick, New Jersey, who holds the patent on the antibiotic and the basic manufacturing process.

GENERAL ASSUMPTIONS

In order to make realistic estimates in this manual, certain assumptions have been made.

1. The costs of the building and general facilities are based on United States prices.

2. Material costs are based on sizes and specifications of materials used in the United States.

3. Labor costs are based on the average for the industry as recently published by the United States Bureau of Labor Statistics.

4. Adequate power and water are available at the plant site.

5. Adequate transportation facilities are available at the plant site.

6. The plant operates eight hours a day, five days a week, and fifty weeks per year.

7. No special provision is made for the training of new personnel, It is assumed that learner's rates are paid in such cases.

8. The following items cannot be estimated realistically:

   A. Land value.
   B. Distribution and selling costs.
   C. In-freight and out-freight.
   D. Administrative costs.
   E. Taxes.

   While general estimates will be made of each of these items, for the purpose of completing cost estimates, adjustment should be made in accordance with actual local costs.

   In fa , all cost estimates contained in this report should be adjusted to conform to local conditions.

9. Most of the equipment used in a pharmaceutical plant is custom designed and built. In order to complete the cost estimates of this report, the price of the equipment does not include the engineering and drafting time required to design the apparatus. Approximately 20% of the cost of specially built equipment should be added to include these costs.

10. Since the chemical processes differ from one pharmaceutical manufacturer to another and are generally regarded as proprietary information, the cost estimates of direct materials are approximate; however, the materials listed under the direct materials section are actual materials used in formulation.

11. Columns are provided in the tables included in this report to facilitate the conversion of cost figures to conform with local costs.

PRODUCT SPECIFICATIONS

Penicillin: The penicillins comprise a group of antibiotics that are biosynthesized by several species of Penicillium mold, belonging to the notatum-chrysogenum group. All penicillins produced in media free of precursors possess the same fundamental chemical structure and differ only with respect to side claims.(page 41)

The most important penicillins used medically are the sodium and potassium salts of Benzyl pencillin, Penicillin G and Penicillin V. Penicillin is a white, odorless, moderately hydroscopic crystalline powder which is not appreciable affected by light and is very soluble in water or dextrose solution.

Streptomycin: Streptomycin is the name of a specific antibiotic produced from Streptomyces griseus; however, the word is used loosely to designate several chemically related compounds. The chemical structure of Streptomycin is shown on page 42.

The salts of Streptomycin are bitter, white to slightly pink or pale brownish granules or powder, oderless or nearly so, hydroscopic, and may deliquesce on exposure to air, but are not affected by air or light.

Tetracycline: Tetracycline is a specific antibiotic generally known by the following trademarks: Achromycin, Panmycin, Polycycline, Stechin, and Tetracyn. It chemical form is shown on page 41. Tetracycline is a yellow, odorless, crystalline powder. It is stable in air, but exposure to strong sunlight causes it to darken.

MANUFACTURING OPERATIONS

The successful operation of a manufacturing plant making antibiotics is a combination of the use of proper ingredients and their processing, production and quality control as well as research. The manufacturing operations in the United States are still undergoing changes as new procedures, formulations, and controls are developed. This report describes the basic processes.

MANUFACTURING PROCEDURE

Although the basic ingredients used to manufacture Penicillin, Streptomycin, and Tetracycline are different, the principal operations are similar and may be separated into four stages. For convenience these may be categorized as follows:

1. Preparation of inoculum or "seed".
2. Biosynthesis or fermentation.
3. Extraction and purification.
4. Finishing

The preparation of the inoculum is performed in a laboratory where healthy, highly productive stains of micro-organisms are cultivated on a small scale and stored at low temperature and low humidity until required for production. There are two ways in which the micro-organisms effect fermentation: one is "surface" fermentation, the other, "submerged" fermentation. Since the "submerged" fermentation is preferred, this report will not discuss the "surface" method.

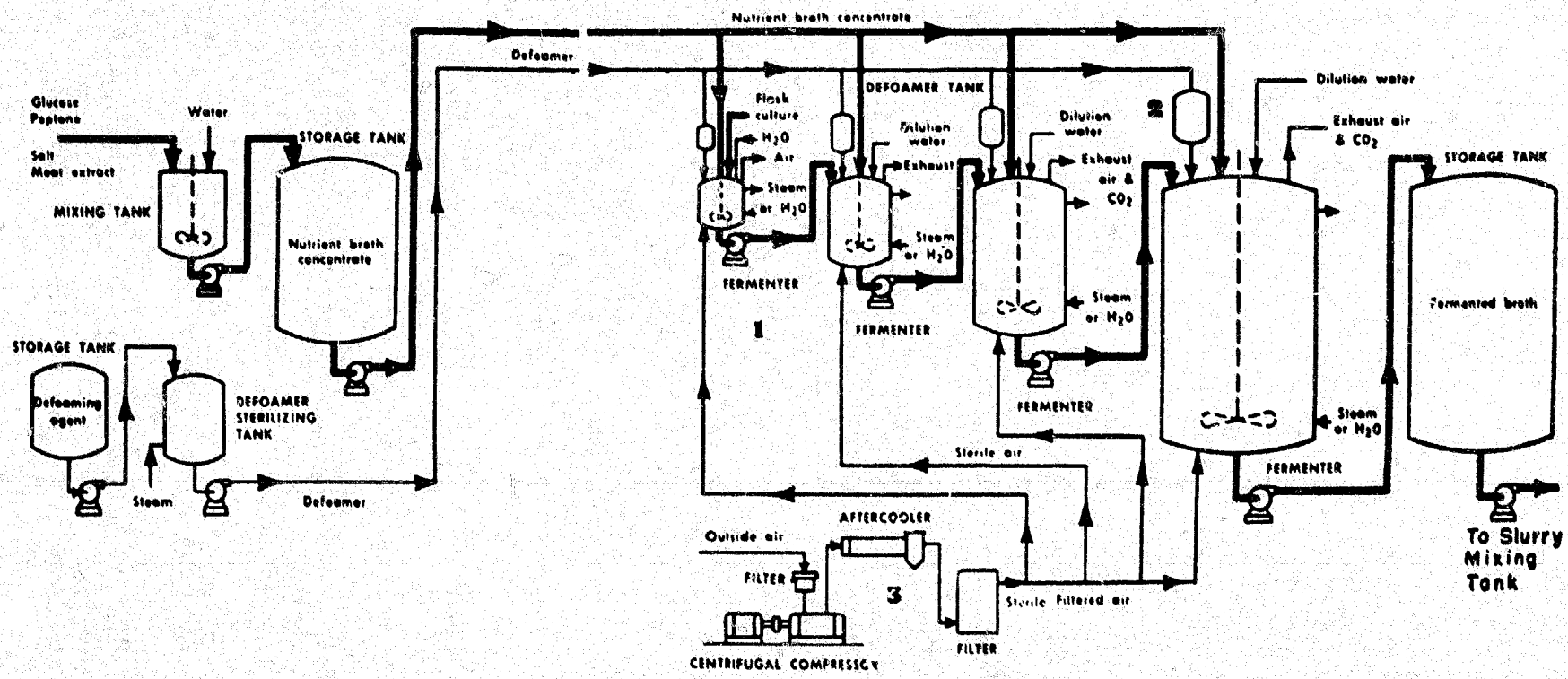


FIGURE 1

NUTRIENT PREPARATION AND FERMENTATION

The process of submerged fermentation involves placing productive spores in a rich nutrient medium where they can grow and reproduce (See Figure I, page 5). The media is slightly different for each antibiotic but basically contains food substances such as meat solids or corn steep, glucose, and Sodium chloride in an aqueous solution. Since air is required for growth, the flask containing the micro-organism and nutrient media is placed on a mechanical shaker to aerate the mixture.

For production, large quantities of highly concentrated nutrient media are mixed and stored until needed.

Before being used, the nutrient or mash is diluted with water to the proper concentration, pumped into the fermenter or culture tank, sterilized at 121°C and allowed to cool down to 25° to 30°C before the inoculus is introduced. After seeding, the biosyntheses take place in four succesive tanks, each larger than the previous one. When maximum growth is achieved in the first tank, the entire contents are pumped into the second tank, where more nutrient is available.

The process continues until a sufficient quantity for a complete batch is reached. The size of the batch is naturally dependent upon the facilities available. For each pound of antibiotic in a batch, 200 tons of raw materials (including solvents which are recovered) and 100,000 gallons of process water are required.

The culture tanks are aseptically maintained and all joints are made with steam fittings. Sterile air is bubbled through the

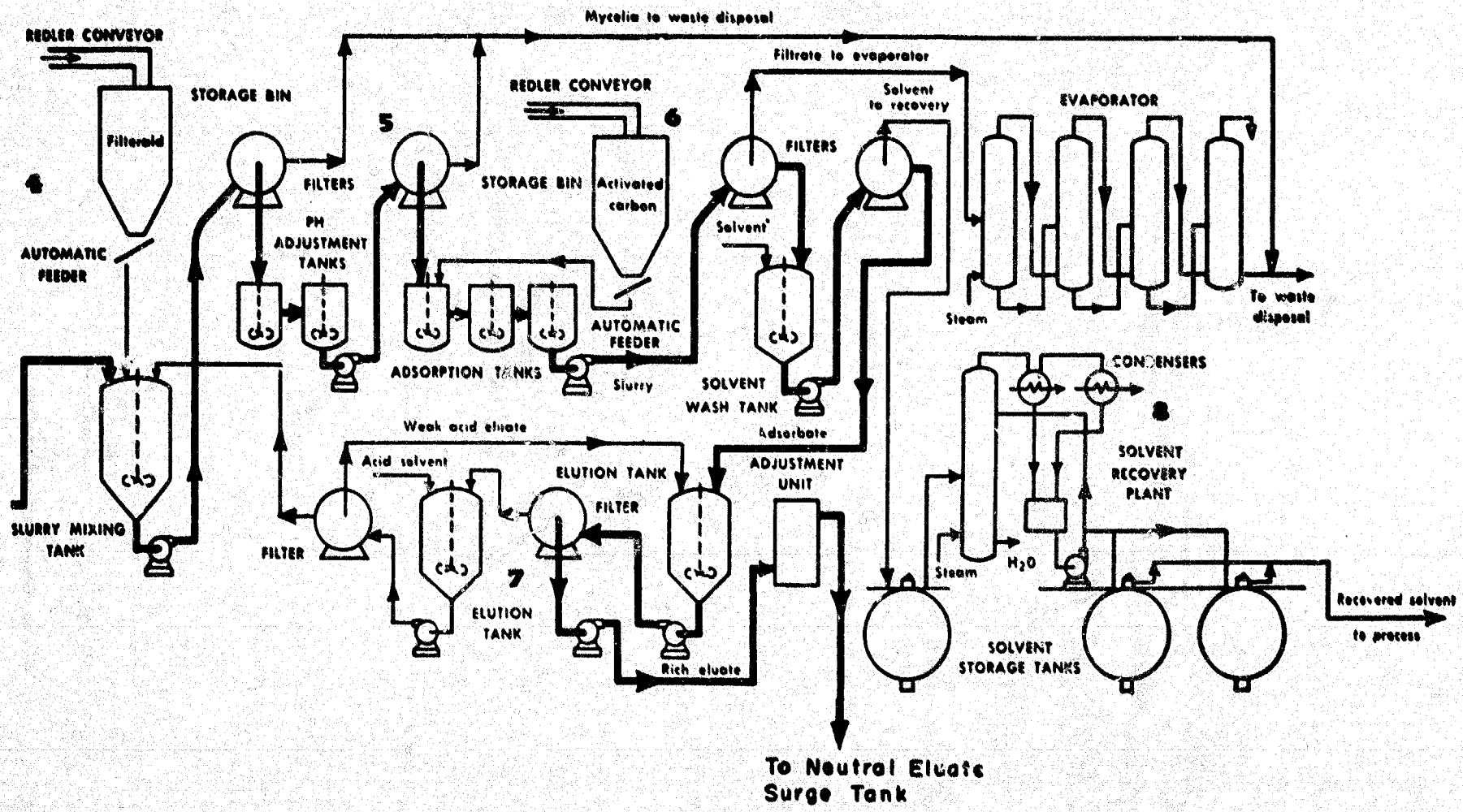


FIGURE 2

ADSORPTION AND ELUTION

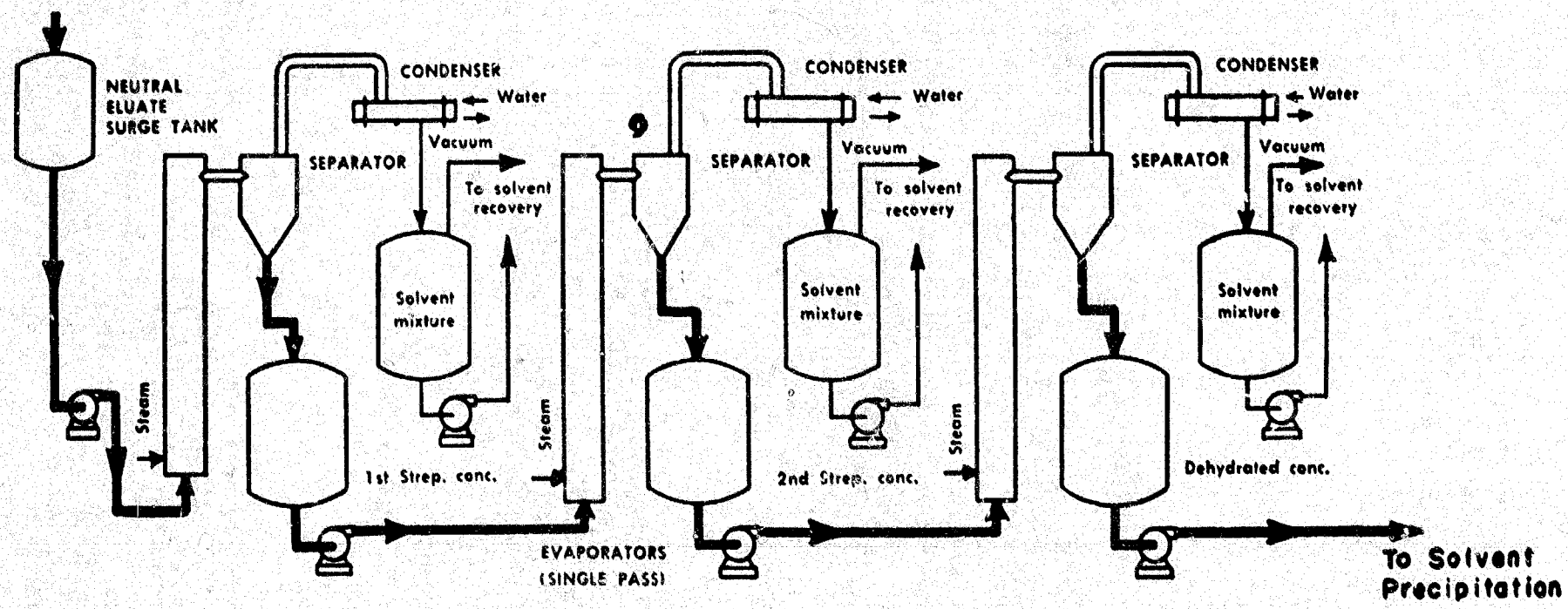


FIGURE 3

CONCENTRATION AND DEHYDRATION

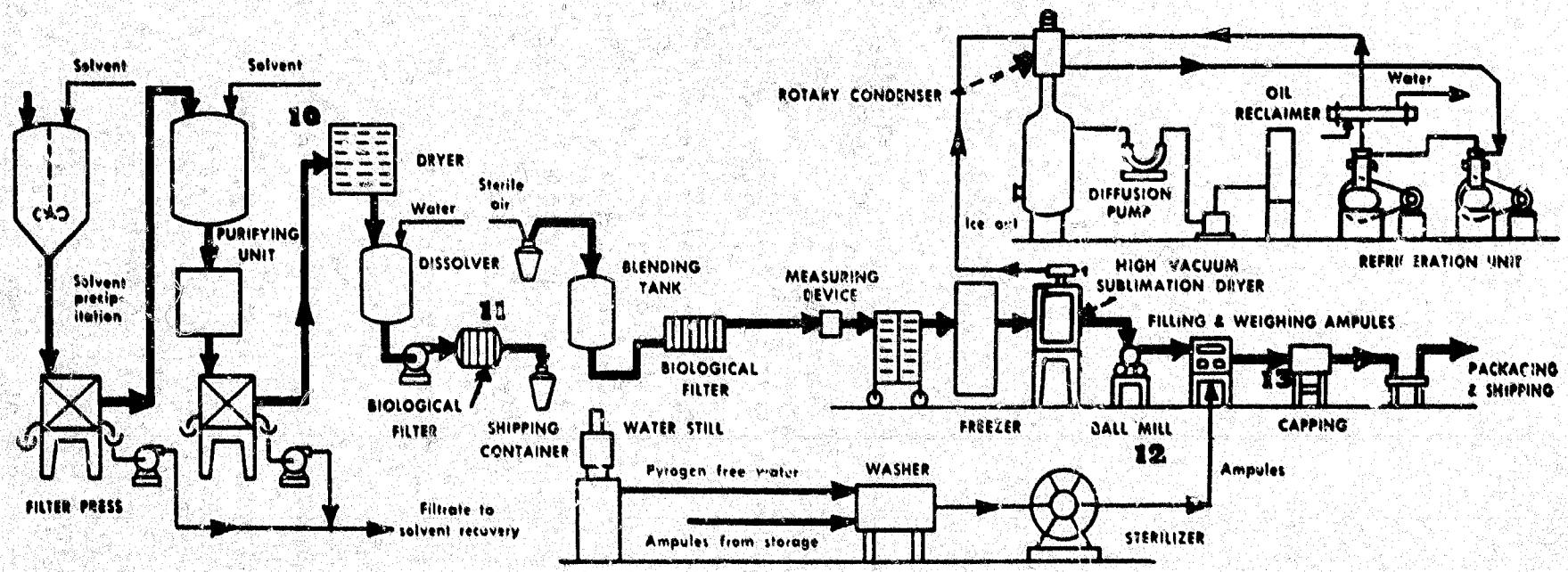


FIGURE 4

PRECIPITATION, PURIFICATION AND FINISHING

the fermentation liquid at a rate of 0.03 cubic feet of air per minute per gallon of liquid. Sterilization of this air is effected by passing it through filters to remove any airborne micro-organisms.

Carbon dioxide which is formed during fermentation, is displaced by the air, and aeration is assisted by a mechanical agitator inside each tank.

During the aeration and fermentation, it is necessary to prevent the liquid from foaming through the use of an anti-foaming agent. It has been found that lard oil used as an anti-foaming agent also acts as a catalyst during the biosynthesis.

After fermentation has continued for several days and has completely saturated the fourth and largest fermentation tank, the recovery process or extraction begins. This process must separate the antibiotic, in concentration of 0.005%, from the great quantity of liquid in which it is dissolved.

Recovery is accomplished in a series of five operations (figure 2, page 7) (1) removal of mycelium by filtration, (2) extraction by absorption on activated charcoal, (3) elution of the antibiotic from the carbon adsorbate, (4) concentration of the eluate by evaporation and dehydration, (5) double solvent precipitation followed by filtration and drying. Upon completion of these five steps, the result is a crude product containing about 25 percent antibiotic. Further purification is accomplished by redissolving the crude material in a solvent and filtering out impurities. The antibiotic is then precipitated, filtered, and dried in a vacuum drier (figure 3, page 8). Finally it is redisolved to form a con-

centrated solution and treated to remove all chemically similar antibiotics which were simultaneously produced with the desired one. It is then passed through a biological filter for further purification (figure 4, page 9).

The finishing operations, consisting of blending, final filtration, freezing, drying by high vacuum sublimation, milling, weighing and packaging, take place in a sterile room. Conditions of the room and workers muxt be carefully controlled to maintain asepsis.

The filtered material is placed in a freezing unit at -40°C, and frozen concentrate is placed in a vacuum drier where sublimination occurs, leaving a cake of antibiotic in salt form. The cakes are reduced to a powder, in a ball mill, and packaged in sterile vials which are to contain weighed aliquots.

MANUFACTURING UNITS

Although fermentation is conducted as a batch process, the recovery is considered as a continous operation.

The manufacturing unit is one pound each of Penicillin, Streptomycin, and Tetracycline.

PROCESSING CONSIDERATIONS

Aseptic working conditions and sterile equipment are essential in the manufacture of antibiotics. Air throughout the manufacturing area must pass through sterilizing filters of an air conditioning system which maintains close temperature and humidity control.

Added precaution include a triethylene glycol aerosol and ultraviolet lamps. Air throughout the plant is sampled and tested regularly by a bacteriologist to check sterility.

Another important consideration is the daily inventory of antibiotics. At the end of each day, each unit of antibiotic must be accounted for and retain its identity so that if a batch is found inferior during any part of the process or in final testing, the entire lot can be discarded. The units used in the accounting procedures are units of antibiotic, where unit is not a weight or volumetric consideration but one of potentcy.

PLANT SITE

The plant site should cover several acres to include land for the initial buildings as well as storage tanks. There should also be area available for expansion.

The plant site should be accessable to large quantities of water, should be near rail facilities and good roads. The estimated cost of the plant site is $50,000.

BUILDING REQUIREMENTS

The building requirements will to a large extent depend upon the quantity of production. A typical plant in the United States has four large buildings of approximately 50,000 square feet each for each antibiotic manufactured. This area includes production area, office space, and research facilities.

The building should be made of concrete or similar material to be

relatively air tight as all the air coming into the plant must pass through sterilizing filters and an air conditioning system. The estimated cost of the buildings is $1,000,000.

POWER

A dependable supply of electric power is required, and it is assumed that this will be available. Electric power is needed to supply lighting, heat ovens, run motors, compressors, pumps, agitators, and blowers. The quantity of electricity used will depend upon the magnitude of the plant. For purposes of the completing of the financial aspect of this report, the annual cost will be estimated at $60,000.

WATER

Water is required for the fermentation process, filtering processes, steam, sterilizing, drinking, sanitation, and fire protection. The estimated annual cost is $2,400.

FUEL

Fuel is required to heat the buildings, produce steam, and heat ovens. In most applications oil, gas, or coal may be used. The estimated annual cost of fuel is $32,000.

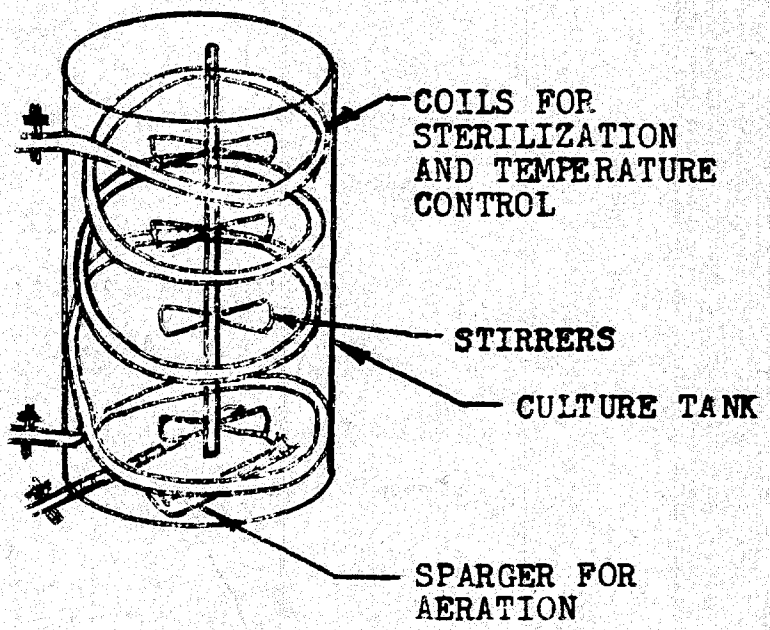
MACHINERY AND EQUIPMENT

Fermentation Tank

The fermentation tank, figure 5, page 14, is where the biosynthesis or growth takes place. Within the tank the antibiotic is grown in a rich nutrient medium. During the growth process, sterile air is forced into the tank under pressure and the entire medium is con-

FIGURE 5

FERMENTER



Simplified diagrammatic representation of the essential features of culture tank for the production of penicillin and other antibiotics by submerged culture technic. Sterile air is introduced under pressure in a highly dispersed state through the sparger. The mold and other solids in the culture medium are kept suspended by the stirrer. Sterilization is effected by running steam through the coiled pipe. Since the tank is hermetically sealed, the temperature and the pressure may be raised so that the fermenter becomes, in effect, a huge autoclave. After sterilization, the medium can be cooled rapidly by circulation of cold water through the pipes. The temperature of the medium can be regulated during incubation by circulation of hot or cold water in the pipe, as required. (Courtesy of J. P. Lippincott & Co.)

stantly agitated by a radial stirrer. A coil of pipe surrounds the tank and is used for several purposes. Steam is introduced into the piping to sterilize the nutrient medium before the spores are added. Cold water is then piped through to cool the tank. During the fermentation process hot or cold water circulates through the coils as is required to maintain a constant temperature of 25° C to 30°C. These tanks are commercially available from 10 gallon pilot plant tanks to 15,000 gallon industrial tanks.

Rotary Drum Filter

The rotary drum filter, **figure 6,** page 16 and figure 7, page 17 removes all of the solid waste from the fermented medium as it leaves the fermenter. The liquid containing the antibiotic is drawn into the drum by suction, leaving the solid wastes on a mold mat which is discarded.

General

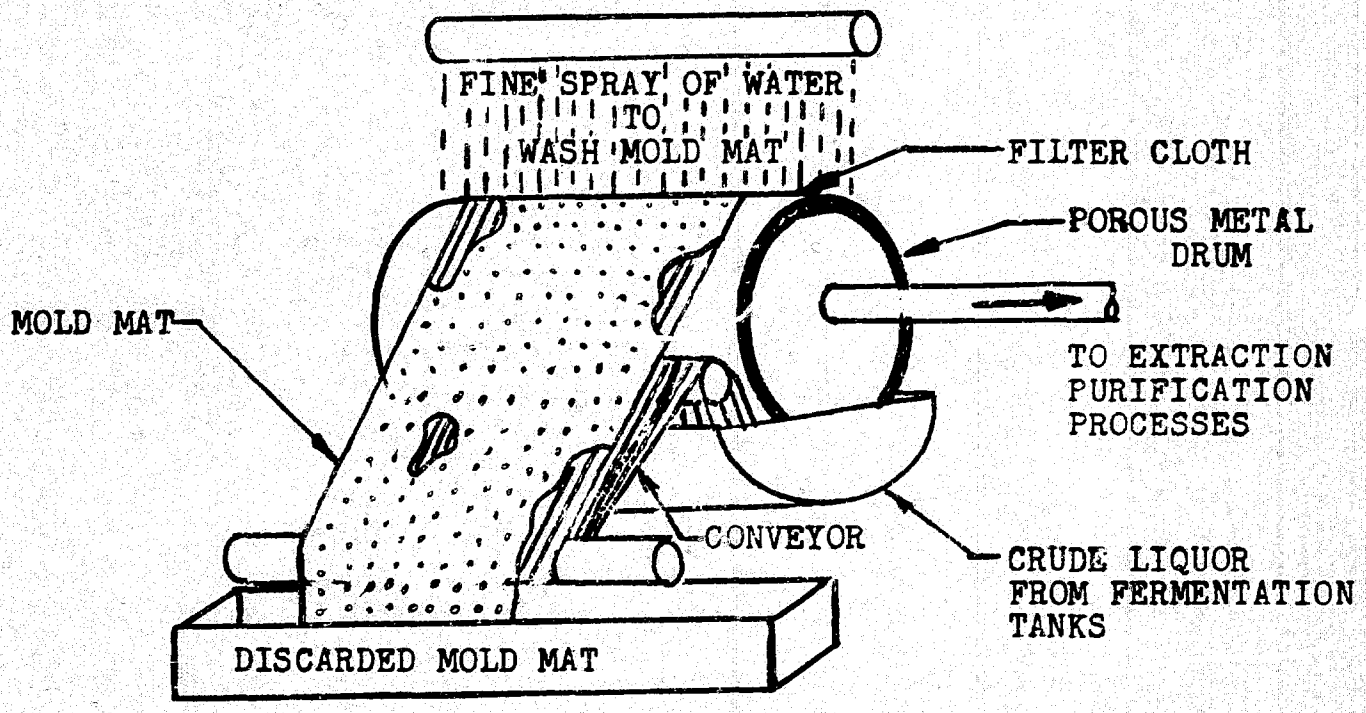
With the exception of storage tanks and pumps, most of the production equipment listed below must be specially designed and custom built.

PRODUCTION EQUIPMENT

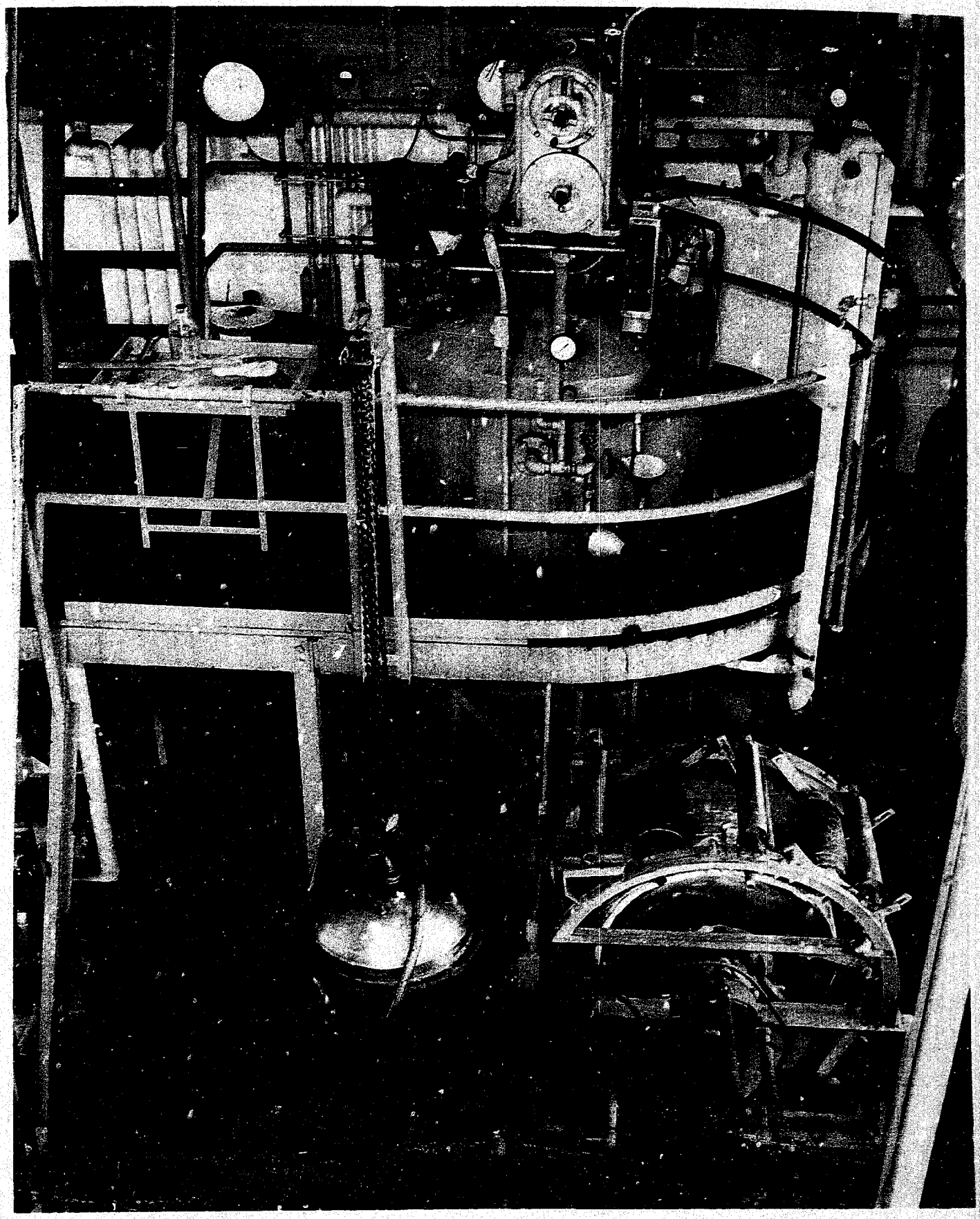
Description	Number Required	Estimated Cost Unit	Estimated Cost Total	Actual Cost
150 Gal. Fermenter	1	$3,000	$ 3,000	_____
500 Gal. Fermenter	1	5,000	5,000	_____
1,500 Gal. Fermenter	1	12,000	12,000	_____
15,000 Gal. Fermenter	1	65,000	65,000	_____
50,000 Gal. Storage Tank	3	20,000	60,000	_____
15,000 Gal. Storage Tank	1	10,000	10,000	_____
5,000 Gal. Storage Tank	1	5,000	5,000	_____

FIGURE 6

ROTARY DRUM FILTER



Rotary drum filter for removal of the mycelim and other solid matter from fermented culture medium prior to extraction of penicillin. This device is, in effect, a huge Buchner filter. The crude liquor is piped into a trough into which a large, porous, metal drum covered with fine cloth dips. As suction is applied to the drum, the liquid enters it and the solid matter is deposited on the cloth. The drum rotates in a counter-clockwise direction, and the solid matter is carried off on a conveyor that consists of a number of strands of twine or fine wire wrapped around the cloth cover and threaded over rollers as indicated. (Courtesy of J. P. Lippincott & Co.)



ROTARY DRUM FILTER AND
LARGE FERMENTOR

Fig. #7

PRODUCTION EQUIPMENT - continued

Description	Number Required	Estimated Cost Unit	Estimated Cost Total	Actual Cost
1,000 Gal. Storage Tank	3	$1,500	$ 4,500	_____
500 Gal. Storage Tank	15	1,200	18,000	_____
150 Gal. Storage Tank	5	400	2,000	_____
1 HP. Pump	3	300	900	_____
5 HP. Pump	15	500	7,500	_____
10 HP. Pump	5	800	4,000	_____
20 HP. Pump	4	2,000	8,000	_____
3 HP. Diffusion Pump	1	550	550	_____
Centrifigal Compressor	2	600	1,200	_____
Rotary Drum Filter	4	20,000	80,000	_____
Evaporator	5	4,000	20,000	_____
Water Condenser	3	800	2,400	_____
Filter Press	2	3,600	7,200	_____
Drier	1	4,500	4,500	_____
Biological Filter	2	4,000	8,000	_____
High Vacuum Subliminal Drier	1	5,400	5,400	_____
Ball Mill	1	5,000	5,000	_____
Sterilizer	1	4,000	4,000	_____
Packaging Machine	1	10,000	10,000	_____
Purifying Unit	1	2,000	2,000	_____
Washer	1	1,500	1,500	_____
Shaker Table	3	1,200	3,600	_____
Total			$360,250	

ADDITIONAL EQUIPMENT

Instrumentation for production equipment to control temperature, humidity, pH sterility and other parameters of process control is estimated at $200,000.

Installation of electrical wiring and process pipe lines which are steam sealed to maintain sterile operating conditions is estimated at $150,000.

Materials handling equipment such as conveyors, portable storage containers, and vehicles such as hand and motor driven trucks is estimated at $120,000.

Laboratory equipment for quality control research and testing is estimated at $175,000.

TOTAL CAPITAL EQUIPMENT

Item	Estimated	Actual
Production Equipment	$ 360,250	_____
Instrumentation	200,000	_____
Installation	150,000	_____
Materials Handling	120,000	_____
Laboratory Equipment	175,000	_____
Total	$1,005,250	

The equipment outlined above will be adequate to produce 800 pounds of each antibiotic per year.

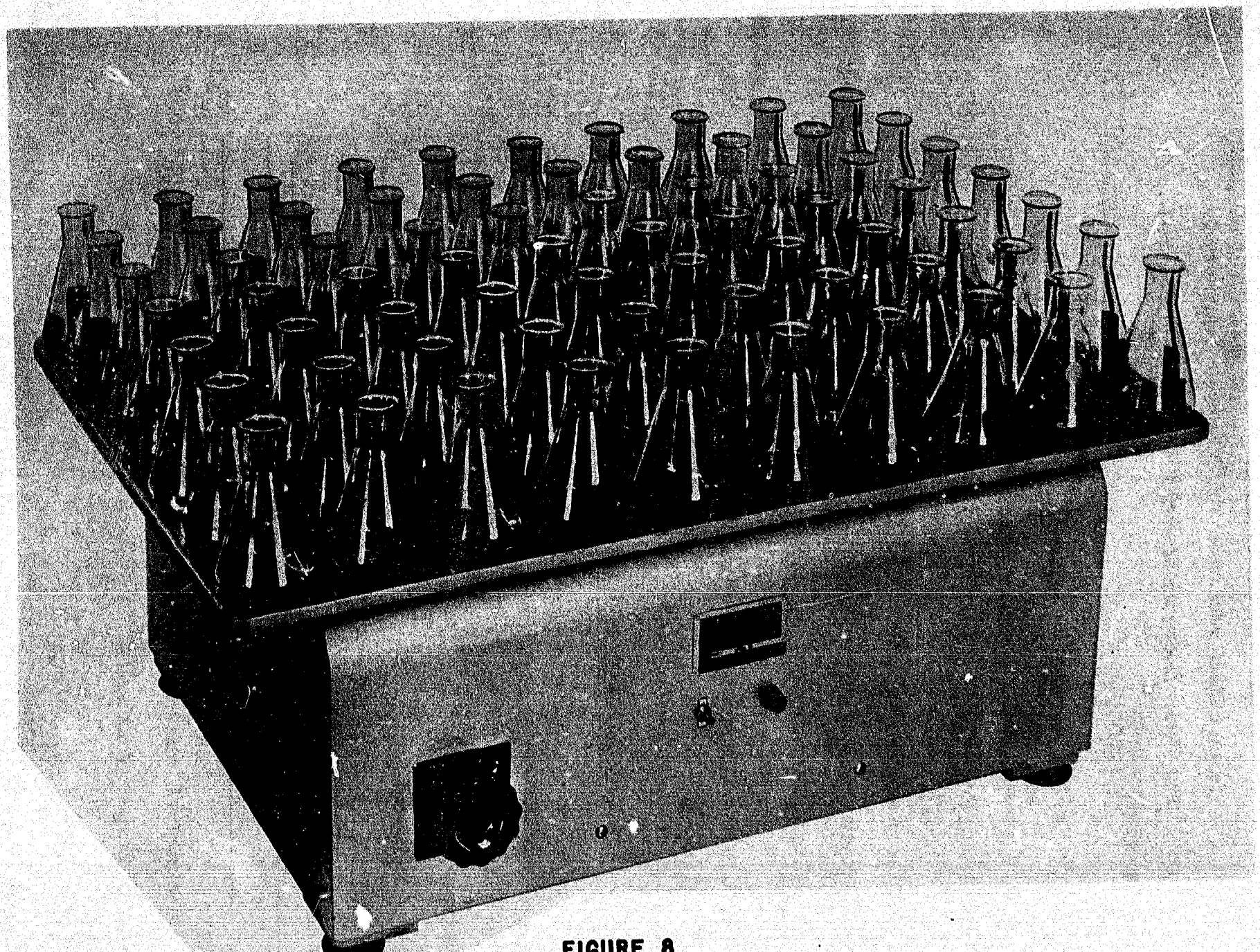


FIGURE 8

LABORATORY SHAKER

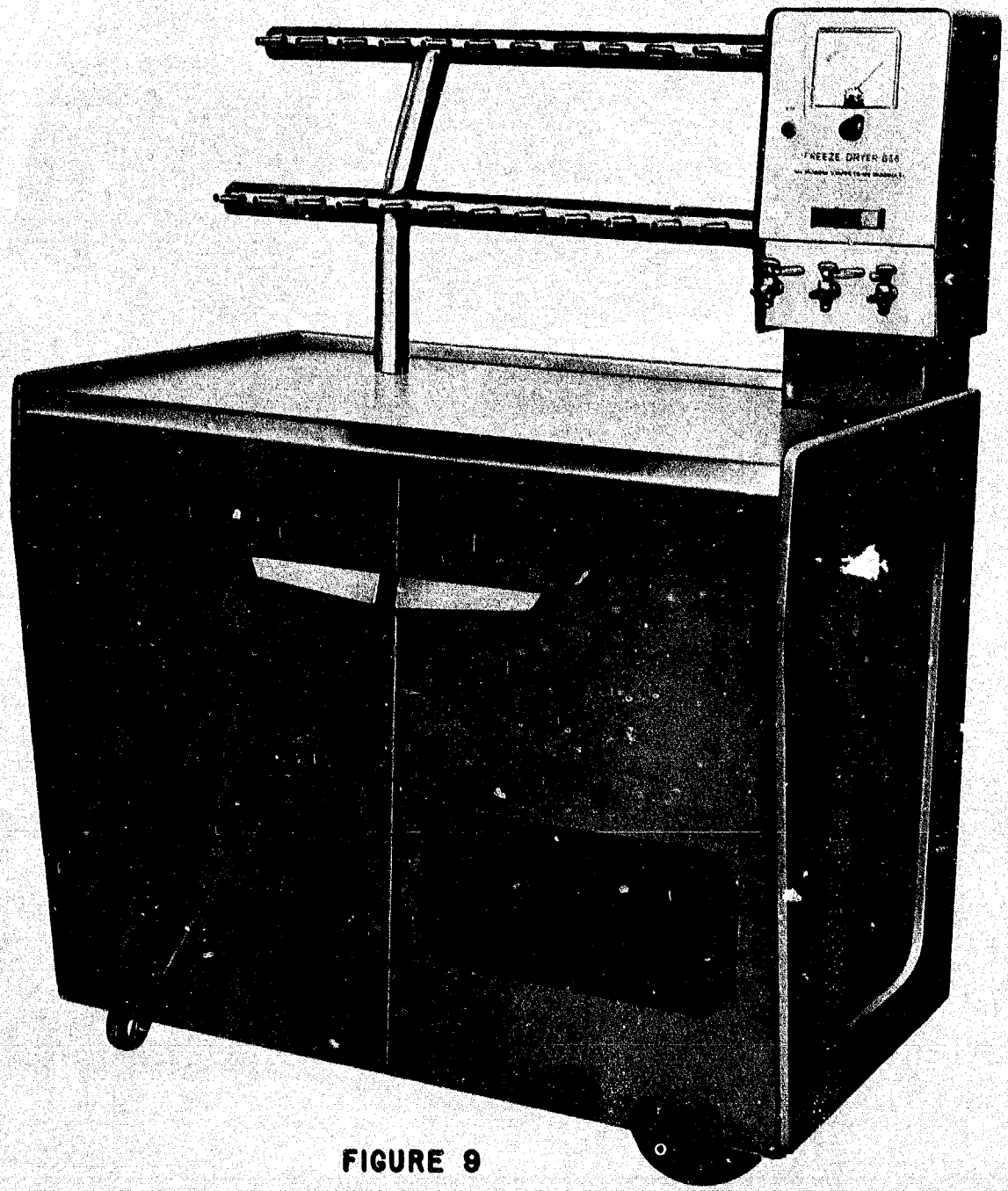


FIGURE 9

LABORATORY FREEZE DRIER

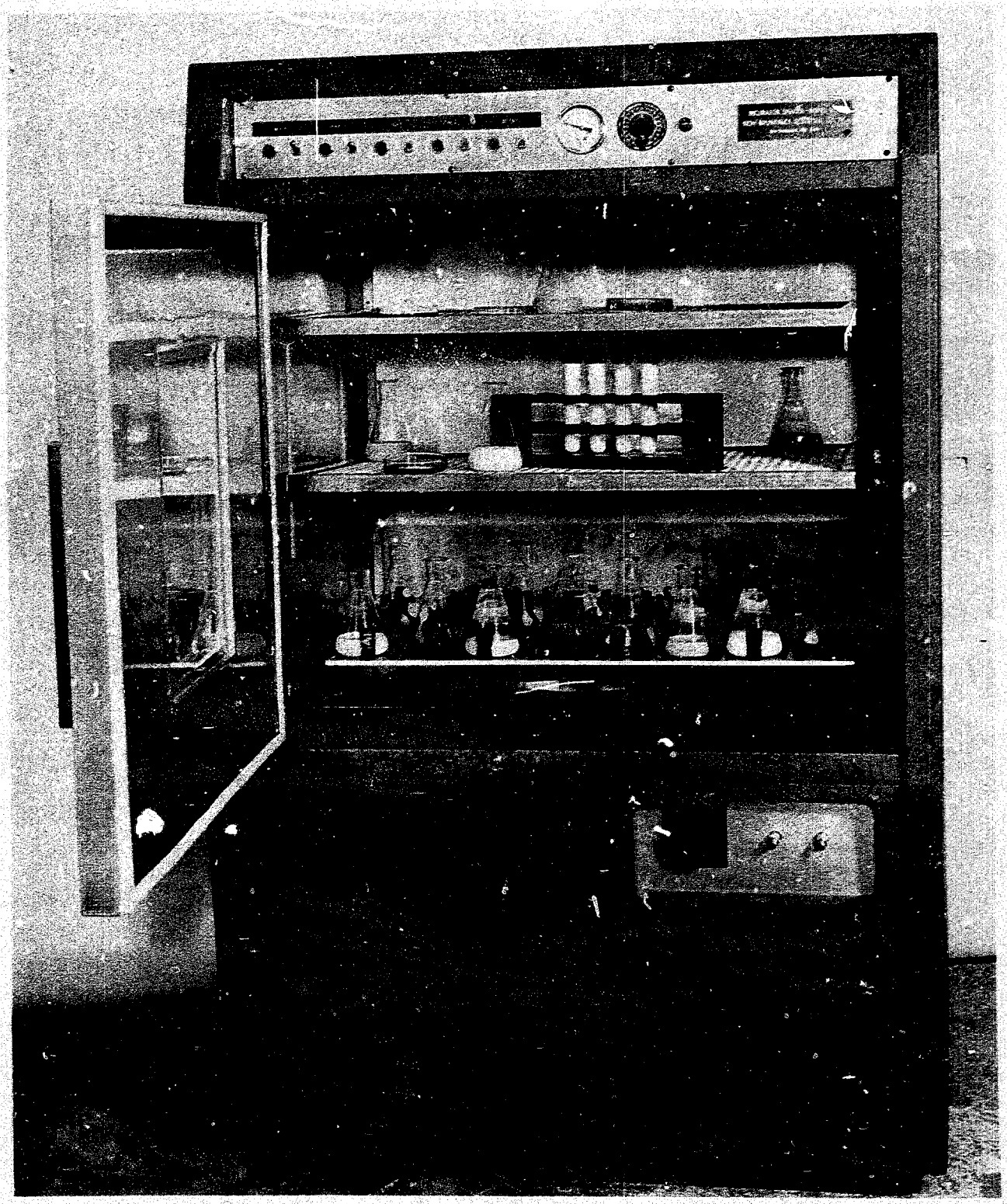


FIGURE 10

CONTROLLED ENVIRONMENT INCUBATOR SHAKER

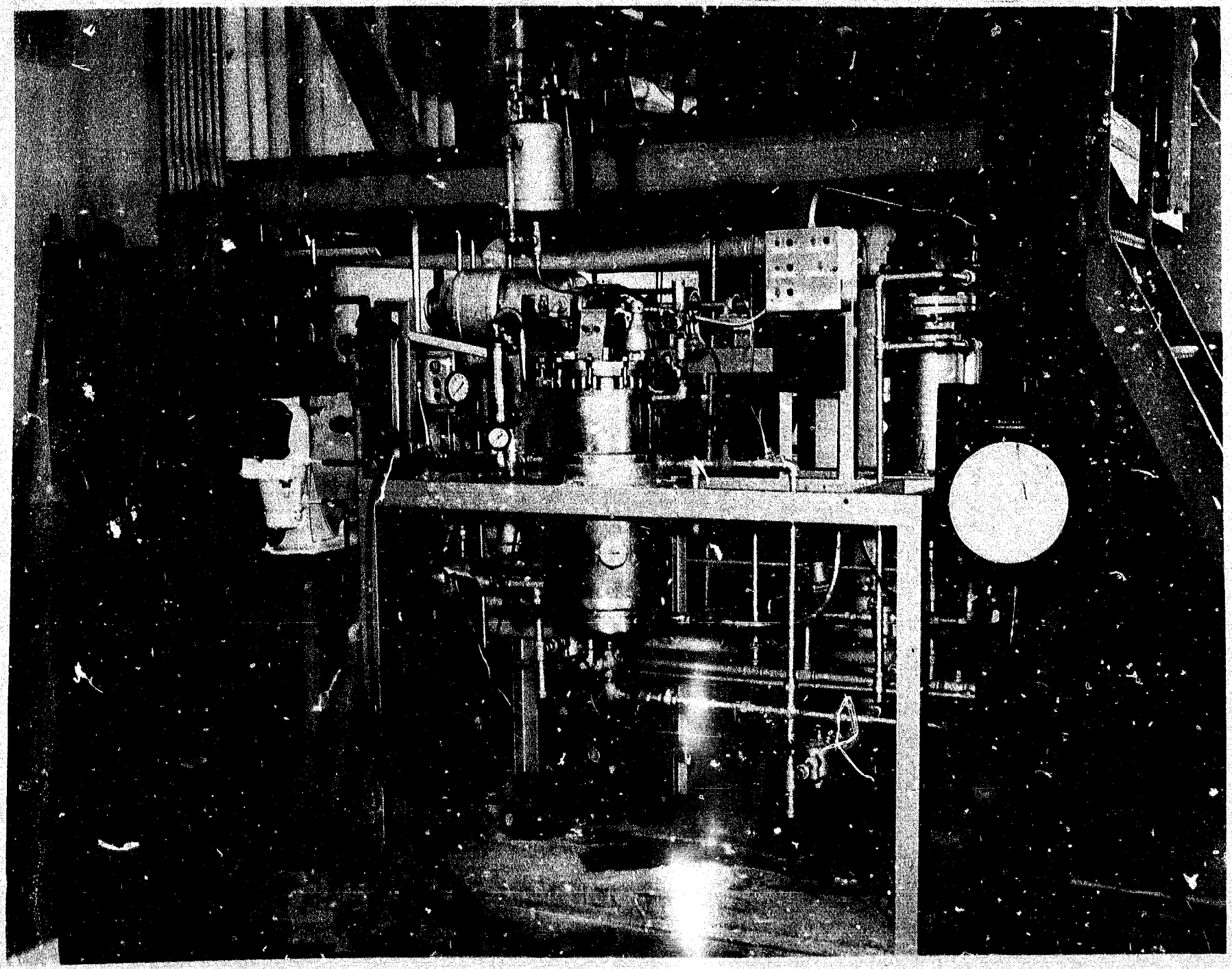


FIGURE 11
TEN GALLON FERMENTOR

Thru the courtesy of Rutgers University, Institute of Microbiology, some typical examples of laboratory equipment are shown on:-

1 - Page 20, figure 8 - Laboratory Shaker

2 - Page 21, figure 9 - Laboratory Freeze Drier

3 - Page 22, figure 10 - Laboratory controlled Environment Incubator Shaker

4 - Page 23, figure 11 - Ten Gallon Fermentor with accessories.

DIRECT MATERIALS

While the specific media employed by the various antibiotic producers is proprietary information of current manufacturers, it is believed that all manufacturer's employ variations of similar formula composed primarily of the following substances:

Material	Percentage
Corn-steep liquor solids	1-5
Lactose	1-3
Glucose	0-1
Sodium nitrate	0-0.5
Calcium carbonate	0-1
Phenylacetic acid	0.01-0.1
Water	Remainder

While the exact composition of the corn-steep liquor is unknown, the proximate analysis on a dry basis is as follows:

Material	Percentage
Total solids	40-60
Total nitrogen	7.8-7.8
Amino nitrogen	2.6-3.3
Lactic acid	12-27
Reducing sugars	1.5-14
Ash	18-20

In addition to these ingredients, small amounts of phynylalanine tyrosine, B-phynylethylamine, and tyramine are also present in the fermentation broth. The quantity of fermentation broth required to produce one pound of each antibiotic is approximately 560 gallons.

In the fermentation of Streptomycin, meat solids are used in place of the corn-steep solids.

In the recovery process, various solvents are used. Most of these are recovered and reused. The following chart contains these solvents and their recovery potency:

TYPE OF ABSORBENT	ELUTING AGENT USED	POTENCY OF PRODUCT OBTAINED UNITS PER MG
Sulfonated Phenol-formaldehyde resin	Aqueous NACL Aqueous H_2SO_4	100
Silicate-exchange resin	Aqueous NACL	50
Sulfonated coal resin	Aqueous NACL Aqueous H_2SO_4	100
Carbon	Acidic Menthanol water	200-350
Fullers earth	Aqueous pyridine hydrochloride	75
Copolymer of methacrylic acid and divinyl benzyl containing 5% divinyl benzene	Aqueous HCL	600
Same as previous containing 10% divinyl benzene	Aqueous HCL	600

ANNUAL COST OF DIRECT MATERIALS

As pointed out previously, the formulations of materials and quantities of each material used by current antibiotic manufacturers is considered as proprietary information and is not available for publication. As a result, a figure of $800,000 is estimated as the cost of direct materials for the purpose of completing the cost estimates of this report. This includes solvents and similar materials which are recovered and reusable.

DIRECT LABOR

Since the control of parameters in all process operations are imperative to a successful production run, all of the personnel directly related to production are considered semi-skilled.

DIRECT LABOR REQUIREMENTS

Operation	Number of Employees	Hourly Rate	Annual Cost Estimated	Annual Cost Actual
Fermentation	3	$2.50	$ 15,000	_____
pH Adjustment	1	3.00	6,000	_____
Absorbtions	2	2.50	10,000	_____
Evaporation	1	2.50	5,000	_____
Solvent Recovery	4	2.00	16,000	_____
Recovery	3	2.00	12,000	_____
Filtering	2	2.50	10,000	_____
Purification	2	2.00	8,000	_____
Blending	2	2.00	8,000	_____
Milling	1	2.00	4,000	_____
Filling	8	2.00	32,000	_____
Weighing	2	2.50	10,000	_____
Packaging	2	2.00	8,000	_____
Helpers	15	1.50	45,000	_____
Total	48		$189,000	

The tabulation above shows the direct labor required to produce 800 pounds of each antibiotic per year.

The above list does not include foremen or other supervisory personnel such as department heads or manufacturing and process engineering personnel that are indirectly involved in production. The employees are listed below under Indirect Labor Requirements.

INDIRECT LABOR REQUIREMENTS

Skill	Number	Salary Per Year	ANNUAL SALARY Estimated	Actual
Managers	4	$12,000	$ 48,000	_____
Engineers	8	8,000	64,000	_____
Biologists	2	8,000	16,000	_____
Microbiologists	2	8,000	16,000	_____
Chemists	4	7,000	28,000	_____
Supervisors	4	6,000	24,000	_____
Laboratory Technicians	10	5,200	52,000	_____
Clerks & Secretaries	10	5,200	52,000	_____
Maintenance	5	5,000	25,000	_____
Shipping & Receiving	4	5,000	20,000	_____
Totals	53		$345,000	

FURNITURE AND FIXTURES

Items	Number	Unit Cost	COST Estimated	Actual
Desk & Chair sets	38	$200	$ 7,600	_____
Filing Cabinets	30	50	1,500	_____
Typewriters	10	150	1,500	_____
Adding Machines	4	200	800	_____
General Fixtures			1,000	_____
Total Cost			$12,400	

SUPPLIES

Item	COST Estimated	COST Actual
Office Supplies	$ 5,000	_____
Maintenance	5,000	_____
Total	$10,000	

FIXED ASSETS

Item	COST Estimated	COST Actual
Land	$ 50,000	_____
Building	1,000,000	_____
Capital Equipment	1,005,250	_____
Furniture and Fixtures	12,400	_____
Total	$2,067,650	

DEPRECIATION

Item	Estimated Cost	Estimated Life	ANNUAL DEPRECIATION Estimated	ANNUAL DEPRECIATION Actual
Building	$1,000,000	25	$ 40,000	_____
Capital Equipment	1,005,250	10	100,525	_____
Furniture & Fixtures	12,400	5	2,480	_____
Total			$143,005	

MANUFACTURING OVERHEAD

Item	ANNUAL COST Estimated	Actual
Power	$ 60,000	_____
Fuel	32,000	_____
Water	2,400	_____
Depreciation	143,005	_____
Supplies	10,000	_____
Total	$247,405	

GENERAL EXPENSES AND SELLING COSTS

Item	ANNUAL COST Estimated	Actual
Indirect Labor	$ 345,000	_____
Supplies	10,000	_____
Insurance	10,000	_____
Selling and Advertising Costs	800,000	_____
Total	$1,165,000	

WORKING CAPITAL

The working capital required will vary depending on the quantities of direct materials purchased and on the terms of sale of the finished product.

It is estimated that a working capital of $400,234 would be required to begin production. This constitutes a 60 day coverage of manufacturing plus overhead costs.

CAPITAL REQUIREMENTS

Item	COST Estimated	COST Actual
Fixed Assets	$2,067,650	_____
Working Capital	400,234	_____
Total	$2,467,884	

SALES REVENUE

The current sale price of Penicillin, Streptomycin and Tetracycline is based on 100 mg. vials. Depending upon the manufacturer, the price of all three varies from $.65 to $1.10 per vial. For the purposes of this report we will select an average figure of $.80 per 100 mg. Therefore, the price per pound is $3,632.

Annual Production	Sales Price	SALES Estimated	SALES Actual
2400 pounds	$3,632/pound	$8,716,800	_____

This computation is based on the production of 800 pounds of each antibiotic per year.

RECAPITULATION OF COSTS, SALES AND PROFITS

Item	Estimated Cost		Actual Cost
Direct Materials	$ 800,000		_____
Direct Labor	189,000		_____
Manufacturing Overhead	247,405		_____
General Expenses and Selling Costs	1,165,000		_____
Total Manufacturing Costs		$2,401,405	_____
Interest on Loans	25,000		_____
Legal Fees	3,000		_____
Auditing	6,000		_____
Unforeseen Expenses	25,000		_____
Total Administrative Costs		59,000	_____
Travel, Bad Debts, Discounts and Allowances		20,000	_____
Total Business Costs		$2,480,405	_____
Profit before Taxes		6,236,395	_____
TOTAL ANNUAL GROSS SALES		$8,716,800	_____

TRAINING

In some areas skilled workers may be available locally. In other areas most of the workers may have to be trained.

If ample skilled workers are not available, adequate training would be assured by using one or more of the following methods:

1. If the plant is designed and installed by a competent engineering firm, the contract should be negotiated, if possible, on a turn-key basis. On this basis the contractor agrees to operate the plant and produce the quality and quantity of the product stated in the contract for an agreed period of time. Such a contract would assure adequate personnel training, since full quantity and quality could not be produced with an untrained staff.

2. The engineering firm that designs and installs the plant can usually make training arrangements to have key personnel placed for training purposes, in a foreign plant. This would provide training for the key personnel while the plant is being installed.

3. If neither of the above methods is possible, then qualified and experienced indivduals should be employed for the key positions, either permanently or temporarily, to perform the key operations and assist in training the organization, even if they must be secured outside the country.

4. The manager should have years of successful experience in this type of business and be fully qualified in all phases of management, including the training of employees.

SAFETY

The requirement for and the cost of a safety program in a pharmaceutical manufacturing plant can be justified on either economic or humanitatian bases. Some of the economic reasons are: reduced labor turnover, less machine shutdown time and less repair cost, and less labor time lost through accidents.

There is always danger of accident and injury in a pharmaceutical plant through burns (including acid and alkali burns), materials handling, and accidents caused by the improper use of machinery. Because of this the manager should take action to bring to the attention of each employee the importance of safety precautions and prompt first aid.

In general, the equipment manuals that are usually furnished with each item of equipment contain guidance for the operators to insure their safety, and these manuals should be made available

to the workers. The **most critical** instructions for operators safety should be displayed as warning signs on or near the equipment affected. Some space provision should be made for a first aid room.

A fire brigade should be established and each member trained as to his responsibility in case of fire. Fire drills should be conducted periodically.

Acid and alkali antidotes: An employee may accidently drink a strong acid or alkali. The symptoms are: Burn and stain on the lips and mouth; burning pain in throat and stomach; straining and vomiting; perhaps suffocation always shock. For acids, the antidote is baking soda, magnesia, lime water or soap-suds. For alkalis, the antidote is vinegar, lemon juice. Also, in both poisons give large doses of olive oil, milk, eggs, or flour and water, to dilute and soothe the parts, and then induce vomiting.

Acid and alkali burns: With either type of burn, wash off as quickly as possible with a large quantity of clean water. For this purpose, emergency showers should be provided. After washing the burned area the amin object is to exclude the air as quickly and completely as possible from the injured part. A 5 percent tannic acid solution is preferred, although if this is not available a thin paste made with water and baking soda may be used as a temporary application. Place several layers of sterile gauze ove the burned area; saturate with 5 percent acid (tannic) solution and bandage loosely.

BUDGET CONTROL

A requisition form designed to provide accurate records of procurement and indicate the purpose of procurement with the least amount of time and effort is shown on page 38.

This form has an account number for each type of the various expenditurès which the manager will review in detail, monthly or oftener, in order to control his expenses. Some items, such as power and water, are usually under contract and are easily checked by reference to monthly bills. For simplification, items (marked with an asterisk below) are omitted from the purchase requisition. V riations in the labor costs are easily reviewed by examination of the payroll vouchers. The simplified type of control thus provided makes certain that the manager can control expenditures promptly.

A sample voucher check is shown on page 39. Voucher checks should be used for the payment of all expenditures and the appropriate book account number placed on each voucher.

At the end of each month the manager will receive a statement of all expenditures broken down by budget accounts. If the expenditures exceed the budgeted monthly allowances of any of the accounts, the bookkeeper will furnish the manager with a break-down of all

expenditures relative to the budgeted accounts exceeded. All these supporting data can be secured by reference to the purchase requisitions and the check vouchers. This reference will enable the manager to determine what caused the over-expenditure and take corrective action.

If at any time during each month it becomes apparent that expenditures will exceed any of the budget accounts, the bookkeeper will bring this to the attention of the manager for his information and action.

BUDGET CONTROL ACCOUNTS

Account Number	Monthly Expense	Monthly Budget	Annual Budget	Actual
AA Administrative	$_____	$ 150	$ 1,800	_____
BB Sales	_____	500	6,000	_____
CC Direct Materials	_____	1743	20,923	_____
DD Supplies	_____	116	1,400	_____
EE Power *	_____	20	250	_____
FF Water*	_____	4	50	_____
GG Fuel	_____	17	200	_____
HH Unforeseen Expense (Reserve Account)	_____	250	3,000	_____
LL Direct Labor *	_____	916	11,000	_____
KK Indirect Labor *	_____	666	8,000	_____
SS Depreciation (Reserve Account)	_____		1,070	_____

MATERIALS AND SUPPLIES

1. Are the majority of materials and supplies available locally?
2. Is the local material market competitive?
3. Is satisfactory delivery of local materials assured at reasonable prices?
4. What materials and supplies must be imported?
5. Are they available in world markets at competitive prices?
6. Would prompt delivery of imported materials and supplies be assured so that large inventories would not be required?

MARKET FACTORS

1. Is there already a demand for the product?
2. How is demand for the product now satisfied?
3. What is the estimated annual increase in local consumption over the next five years?

4. If the product is already being manufactured, can the existing and estimated future local market absorb production of the new plant without price-cutting or other dislocations?

5. Would the estimated sales price and quality of the new product make it competitive with an imported equivalent? After adjusting cost to local conditions, is the estimated sales price of the product so high that tariff protection is necessary to protect it from imports?

MARKETING PROBLEMS

1. In calculating costs of the product, has adequate allowance been made for the expense of a sales department, advertising, and promotion that might be required?
2. Do marketing and distribution facilities for the product exist?
3. What types of organizations will the product be sold to?

ECONOMIC FACTORS

1. How much foreign exchange (and in what currency) is required to import machinery, equipment, and supplies?
   A. How much foreign exchange (and in what currency) is required for annual interest payments and amortization of any loans contracted to import machinery and equipment, or for payment of royalties and technical services?
   B. How much foreign exchange (and in what currency) is required for annual import of raw materials and supplies?
   C. What are estimated annual foreign exchange earnings and in what currencies?
   D. Has careful consideration been given to the possibility of depreciation in the foreign exchange value of the local currency?
   E. Has careful consideration been given to the possibility of import controls, or restrictions on availabilities of foreign exchange necessary to operate the business?
   F. What benefits would the new business bring to the economy in the use of local raw materials in employment and in technology?
   G. Do dependable facilities exist for transportation, power, fuel, water, and sewage?

PERSONNEL

1. Is there an adequate skilled labor supply near the plant location?
2. Can the problem of training competent management and supervisory personnel be solved?

LAWS AND REGULATIONS

1. Do existing labor laws, government regulations, laws and taxes favor establishment of new business?

FINANCIAL FACTORS

1. Technical advice on selection of machinery and equipment.
   - A. In selecting the machinery and equipment for the new plant, have reputable and competent engineers and technicians been sonsulted?
   - B. Have they been asked for advice on the most suitable types of machinery and equipment for the process and locality?
   - C. Have they carefully compared costs of various suppliers?
   - D. Credit terms offered purchasers?

FINANCIAL REQUIREMENTS OF THE PROJECT

1. In estimating the cost of the project, has careful consideration been given to:
   - A. The effect on costs of delays in construction schedules?
   - B. In delivery and installation of machinery and equipment?
   - C. In import of essential raw materials and supplies?

2. In calculating cash flow and working capital requirements, has careful consideration been given to:
   - A. Maintaining adequate inventories of raw materials?
   - B. Supplies and spare parts?
   - C. The time required to liquidate credit sales to customers and bad debts?
   - D. The period necessary to get the plant into production?
   - E. Cash required to amortize its principal loans?

3. If the economy is in a period of inflation, has full allowance been made for the influence of rising prices and wages on the cost of the projects and on working capital requirements?

SHORT TERM BANK CREDITS

1. Has it been possible to make arrangements with local banks to finance short-term working ckapital requirements of the business?

FINANCIAL PLAN

1. Has a definite plan to finance the project been worked out?
   - A. Is sufficient capital available locally?
   - B. If not, what is the plan to obtain the required capital?

GLOSSARY

ASEPTIC - Not septic; free from septic material.

BIOSYNTHESIS - The building up of a chemical compound in the physiologic processes of a living organism.

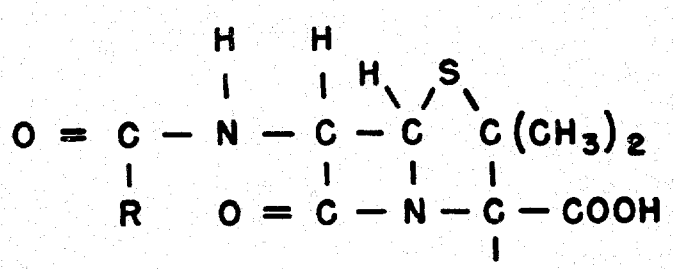
DELIQUESCE - To dissolve gradually and become liquid by attracting and absorbing moisture from the air.

INOCULUM - A highly productive strain of fungi used to seed a batch of fermentation liquid.

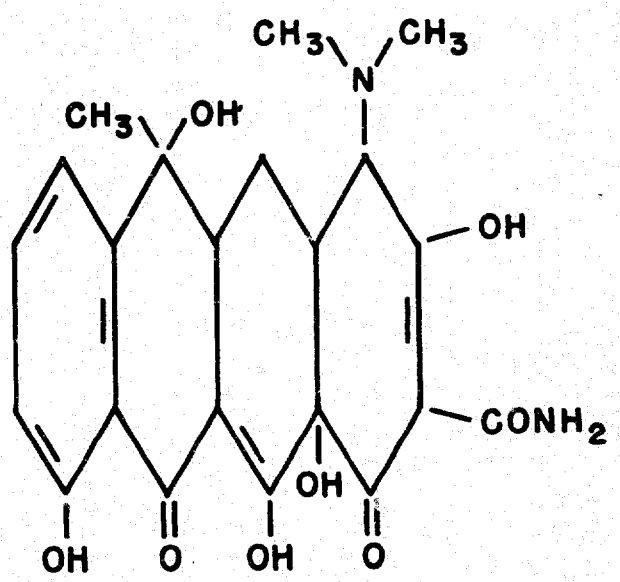
STERILE - A condition in which no living organism is present.

SUBLIMATION - The process of converting ice directly to water vapor.

CHEMICAL FORMULAS :

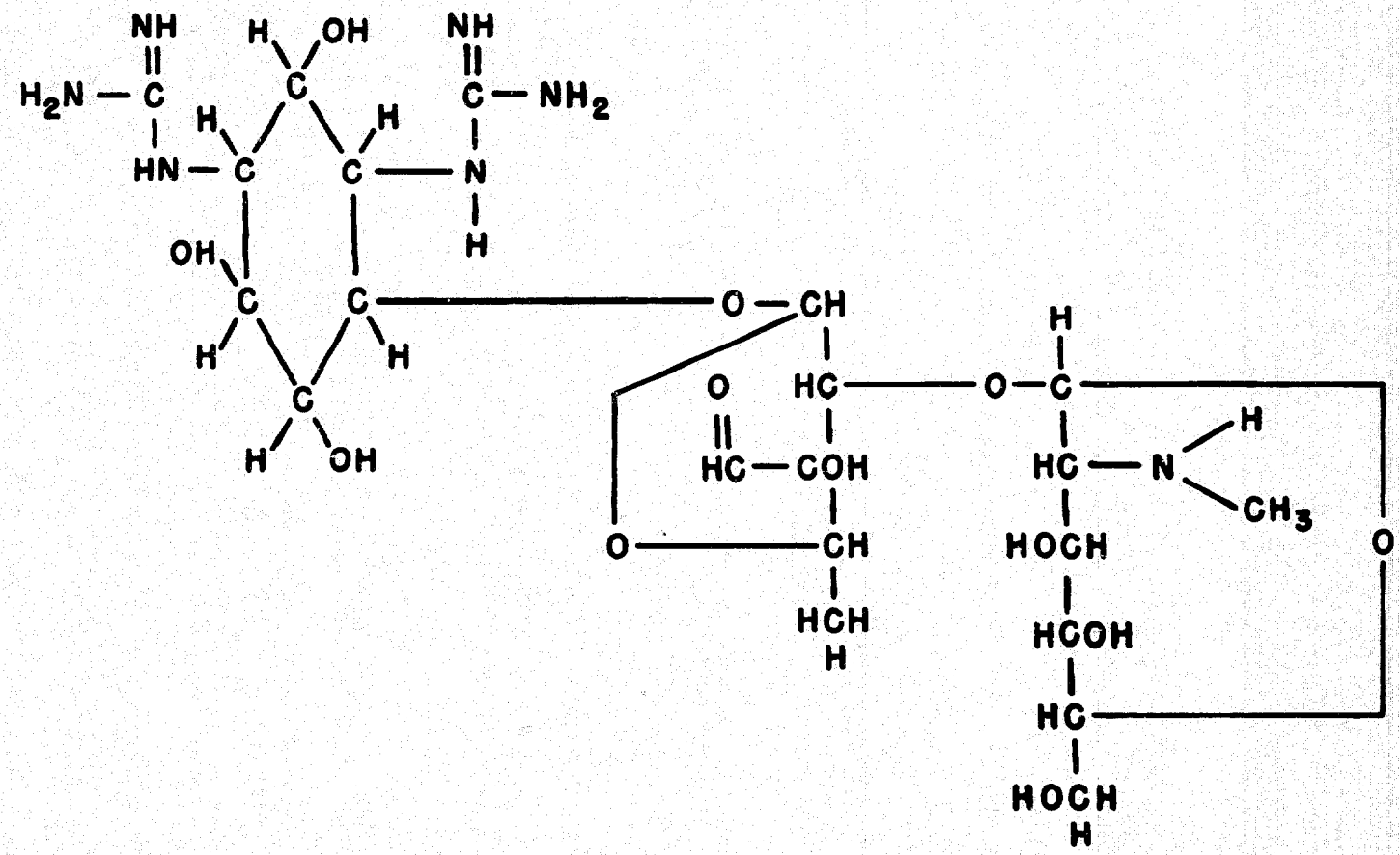


PENICILLIN



TETRACYCLINE

CHEMICAL FORMULAS (CONT'D) :



STREPTOMYCIN

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