If we were to select ten indispensable drugs in the practice of medicine, digitalis, would be one of them. We must not forget that Withering gave us this drug and, furthermore, taught us the clinical use of it, for he was really a great clinician, as well as a great investigator.

Withering suffered from tuberculosis, and in 1793 he published an excellent modern treatment for that disease. He died of tuberculosis in 1799. When dying, one of the most celebrated of puns was uttered by a friend, who remarked that "The Flower of Physicians was now withering." He lies buried in Edgbaston Churchyard, and the foxglove appropriately adorns his monument.

MEDICINE MAKING AS DEPICTED BY MUSEUM DIORAMAS.*

BY CHARLES WHITEBREAD.[1]

Museums do what they can to give publicity to collections of interest to special groups by encouraging staff members to prepare papers for presentation at conventions and for publication in association journals. This is done to make the collections of use to those who do not find it convenient to visit the museum.

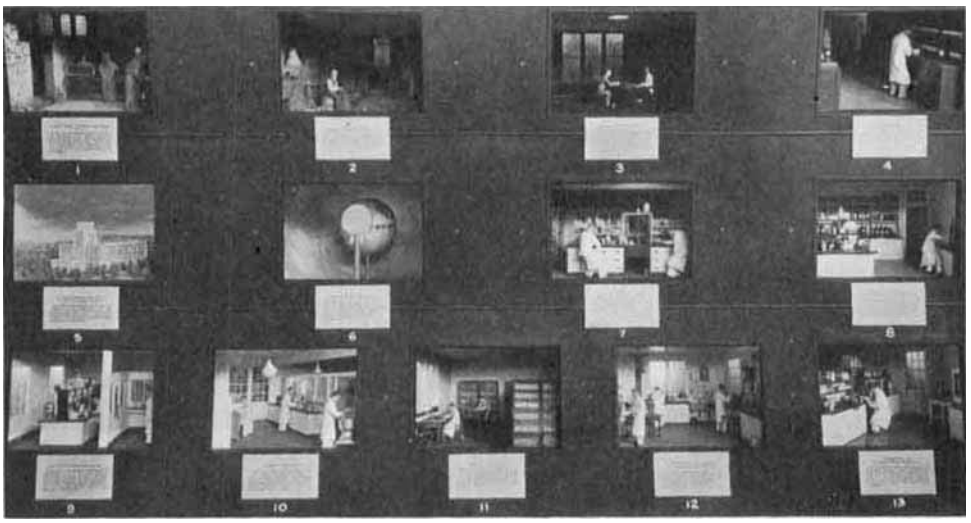

Fig. A.—Dioramas of historical and scientific phases of medicine-making.—*Courtesy of U. S. National Museum.*

The collection of dioramas outlined here illustrates historical and modern phases of medicine making. Pictures of the dioramas are shown, the general labels being lettered and the descriptive legends numbered. These labels and legends were prepared for the laity, but they will be of interest to members of the medical and pharmaceutical professions as well. Reference to the letters and numbers in the following text and illustrations will make it easy to follow the story.

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* Section on Historical Pharmacy, A. PH. A., Portland meeting, 1935.

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A. THE MANUFACTURE OF MEDICINES.

Up to comparatively recent times medicines consisted largely of salves, infusions, powders and decoctions. All of the preparations were crude and those intended to be taken by mouth, nasty in appearance and vile-tasting. There were no standards of uniformity other than a few books of recipes.

With the growth of medical and pharmaceutical knowledge, the ramifications of pharmacy have become so extensive that specialization is imperative. It is no longer practical or possible for one man to undertake, along with the filling of prescriptions and the management of a retail store, the collection of materials from all over the world, and the elaborate processing, assaying, compounding, standardizing, etc., of the great variety of things required by the medical profession. These later phases of pharmacy have been separated from the rest and given over to organizations especially equipped for the purpose—pharmaceutical manufacturers.

The following scenes show how medicine making has progressed, and give glimpses of a typical pharmaceutical manufacturing plant to indicate the hundreds of specialized operators and operations that are required and the careful laboratory testing that is necessary to make the medicines of the present day.

1. A Monastery Apothecary Shop.
(17th century.)

In the 17th and 18th centuries apothecaries were shopkeepers who collected medicinal herbs and chemicals and prescribed them for the sick. During the Dark Ages apothecaries were often monks who ministered to the physical as well as the spiritual ailments of their patients.

2. A Pharmaceutical Laboratory.
(19th century.)

In the early 19th century pharmacy began to emerge as a science separate from medicine. The apothecary, then called a pharmacist, devoted his time to collecting and compounding medicines, while the physician became a specialist in caring for the sick.

3. Doctor and Detail Man.

Pharmaceutical manufacturers send trained representatives known as detail men to visit members of the medical profession. These representatives not only furnish information concerning new medicines, but establish personal contacts with physicians thus making it possible to coördinate the findings of the laboratory with clinical needs.

4. A Modern Prescription Pharmacy.

Modern pharmacies are conducted for the benefit of physicians and the public at large. The pharmacist of to-day obtains his medicinal preparations, already prepared and standardized, from pharmaceutical manufacturers. He then compounds and dispenses them in accordance with physicians' prescriptions.

5. Modern Pharmaceutical Manufacturing Plant.

Several thousand medicinal substances are in constant use by the medical profession. The manufacturing plants required to make these are of necessity quite extensive. Every effort is made to have working conditions pleasant and healthful in all respects.

6. A World of Raw Materials.

The materials from which medicinal substances are derived come from the far corners of the earth. Some are animal, some vegetable and some mineral in origin. Many of the newer drugs are obtained as by-products of other industries or are prepared synthetically from other chemicals.

7. Control of Raw Material Purchases.

The identification and assay of raw material are of primary importance in controlling the quality of the finished product. The man at the left is studying a botanical drug to insure its exact uniformity to official requirements. The man at the right is engaged in extracting the alkaloid of another specimen to determine its drug potency.

8. Chemical Control of Various Stages of Manufacture.

This is another control laboratory. In the rear, two chemists are analyzing specimens of products taken at various stages of the manufacturing process. In the foreground, a finished product is being checked for accuracy of formula and also physical characteristics, such as appearance, disintegration, solubility, time, etc.

9. Bacteriological Research.

Microscopic living organisms produce infectious diseases in man. This scene shows a group of bacteriologists at work. Through study of these organisms and their toxic products, in which industrial laboratories participate, much progress has been made against these diseases.

10. Chemical Research.

Here is a view of a chemical laboratory. One of the chemists is altering the structure of a known chemical compound. The discovery of new chemical substances and the synthetic preparation of others known to exist but difficult or expensive to obtain is a field of unlimited possibility for progress.

11. Library Facilities.

Progressive research work involves the frequent publication of observations as well as the necessity for keeping informed concerning the publications of other laboratories. For this purpose, pharmaceutical manufacturers must maintain complete periodical and reference libraries.

12. Pharmaceutical Research and Biological Extraction.

The study of the action of drugs by determining their effects on animal tissues and functions and the isolation and recovery of physiologically active extracts of animal tissue are two highly important divisions of pharmaceutical research.

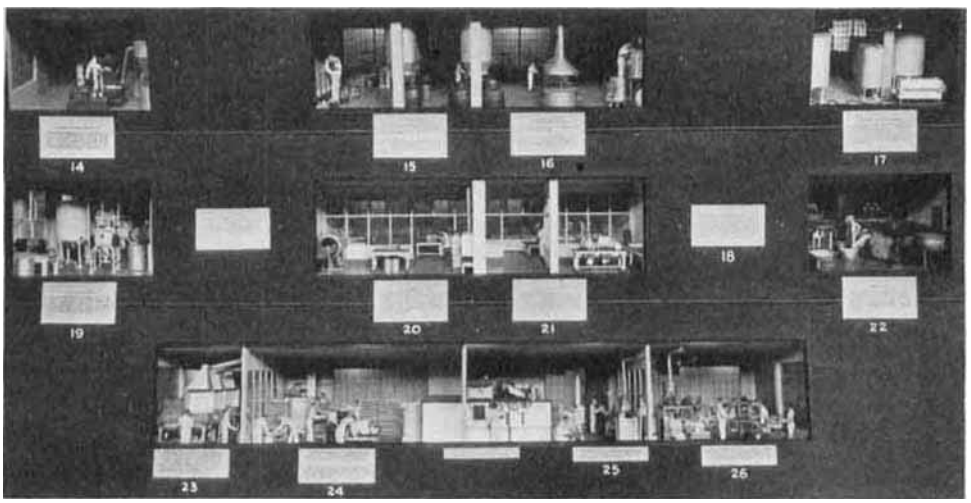

Fig. B.—Industrial scenes in a modern pharmaceutical manufacturing establishment.—*Courtesy of U. S. National Museum.*

13. Laboratory of Experimental Pharmacy.

The above scene shows a laboratory of experimental pharmacy where manufacturing methods are worked out on a laboratory scale, and where such problems as color, taste, appearance and stability are determined for each product before it is given to the plant for actual production.

B. THE MANUFACTURE OF MEDICINES.

Extraction of medicinal substances from drug-bearing leaves, barks, beans and roots may be likened in some respects to the ordinary percolation of coffee. The crude material is first ground or milled, then packed into the percolators while it is moist and allowed to macerate or soak for a while before the percolate containing the extractive is drained off.

The fluid percolate is concentrated by evaporation. In some instances "open evaporation," by merely boiling the fluid is practical. Often, however, heat may destroy or alter the properties of the drug so that it is necessary to concentrate by distilling in a vacuum at low temperature. Powdered extracts are obtained by distilling off all the fluid and drying the residue to a solid form. The extracts obtained in this way may then be standardized and incorporated into the form of the desired product.

Scenes 23 to 26 show how granular effervescent salts are made. An effervescent preparation is obtained by putting a dry acid and a dry carbonate into water simultaneously. The carbon dioxide gas which is liberated produces the effervescence as it bubbles through the water. In order to prepare a granular effervescent salt it is necessary to mix the dry powders, moisten them just enough to allow them to cake slightly and then remove the moisture to check the reaction before an appreciable amount of gas has escaped. With automatic controls and with conditioned air, this may be accomplished with such precision that the resulting product is uniform in chemical composition.

14. Corner of Milling Room.

The balloon-shaped bags over each mill serve to collect and confine the dust from the milling process so that the air is clean and clear at all times. Dust-free air of this kind protects the workers and prevents contamination of the various batches of material being ground.

15. Percolation.

The ground, moistened drug is packed into small percolators. The fluid, or menstruum, used varies with different drugs but usually contains alcohol. The percolate contains the extracted drug. This must be sent to the control laboratory to determine the concentration of the active principle.

16. Evaporation and Vacuum Distillation.

Aqueous extracts are concentrated in steam-jacketed evaporating tanks. Vacuum stills concentrate, at low temperature, percolates containing alcohol or drugs which might deteriorate if subjected to strong heat. The alcohol is recovered and rectified by further distillation.

17. Preparation of Elixirs.

The mixing of ingredients is accomplished by mechanical stirring devices in glass-lined tanks, varying in capacity from 5 to 1000 gallons. Subsequent clarification and filtering is accomplished by mechanically pumping the elixir through a large filter press and back into another tank.

18. Pharmaceutical Manufacturers.

Many great organizations similar to the one depicted in this series of dioramas have been built up to coöperate with modern pharmacists and to supply them with uniform, dependable and standardized therapeutic agents in keeping with the most recent advances in medical science.

19. Emulsification.

Some emulsions can be made with a high speed vacuum mixer, not unlike a large egg beater, operating in a closed tank. With others, however, particularly where it is necessary to break the dispersed phase into particles of colloidal dimensions, colloid mills are used.

20. Ampuls.

Sterile solutions are packaged in sealed glass containers called ampuls. After the solution is placed in ampuls with special asceptic technique and sealed it may again be sterilized by immersing the ampuls in hot water or subjecting them to high temperature produced by steam under pressure.

21. Sterile Solutions.

Solutions of drugs which are to be injected into the tissues or into the blood stream, must be prepared with great exactness to keep them free from contamination with foreign materials. Each solution is passed through a porcelain filter to remove all bacteria without exposing the product to the air.

22. Ointments.

Ointments are made by stirring the desired medicinal ingredients into the correct mixture of melted greases, fats and waxes. After cooling, a mixture of this kind returns to a semi-solid consistency and is then milled with special equipment such as that shown in the center of the room.

23. Granular Effervescent Salts.

The ingredients of a granular effervescent salt are weighed and mixed in an air-conditioned room. Two operators check each weight to guard against error. The mixers are operated a sufficient length of time to obtain a thoroughly uniform mixture. Each mixture is assayed to insure uniformity.

24. Granular Effervescent Salts.

The dry mixture is spread on trays and subjected to an atmosphere of extreme humidity. This is done in the cabinet at the rear. The moist granules are then screened, placed back on the trays and passed into drying tunnels where the atmosphere is again automatically controlled.

25 and 26. Granular Effervescent Salts.

The dry granules as they emerge from the tunnel are removed from the trays, again screened and collected in hoppers. The hoppers are used to load the filling machines from which the filled bottles pass on a continuous belt to the capping, labeling and cartoning machines in succession.

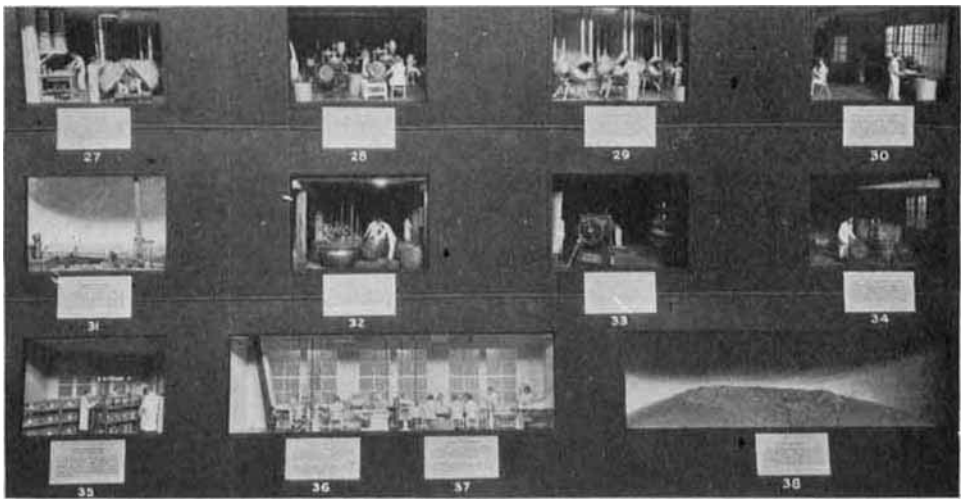

Fig. C.—A continuation of the industrial scenes, the final dioramas dealing with standardization, finishing, packaging and distributing.—*Courtesy of U. S. National Museum.*

C. THE MANUFACTURE OF MEDICINES.

One of the earliest improvements in oral medication was the development of the use of pills as a method of giving medicine in concentrated form. By swallowing a whole pill the patient was able to avoid its bad taste. The earliest type was the so-called mass pill made by moistening powders with a sticky substance and rolling them into pills while they are of a doughy consistency. The invention of a method of coating the pills with sugar was a further refinement in the interest of taste.

The next forward step was the development of the friable pill process in which the pills are made in large revolving tubs by gradually adding the powdered mixture to a previously counted number of starters without the use of a sticky excipient. In this process the pills gradually build themselves up like a snowball by adherence of the moist powder to the starters as the tubs revolve. With a sugar coating this form of pill presents the advantages of the older type plus the additional advantages of friability and greater accuracy of dosage. The next advance was the development and refinement of the process for compressing tablets. It is now possible to punch powders into tablets by machine with an accuracy equal to that obtained in friable pills and at less cost.

The problem of dispensing to retailers is a complicated one. For each product thought must be given to the type of package which is most suitable not only from the standpoint of convenience, cost and appearance, but also with respect to stability after it leaves the plant. Moreover, each package of each manufactured lot must bear its individual lot number. This makes it possible to trace the entire manufacturing history of any single bottle of medicine on the market at any time.

27. Friable Pills.

An operator is shown pouring the powders slowly onto the starters in the revolving tubs, moistening the mixture at the same time. When the pills have attained the desired size as measured in the sizer which is shown at the left, they are dried in ovens before being coated.

28. Compressed Tablets.

Powdered drug mixtures are converted into minute granules by moistening, drying and screening. They are then punched into tablets by rotary compressing machines. The operator checks the weight of the tablets for each machine at 15-minute intervals to be sure that the punches retain their correct adjustment.

29. Coating of Pills and Tablets.

Pills or tablets are coated by being rolled in sugar syrup in revolving tubs. Color coatings are applied in the same way. After the coatings are applied a sample of each lot is sent to the Control Laboratory for chemical assay, and for testing disintegration and solubility time.

30. Filling Hard Gelatin Capsules.

Special filling equipment designed to fill empty gelatin capsules with an exact weight of powder renders this form of medication available for those who desire it. This type of filling is carried out in conditioned air, and the capsules are put into bottles and sealed before leaving the room.

31. Fishing for Cod—Lofoten, Norway.

From the livers of cod fish are obtained the growth-promoting vitamin A and the antirachitic vitamin D. At certain seasons the fish migrate to the coasts of Norway and Newfoundland. Codfishing is largely confined to these areas and to only a few weeks each year.

32. Extraction of Cod Liver Oil.

The finest quality of cod liver oil can be obtained only when the livers are removed from the fish as soon as possible after they are caught, and the oil is extracted at once in vacuum equipment to preserve the vitamin content and prevent the development of rancidity.

33. Removal of Cod Liver Oil Stearin.

The stearin is removed from cod liver oil so that the oil will not thicken or solidify when kept in a refrigerator. To do this, the oil is chilled and the solidified stearin removed by pressure filtration. The by-product, cod liver stearin, is used in the manufacture of soap.

34. Cod Liver Oil in Steel Drums.

The destearinated oil is then graded according to its vitamin potency in preparation for shipment. It is placed in air-tight steel drums under carbon dioxide gas to prevent deterioration by contact with air en route, and is transported to the United States by steamship.

35. Standardization of Cod Liver Oil.

On arrival in this country the higher grades of oil are again assayed and standardized on the basis of natural vitamin content. The potency with respect to vitamins A and D is accurately determined by biological standardization using albino rats and checked by chemical methods.

36. Filling Bottles.

Washed bottles are brought to the filling machines by conveyors. As they are filled carbon dioxide gas is forced into them to displace the air and protect the product. The filled bottles are inspected through magnifying glasses as they pass along the conveyor belt to the capping machines.

37. Finishing Bottles.

A moving belt carries the sealed bottles to the labeling machines where a label is put on each bottle, after which the bottles are cartoned in single packages and larger lots. The packages are put into shipping containers and conveyed directly to the warehouse to await shipment.

38. Distribution.

The completed product is shipped to branch warehouses conveniently located at central points in the various sections of the country. From these, wholesalers in the principal cities and retailers in every corner of the country may be served promptly with supplies to fill their needs.

This splendid collection of dioramas was contributed to the Museum by The Upjohn Company, Kalamazoo, Michigan. The subjects to be illustrated were chosen by Dr. E. Gifford Upjohn and those who worked with him. Most of the dioramas are actual scenes of the Upjohn offices and laboratories. The Diorama Corporation of America, Chicago, Illinois, made the dioramas.

Much credit is due The Upjohn Company for its public spiritedness in presenting in such an impressive manner some of the professional and scientific aspects of medicine making—the art of the pharmacist.

This collection of dioramas has been on exhibition since November 1934, and has elicited much favorable comment. It is hoped that members of the association will take the time to inspect this exhibit when they visit the city of Washington.

UNDERGRADUATE RESEARCH.*

BY LAWRENCE H. BALDINGER.[1]

Undergraduate research, as referred to in this paper, includes that work of an investigative nature, curricular or extra-curricular, assigned to students working for a bachelor's degree. This topic is undoubtedly of more interest to those engaged in the teaching of pharmacy than to those engaged in commercial pursuits. Individuals in the latter group, however, can do much by assisting in this work and by realizing the possibilities of the intelligent application of undergraduate research in developing the scientific and professional attitude of our student pharmacists. Ira Remsen once wrote (1): "There is nothing mysterious about research. Every human being, in fact every animal, is by nature engaged in research, that is to say, trying to find out something about its environment." Research, fundamental or industrial, undergraduate or graduate, is one of the best means of acquiring new information, of developing in the student the qualities of originality, accuracy, reliability, a regard for professional ethics and a respect for hard work and properly directed imagination.

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* Section on Education and Legislation, Portland meeting, 1935.

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