Section on Historical Pharmacy

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FORTY-FIVE YEARS OF MANUFACTURING PHARMACY.

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In view of the fact that the American Pharmaceutical Association is meeting this year (1914) in the recognized center of the pharmaceutical industry in America, the Secretary of the Historical Section suggested that a brief history of Parke, Davis & Company, and some account of their connection with advances in pharmacy and medicine would be appropriate to the occasion, and of special interest to all those present who have made a tour of inspection through these laboratories.

To you gentlemen, who, in your daily work, have reason to be familiar with the preparations of Parke, Davis & Company, it is almost unnecessary to speak with regard to present conditions and you are, in a measure, familiar with the extent of these laboratories and the purposes that animate them. It is, however, probable that many of the present members of the American Pharmaceutical Association are not familiar with the early history and growth of this firm and particularly the connection it has had with the development of pharmaceutical preparations; so it will not be amiss to give a brief account of the firm itself before speaking of its connection with medicinal progress.

DEVELOPMENT OF PARKE, DAVIS & CO.

Up to the time of the early sixties it had been the almost universal custom for each pharmacist to prepare for himself such galenical preparations as he needed, but about this time several firms began manufacturing work on a small scale, developing this in most cases in retail drug stores that had been established for some years. The idea of centralized manufacture of medicinal preparations was just in its infancy and was probably not recognized as such at that time, but there seemed to be a field for such a firm, and Dr. S. P. Duffield, after having previously entered into two brief partnership arrangements with other men, formed a co-partnership with H. C. Parke on May 7, 1867. This firm continued to do business until 1869, when Dr. A. F. Jennings bought out the interest of Dr. Duffield and the firm became Parke, Jennings & Company, George S. Davis being one of the company. On November 16, 1871, Dr. Jennings retired from the firm and it became, for the first time, Parke, Davis & Company, existing as a co-partnership, and continued as this until January 14, 1875, at which time, as it was developing rapidly and it seemed desirable to perpetuate the firm in some form better than a

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co-partnership, it was incorporated with a capital stock of $125,000, of which $81,950 was paid in.

All this time the laboratory had been located at the corner of Cass and Henry Streets, Detroit, with an office at the same place, and not until 1875, about the time of incorporation, was it moved to its present location. At this time the office was moved to 52 Larned Street, West, where it remained until 1877, when it was transferred to the site of the present laboratories. From this time on the laboratories gradually increased in size until at present they cover several blocks and have, besides their Detroit laboratory, branches in Canada and England, where manufacturing is carried on, and branch offices in almost all parts of the world.

Guiding Principles:—The tendency of modern business has, for many years, been to emphasize the necessity of absolute integrity, both in fact and in spirit, in all dealings, and this idea that has begun to very thoroughly permeate all our business institutions was, it seems to me, one of the chief reasons for the rapid and permanent growth of a business that begun so short a time ago and has increased so tremendously. I can not better illustrate what I mean than to quote from a little leaflet printed many years ago when the firm was young, setting forth their beliefs, and which they entitled "Our Creed and Code":—

"We believe, that, in combating disease, only the best quality of drugs is permissible, and that to their manipulation should be applied the highest scientific skill.

"We believe that the issuing of inferior medicines of any kind is unjustifiable from any point of view.

"We believe in standing solely upon the intrinsic merits of our preparations, and in making no false pretenses; in doing the best that scientific knowledge and skill will accomplish and in doing it honestly and faithfully.

"We believe in working fully in harmony with our pharmacal and medical friends, and in gratefully accepting any suggestions that may tend to our mutual profit. Our watchwords are *Purity, Accuracy, Reliability.*"

Historical Periods:—The history of Manufacturing Pharmacy as a whole and of Parke, Davis & Co., may be divided into four periods characterized by the most important activity of the time, which periods are practically identical in date especially the last three, as this firm in each of these was the leader in the special work involved. These periods are as follows:—

1. Formative Period—1867 to 1874.
2. Botanical Research Period—1875 to 1882.
3. Standardization Period—1882 to 1894.
4. Biological Period—1895 to present time.

These are of course not sharply defined, the work characteristic of each of the last three was in the course of development for some time before the dates assigned and the appearance of a new line of work by no means indicated a termination of previous endeavors, in fact, it frequently widened the scope of all investigations. For these reasons we cannot deal with each period by itself except in a general way, but in most cases trace each line of products or development of process through its entire history. For want of time these accounts must perforce be brief as possible.

Fluid Extracts:—The first products manufactured in the early laboratory were a few chemicals and a line of fluid extracts, and it is interesting to note that the

firm considered the process of maceration of the drug with the menstruum and extraction by hydraulic pressure as the most satisfactory one, as it avoided the use of heat in concentrating weak percolates. It is true that quite a while before this, the process of percolation had been introduced, but the firm, feeling that the experience with this method which they and others had so far acquired, was not sufficient to insure it giving the best possible fluid extracts on a small manufacturing scale, and also being fearful of the vacuum apparatus of that time, decided to adhere to the older method for some time longer and in one of their early price lists state, "We neither percolate nor use heat in any form whatever."

In 1882 a combination process involving percolation as well as maceration was evolved, and this in a few years gave way to percolation exclusively. At the present time, as everyone knows, the process of cold repercolation has been so carefully worked out that it is the best means of extracting drugs and the most economical of solvents used. To the simple percolation by gravity there is now, in many cases, added the use of compressed air, which, besides hastening the percolation, renders it more thorough by forcing the menstruum into the structure of the drug.

After the business had been organized and acquired a little momentum through a few years of experience, the members of the firm began to look around for new things that would be both useful to pharmacists in general and profitable to themselves. As fluid extracts of various drugs were so widely used, it was but natural to look for unknown or little used plants that might be of medicinal value, and to this end, a systematic search was begun about 1874, which continued for many years, and gradually developed along other lines. If a new plant was heard of from the far west of the United States or some foreign country, if the suggestion was made by any physician through correspondence or by a published paper as to the efficacy of a heretofore unused plant, it was immediately investigated and if it gave promise of being really useful, supplies were obtained and the fluid extract distributed to physicians.

Botanical Research:—At this same time, through these same years, an immense volume of literature was prepared by the firm from the reports of physicians and other scientific men all over the country giving detailed accounts of the botanical character of the new drugs and their medicinal properties. Some few well-known preparations are generally recognized as having been introduced by Parke, Davis & Company, but it may surprise you even as much as it has the writer, to find how many drugs now prominently known, were originally brought to the attention of the medical profession by this young firm, especially when it is considered that at the time they were doing this work, the financial outlook was anything but pleasing, as the influence of the panic of 1873 was still strongly felt.

In the course of these investigations Parke, Davis & Co., through representatives, explored the northern parts of California, Washington, Oregon, British Columbia and Mexico. One representative was sent to the Fiji Islands to obtain a supply of the drug Tonga; another going to the West Indies brought back Jamaica Dogwood and a few other less important drugs. A special representative, dispatched in 1881, made a trip from the mouth of the Amazon River about 2500 miles into the interior, and as a result of this expedition the drug Manaca

was added to the growing list of new remedial agents. About the same time another representative proceeded inland from Buenos Aires on horse-back clear across the mountain range to the Pacific coast. This work resulted in the discovery of the herb Chekan, and the obtaining of supplies of Boldo, Quebracho and some other Chilian drugs. In 1885, Dr. H. H. Rusby made an extensive trip in South America, in the interests of Parke, Davis & Co., as a result of which he brought back much scientific information and among many other plants the drugs Pichi and Cocillana, together with obtaining extensive supplies of Coca from Peru.

As you are aware it is almost impossible to locate absolutely the first medicinal use of a drug that has been known for years and a distinction must be made between the one who may first find a medicinal use for a plant and him who makes this common knowledge or brings a drug from obscurity to a place of more or less prominence in Materia Medica.

The somewhat extensive list following includes all but a few drugs of evanescent usefulness that have been introduced to medical use by Parke, Davis & Co. In all cases preparations of these drugs were practically unknown in the United States except as they may have had a very restricted local use and some of the most important ones were absolutely new to the medical profession, as for example, Cascara, Yerba Santa, Berberis, Grindelia, etc. The writer has spent considerable time going over old literature of the firm and other journals to verify as far as possible, the priority of introduction of these drugs and has found a number for which the firm does not ordinarily claim credit that they seem to have been chiefly instrumental in introducing, at least in the United States. It has not been possible to make a complete search of journal literature and find the earliest mention of all these drugs but the dates given being those at which the Fluid Extracts were first put on the market by Parke, Davis & Co., undoubtedly are the first appearance of such preparations of all these drugs. The names in italics, are drugs recognized in the U. S. P. eighth revision.

1869—*Black Haw.*
1874—*Guarana.*
1874—*Eucalyptus Globulus.*
1874—Bearsfoot.
1875—*Coca.*
1876—Cereus Grandiflorus.
1876—*Muskroot* (*Sumbul.*)
1876—*Jaborandi* (*Pilocarpus.*)
1876—Sundew
1876—Evening Primrose.
1876—Bladderwrack.
1876—*Damiana.*
1876—*Yerba Santa.*
1876—*Grindelia robusta.*
1876—Sandalwood.
1877—*Grindelia Squarrosa.*
1877—Ustilago Maydis.
1877—Kava-Kava.
1877—Ailanthus Glandulosa.
1877—Urtica Dioica.
1877—*Berberis Aquifolium.*
1877—Boldo Leaves.
1877—*Cascara Sagrada.*
1877—Five-flowered Gentian.
1877—Kamala.
1877—Guaco.
1877—Paraguay Tea.
1878—Cedron Seed.
1878—Coto Bark.
1878—Cereus Bonplandii.
1878—Quinine Flower.
1878—Areca Nuts.
1878—Shepherd's Purse.
1878—Yerba Reuma.
1878—Great Laurel.
1878—Indian Blackroot.
1879—Jamaica Dogwood.
1879—Rhus Aromatica.
1879—Manaca.
1879—Quebracho Bark Powd. F. E., 1881.
1879—*Saw Palmetto.*
1881—Tonga.
1881—*Corn Silk.*
1882—Sierra Salvia.
1882—*Convallaria.*
1882—Cheken.
1886—Pichi.
1888—Cocillana.
1908—Cannabis Americana.

As I have said, some of these drugs had been used in their local habitat for a long time, as for example, Coca, which had been known for centuries in Peru and used widely in the mountains of South America, and its chemical constituent had been investigated in Europe, but it had not been introduced into this country to any appreciable extent. Again, Manaca had, prior to 1879, been recognized in the Brazilian Pharmacopœia, but was practically unknown outside this country and had not been used in the United States. Sandalwood has, of course, been known in India for centuries, but its medicinal use, especially in the form of a fluid extract of the wood, had received practically no attention in the United States.

It is interesting to note at this time that of the total number of drugs mentioned, twenty of them are at the present time recognized in the United States Pharmacopœia or National Formulary, and thirty-two of their fluid extracts are still in sufficient demand to warrant manufacture by Parke, Davis & Company. Another interesting feature is that the majority of these drugs appeared within three years, viz., 1876-77-78. Altogether approximately fifty different drugs have either been introduced as entirely new by this firm, or have been taken from great obscurity and brought to some degree of prominence.

Publications:—Closely associated with the introduction of new remedies was the dissemination of knowledge concerning them, and so from occasional bulletins giving information on this subject, there gradually developed a systematic series of publications. A Publication Department was organized entirely independent of the manufacturing and sales work, and journals dealing with pharmacy, therapeutics and surgery in their purely scientific aspects began to be published, not all of them at once, but in the course of time.

From the early bulletins there first developed a journal entitled "New Preparations," beginning in January, 1877, and published quarterly for this and the next year, and then monthly during 1879. The legend on the title page indicates its purpose, viz., "A quarterly journal of medicine devoted to the new therapeutical agents." In 1880 the scope of this publication was modified somewhat, and its size increased, and it began to be published as "The Therapeutic Gazette" devoted exclusively to therapeutics. From that time since, it has continued to the present day as one of the well known medical publications of the country.

As a publication of a different and more local character, there began in 1877 "The Detroit Lancet" which, in 1886, was changed to "The American Lancet," and so continued until 1893.

In January, 1883, another journal entitled "The Medical Age" was begun which, as referred to on the title page, was "A semi-monthly journal of medicine and surgery." The publication of this continued until the close of 1906, at which time it was incorporated with The Therapeutic Gazette.

In April, 1895, a somewhat similar journal was introduced under the title "Medicine" which was a monthly journal of medicine and surgery. In January, 1907, it was also combined with the Therapeutic Gazette.

These facts are probably generally known, but it may not be so well understood that for many years this firm were the publishers of the Index Medicus of world-wide reputation. A brief statement of the vicissitudes of this publication may not

be amiss. It was started in 1879 under the editorship of Dr. J. S. Billings of the U. S. Army, and Dr. Robert Fletcher as his assistant, and published by F. Leypoldt in 1884 of New York. It continued thus until the death of Mr. Leypoldt in 1884, when an announcement was made that it would be discontinued, as it had been published at a considerable loss, and they did not know of anyone who would finance it. After three months intermission, it was taken over by Mr. George S. Davis, representing the Publication Department of Parke, Davis & Company, brought up to date in the first issue of 1885 and continued to be published under these auspices until April, 1895. The publication was then taken over by the editors and after some other changes during the next few years, it was finally placed in the hands of the Carnegie Institute in 1903, where it now remains.

As exclusively related to pharmacy and of interest to pharmacists, there was begun in January, 1887, "The Druggists' Bulletin" which was stated to be "A monthly Epitome of Pharmaceutical progress and news." Starting with a very small beginning, it continued under this title until the close of 1890, when it was changed to "The Bulletin of Pharmacy," as which it is now well known to you all.

Of these various publications, the two which now remain as a sifting out of that which has gone before are "The Therapeutic Gazette" and "The Bulletin of Pharmacy."

Standardization:—As the activity in the search for new drugs began to wane, there appeared the forerunner of what, it seems to me, is the most important advance in pharmacy that has occurred in modern times, viz., the application of the principle of standardization, or uniformity in production of preparations of drugs. With no flourish of trumpets and little realization of what is heralded, in September, 1879, there appeared a preparation known as Liquor Ergotæ Purificatus, which was a fluid preparation of ergot, standardized by a simple form of assay so that each different lot was of uniform character. The assay appears to us, at this day, as very crude and inefficient, but we must remember that this was simply the beginning, and any kind of an attempt to give uniformity of strength was an advance upon untraveled ground.

According to the best researches of the time, the activity of the ergot was supposed to be chiefly in the sclerotic acid, and a crude estimation of this was made by the precipitation of the organic acid with lead acetate. The standard was this: "Ten cc. of the normal liquid require for complete precipitation, 100 cc. of a solution containing 1% of crystalized lead acetate."

This truly appears to us with the retrospect of forty-five years of experience, as almost laughable, but it was the best that the knowledge of the times afforded and was a step toward the dreams of the future which were beginning to take form in actuality. With this there began a systematic investigation of the possibility of rendering uniform, fluid preparations of many drugs with the result that in February, 1883, there was publicly announced a list of twenty normal liquids which were actually fluid extracts standardized by some form of assay, in most cases an estimation of the alkaloids which they contained. The man responsible for the beginning of these assayed fluid extracts and who established

the analytical methods for their control is Dr. A. B. Lyons, to whom in this, as in many other things, pharmacy owes much.

The process for the determination of the alkaloids chiefly employed was the now obsolete method of titration with Mayer's reagent, but it is evident that the years from '79 to '83 had been well spent, when we note that the alkaloidal standards of strength adopted for preparations of "normal liquid belladonna" leaves and root were, in each case 0.44% of alkaloid and the present U. S. P. standard for fluid extract belladonna root is 0.4 and for the leaves 0.3%, the "normal liquid ipecac" was 1.5% alkaloid, the same as now official for the fluid extract. The standard for "normal liquid nux vomica" was a little lower than the present U. S. P. standard for fluid extract, it being then 1.5% of total alkaloids as against 1% of strychnine at the present time. This last mentioned fluid is chiefly interesting for the fact that the assay process more nearly approximated that used at present than any other, it being carried out by adding a few drops of dilute sulphuric acid to the liquid, evaporating off the alcohol, washing the residue with ether, taking it up at the same time with water, finally rendering alkaline with caustic soda, shaking out the alkaloid with a mixture of chloroform and ether, and weighing the product so obtained.

Of the further development of the chemical standardization of drugs and their preparations it is almost unnecessary to speak, but it is worthy of notice that the work instituted by this firm and followed in later years by a host of helpers has always kept far in advance of the official requirements of the various Pharmacopœias as they have been established.

As an extension of the work of standardization of drugs and their preparations, there appeared, with the beginning of the biological period in 1894, the first fluids that were standardized by physiological assay as distinct from any chemical assay. It is an interesting coincidence that the first fluid so standardized was also the first one whose uniform production had been attempted by a chemical assay, viz., fluid extract Ergot. Following this there came, at intervals, standardized products of a number of other drugs, such as the various heart tonics with which you are entirely familiar. The development of different methods of physiological test is outside the scope of this paper, and has been described extensively in other publications. Suffice it to say that this general principle, whether applied along chemical or physiological lines, has undergone many changes with the establishment of improved methods of work, and still gives promise of much further development that will widen its present extensive scope.

Going back now to an earlier time, let us consider very briefly some of the different lines of pharmaceutical manufacture that have been developed. It would require too much time and space to treat separately and in detail different lines of products like pills or tablets or ampoules, etc., and so perforce they must be considered very briefly, emphasizing only the most salient features of improvements that from time to time have been made in their preparation.

Tablets:—There have been many interesting features in connection with the development of tablet manufacture, but none of them are such that they can be called important advances in pharmaceutical manufacturing, and it is only necessary to say that the gradual development of this line of products during the years

that they have been in vogue has had to do chiefly with the mechanical perfection of the tablets, their speed of solubility or disintegration, and detailed knowledge about how best to handle an almost infinite variety of substances used in them.

The most important manufacturing advance has been the development of new machinery, so that where originally a few tablets might be made by the retail druggist by hand and later by a machine giving a single tablet at each impression, we have now especially designed machinery such as has been built in the machine shops of Parke, Davis & Co., which have a capacity of a million and a half tablets per ten-hour day. This development has recently been described at length by Dr. L. E. Kebler in his paper presented to this association last year.

Pills:—The origin of pill manufacture in a small way is lost in obscurity. By this I mean the preparation of pills by the retail druggist. It is very natural, therefore, that on the manufacturing scale, it should be one of the first products made, together with the fluid extracts of drugs. Here again the development of the product coincides with the development of automatic machinery, and you are all of you well informed regarding recent improvements in such machines. The strides that have been taken measure up well with those in tablet manufacture. Where their production was formerly, by hand, limited to a few thousand per day, a single machine will now turn out anywhere from five hundred thousand to two million pills in a day, depending upon the size of the pill. The old method of gelatin-coating pills by impaling them on pins and dipping in gelatin solution was done away with by Parke, Davis & Co. when they originated the machinery for holding the pills by vacuum while being dipped.

The most important modification of pills in the last few years is the introduction of the so-called "Soft Mass Pill," so made that the interior is quite soft and protected by the hard shell of the coating, just thick enough so that the entire pill may be easily crushed between the fingers. This pill is made by the mass process and retains its softness for many years.

In this connection it is interesting to note that Parke, Davis & Co. who introduced this pill in 1909, evidently felt that this was a desirable attainment a great many years ago, as back in 1875, they are careful to state that their pills are especially desirable because they are "coated while the mass is yet soft." At that time, however, the idea of the soft mass was not at all what it is to-day.

Pepsin:—The extensive use of digestive ferments is of comparatively modern origin, and this firm has had very much to do with the development of pepsin manufacture and rendering the use of this digestant popular and convenient. The introduction of different strengths of pepsin as made by Parke, Davis & Co. may be considered as identical with the development of pepsin manufacture thus indicated.

In 1874 they introduced a Saccharated Pepsin of such a strength that "five grains would digest sixty grains of coagulated albumin," being thus of a 1:12 strength. This was considered a very excellent product, although so weak that it would be counted as worthless to-day, and thrown away as waste. The mixture of the Pepsin with milk sugar was necessary because of the exceedingly hygroscopic nature of Pepsin thus made, owing to the presence of a considerable amount of peptone, which they had not yet learned how to separate from the Pepsin. In February, 1881, there appeared a pepsin of which they were rather

proud, which was dignified with the name "Concentrated," it being so strong that one grain would digest 100 grains of coagulated albumin, but this achievement was very quickly improved upon so that in February, 1883, there was presented a so-called "pure" pepsin, which was stated to have an activity of 1:450 to 1:500. In the meantime, the U. S. P. of 1880 had appeared and had made official a Saccharated pepsin with a strength of 1:50. About the same time some one got the idea that pepsin prepared from sheep stomachs, was in some way better than that prepared from hogs stomachs, so with the idea of being fully abreast of the latest developments the firm put out at this time a so-called pure Sheep Pepsin having a strength of 1:350 to 1:450. This sheep pepsin was short-lived, however, and in a few years was again taken from the market as there was no reason why it was any better medicinally than the established variety. In January, 1885, the development of pepsin had proceeded to such an extent that the peptones could be largely removed and the pepsin produced in a scale form which is now so universally known. Between this and the year 1888 continued researches brought about a tremendous advance and in that year a pure pepsin in scale form free from peptones and marked "Non-hygroscopie," (which it certainly was as compared to previous productions) and having a strength of 1:2000, was placed on the market; also a powdered pepsin of the same strength was supplied, and for the first time there appeared a solution of pepsin in glycerin called Glycerole Pepsin, of such a strength that one minim would digest 100 grains of coagulated albumin.

There was now no further change in commercial supplies of pepsin until 1893, at which time as the result of continued and rather epoch-making experiments, there were placed on the market a line of pepsins of different strengths in scale form, including 1:2000, 1:3000 and 1:4000 strength, a glycerole pepsin having a strength of 1:300 and while not regularly listed, it was arranged that supplies of pepsin having any strength up to about 1:15000 would be furnished on demand. The next year, 1894, appeared the 1890 Revision of the U. S. P. which made official a pepsin of a strength of 1:3000 and a saccharated pepsin of 1:300, which have remained to the present time as the official standards.

At the same time, with the development of the pepsin manufacture, there has gone with it hand in hand the development of methods of testing pepsin, and while the strengths of pepsin as claimed many years ago were approximately correct, they are certainly not the same as would be shown by our present day methods of assay. The pepsin supplied even up to as late as 1890 or 1893 was probably much weaker than would be indicated by our present methods of assay. The general idea of the test has not varied greatly, but our experience has increased and our interpretation of results has been modified. This is very forcibly shown by the fact that quite recently a test was made of a sample of pepsin prepared about twenty years ago and which, at that time, was considered to be 1:20000 strength. This has been kept under the best possible circumstances, so that deterioration that had occurred was certainly very little, but the test showed that it would now be considered only about 1:10000. The fact that the U. S. P. standard has not varied for almost twenty years past does not indicate that there have not been advances in this length of time for I am able to show you to-day a

sample of pepsin testing 1:25000 by present tests, which is therefore, approximately five times as strong as the pepsin prepared twenty years ago. This high powered old sample was more the result of good luck than accurate knowledge and it was practically impossible to duplicate it, but this new sample can be duplicated at any time, although, of course, the expense of making so powerful a product would be considerable, but strengths of 6000, 8000 and 10,000 are easily made.

As in the manufacture of extracts of drugs, so in pepsin manufacture the development of highly efficient vacuum apparatus has had much to do with the improved processes.

Pancreatin:—As closely associated with pepsin, we naturally think of the ferment Pancreatin. Here the development has not been so spectacular as in the case of pepsin, but it is nevertheless considerable. In 1877 a saccharated pancreatin was placed on the market, for which no standard of strength was given, there being no recognized way of determining the strength at that time.

In February, 1881, there appeared the following test which, crude as it was, attempted to give some definite information about the product; "Ten grains will emulsify ½ to 1 oz. cod liver oil with water in sufficient quantity." This test was continued as a standard until 1884, at which time a so-called "pure" pancreatin and also a liquid concentrated pancreatin were put on the market, the first of which being of such a strength that five grains would peptonize one pint of milk in half an hour, and the latter required two fluidrachms to accomplish the same results. The same standard of strength, as far as the peptonizing of milk is concerned, remains to the present day. The Eighth Revision of the U. S. P. established a starch conversion test requiring that one part of the pancreatin should be able to digest 25 parts of cooked starch.

The development of a commercial pancreatin supplied by Parke, Davis & Co. since the introduction of this Pharmacopœia has gone to such an extent that its regular product now has the ability to digest 150 parts of starch for each part of pancreatin.

Taka-Diastase:—For many years it was known that a ferment, having some digestive action on starch, was produced during the growth of various fungi. Researches, both in Germany and Japan, began to develop considerable information on this subject, and in 1895 the first medicinal application of a ferment of this kind was made, when Parke, Davis & Co. introduced Taka-Diastase as a result of the researches of Dr. Takamine. As first supplied it had the power of digesting or converting into assimilable substances one hundred times its weight of starch, but, through continued research, it has been possible to greatly increase its digestive activity, so that, at the present time, it has three times its original strength.

Capsules:—Turning now from medicinal products to what may be considered accessories in pharmaceutical practice, we would note especially the development of empty capsules. These were not original with this firm, having been first prepared in a very crude form by A. Mothes, a French pharmacist, in 1833, and first made in the U. S. by H. Planten in 1834 or 1835, but they were not recognized as being particularly valuable, and no perceptible advance was made in their

manufacture for many years, and the history of the greatest development of capsule manufacture is coincident with the connection of Parke, Davis & Co. with their production. In early years the firm did not actually own the plant, but they controlled the entire output of an associated factory, which was to all intents and purposes their own.

The first capsules which they listed were in 1875, and consisted of three sizes, what are now known as Nos. 1, 2 and 3. They were still rather crude, but an attempt was made to give them a smooth and transparent appearance, and to produce a body with cap slightly larger so that they would fit properly together, and the gelatin used was the best obtainable at that time, as at present. The novelty of the empty gelatine capsules is very well shown by the description of them in advertisements in the late '70s, such as the following: "Our capsules are composed of two small tubes of prepared gelatin, one sliding into the other, and each closed at one end. The remedy employed is then separated into the proper dosage, one of which is placed in the smaller tube, which is then telescoped into the larger. It is now in the shape of a small cylinder, ½ inch in length, ¼ inch in width, closed at both ends," or the following: "The gelatin on being moistened becomes slippery and is readily swallowed with the aid of a little water."

Though they were so little known to the pharmacist the public knowledge of them was even less, as was evidenced by an item in the Louisville Medical News in 1877, where a physician states that an intelligent gentleman had been given capsules to take without specific directions, and later informed the physician that he "did not like them at all," his idea of taking them being "to peel off the hulls and put the stuff in water."

From a very slow and laborious process, the manufacture of empty capsules has come to be one of speed and remarkable perfection, and nowhere can be found a more wonderful development of special machinery than is connected with the capsule industry. More space could be given to this alone, but for further information, which it is impossible to include here, reference may be made to the article by Warren Wilkie in the Bulletin of Pharmacy, 1913, page 382.

Biological Manufacture:—We come now to what we have called the fourth period in the development of manufacturing pharmacy, viz., the biological period, and use the term in a broader sense than it is popularly employed. In this connection one naturally thinks of vaccine for producing immunity against smallpox, but this was developed nearly one hundred years before the appearance of antitoxins or bacterial vaccines.

On the border line between medication by drugs of mineral or vegetable origin on one side, and products derived from bacteria on the other, lie a number of animal substances which modern materia medica includes, as some of its most potent agents. Substances that, to one unfamiliar with the trend of medical research through the last twenty years, would seem to savor of the necromancy of the middle ages. The results obtained from the various products of the so-called "ductless glands," have been so remarkable that they have attracted considerable popular attention, and have, in some cases, almost revolutionized the medical treatment of obscure and hitherto baffling diseases. This work, very naturally,

began first, with the use of the desiccated glands themselves, followed, almost immediately, by attempts to isolate some definite active principle. As a result of this, first, and so far, most important, there was isolated by Dr. Takamine, the active principle of the suprarenal gland, Adrenalin, which became commercially available in January, 1901. Since that time it has risen rapidly into the very front rank of important remedial agents and it needs no further statement concerning it in this connection.

As a more recent and almost equally important work, though in somewhat different line, there has come the commercial development of an extract of the pituitary gland, known by this firm as Pituitrin, and supplied first in 1909, embodying the active constituent of the posterior lobe of the gland. The exact nature of this active principle has not yet been definitely determined, but at the present time much attention is being paid to it and also to the value of the anterior lobe of this gland, for a long time discarded and considered of no value.

Along with the use of these two glands medicinally, there has come about also the use of the thyroid gland, either in desiccated form or as some especially prepared substance derived from it. The thyroid gland has been under investigation for many years and the exact nature of its active constituents is not yet understood, but there probably remains, in the future, much knowledge of this gland that will be of even greater value than that possessed to-day.

The gradual development of definite therapeutic uses for a number of other glandular products is now in progress, most prominent among which may be mentioned the Pineal and Para-thyroid glands, but what shall be the results of this, as regards the isolation of any definite active body or a thorough understanding of their uses, and the employment of them in therapeutics, is yet chiefly a thing of the future, although apparently not far distant.

What shall be the ultimate result of the study of these glandular products will remain for some historian of many years to come to set forth.

The commercial beginning of what is generally spoken of as biological work was in 1894, and the events that preceded it are worthy of a moment's notice. In 1887 Professor Sewall of the University of Michigan directed attention to the immunization of pigeons against rattlesnake venom. This is probably the first published reference to the establishment of immunity. Following this, during the next six or seven years, there appeared a number of papers dealing with the establishment of immunity against various poisons, such as ricin, abrin, etc. of vegetable origin, and toward the close of this time there came the epoch-making work of Roux, Behring, his assistant, Kitisato and Aronson. The publications of Behring and Roux really mark the beginning of the idea of producing, on a manufacturing scale, a substance that would produce immunity to diphtheria and other diseases which were of bacterial origin.

The firm of Parke, Davis & Co. early saw the possibilities in the field so opened up and in 1894 established, in a small way a department for pharmacological work and for the production of diphtheria antitoxin. The first equipment was small, and the total number of animals included a few guinea pigs for necessary tests and three horses for the production of the antitoxic serum.

Early in 1895, public mention was made of the fact that they would, in a very

short time, be able to supply diphtheria antitoxin, and by 1896 three different packages were on the market, viz., one containing 600 units, one of 1000 and one of 1500. The next year a bulb containing a prophylactic treatment of 250 units was placed on the market, and one of 2000 units.

In 1898 appeared, for the first time, a package containing 3000 units and from this time on, for some time, the strength of dosage was not greatly increased, but the effort was made to cut down the amount necessary to obtain the same potency. Very considerable advances along this line had already been made. The first serum made contained about fifty to sixty antitoxic units per cc., but very quickly the strength of the serum was increased, and it is a notable fact that one of the most potent serums was taken from a horse used in 1898, this serum being so powerful that one cc. contained 2000 antitoxic units. At that time, the reasons for this remarkable potency were not well understood, but it seems now that it was due to some unknown difference in the animal, as great variation is found in the serum that is obtained from different animals. Since that time the continued effort has been to increase the potency of the serum by concentrating it in some way after it is first obtained, as the result of which the so-called serum globulins or concentrated serum have been supplied, which now contain a very much larger number of antitoxic units.

In 1897 antistreptococcic serum, and in the same year anti-tetanic serum both in liquid and dry form, were placed upon the market. An anti-tubercle serum appeared in 1898, and in 1899 and 1900 respectively there appeared, for veterinary use, two new products, blackleg vaccine, and anthrax vaccine, which were of a different type and are more closely related to the bacterial vaccines of later development than they are to serums.

The brilliant and rapid development of bacterial vaccines is of such recent date that all of you are well acquainted with it, and there is no need to do more than to record the fact that it has its origin in the work of Sir A. E. Wright and that the first commercial preparation of bacterial vaccine was made by Parke, Davis & Co. in 1907. Since that time the number of them has greatly increased, and the development has been so rapid and is still going on to such an extent that these productions can not properly be treated in a historical paper as they have not yet the antiquity that renders them of historical nature, but are a very present and active force in pharmaceutical work.

As the latest addition to biological products for medicinal use, we come to the phylacogens which give promise of having an even more brilliant future than their precursors, the bacterial vaccines, but again these are of so recent origin that they are not appropriately treated in a paper of this type, and can only be mentioned.

In taking a general survey of the pharmaceutical industry from a manufacturing standpoint, one of the most striking developments is that of the apparatus and machinery employed and the use that has been made of machines originally designed for other industries. It is characteristic of the development of medicine and pharmacy in general that they have been quick to take advantage of knowledge gained from every available source and this has been especially true of apparatus employed.

We have already noted something of the remarkable development in special machinery in the manufacture of capsules, pills and tablets, all of which are peculiar to the manufacture of medicines, and one could very easily deal with the development of this machinery entirely apart from any of the products and processes themselves. Aside from the special machines just mentioned, probably no one thing has had so much effect on medicinal products as the great improvement in different types of vacuum apparatus in the last fifteen or twenty years. Vacuum stills for the recovery of liquids or the concentration of fluids where the solid residue is desired, vacuum dryers for the handling of products such as dry extracts of drugs or granular effervescent salts, and even the use of vacuum pumps for filtration, for the handling of liquids in quantity and numerous other minor purposes make it unusually important in a wide scope of work.

From the baking industry we have taken over the type of mixers there used as being the best for pharmaceutical processes; from the flour mill we have adapted the roller mills to be used in handling tablet granulation; from the liquor industry we have adapted stills and vacuum pans of various forms; from the laundries we have taken special types of centrifugal machines; from the sugar industry, centrifugal machines of different design for other purposes, from the manufacture of confectionery we have derived lozenge machinery and notably the type of pans for sugar-coating pills and tablets which are the same as have been used for sugar-coating nuts; from the paint manufacturers we have taken over the mills for grinding paints and put them to use for grinding ointments and have taken their automatic filling machinery for use in filling tubes of tooth-paste ointments, etc. In fact, wherever a machine has been found that could, in any way, be adapted to pharmaceutical practice, it has been done, and used as it was, or, as frequently the case, after some modifications.

It is sometimes hard for the historian to refrain from assuming the role of prophet, but it is plainly evident to all that a great change in medicinal preparations is occurring, the old galenicals in many cases giving way to products from the biological field, and it requires no seer with supernatural vision to see still greater changes in the future, both in materials and methods, and the establishment of a more potent and definite materia medica.

Laboratories of Parke, Davis & Co.

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