4. Be a specialist in drugs and prescriptions and emphasize the fact to the medical profession and the laity as well.

5. Study the official preparations—both U. S. P. and N. F. Try and suggest improved formula for present or any new preparation. The new Year Book now affords a fine outlet for all such original work.

6. Make all the preparations and chemicals you can. It is more economical and the experience is invaluable. There can be no better nor purer drug than U. S. P. and N. F.

7. Make your prescription counter a model of neatness and order, as nowhere else is the character of the store so apparent to the physician. Let neatness and accuracy characterize all your work.

8. Read the drug journals and afterwards bind them at small cost for reference. To a practical pharmacist, reference works are as indispensible as mortar and pestle.

9. Be ethical—which simply means honesty in practice in all your dealings with the public.

And finally, take inspiration occasionally from the maxim of Franklin: "Keep thy shop, and thy shop will keep thee."

In concluding this discursive address, I desire at this time to extend my sincere thanks to the Association which has so signally honored me with this important office, to my associates for their kindly assistance, to the numerous contributors to this year's work, and to the unselfish company of men who are directing pharmacy's onward march of progress—the Council of the American Pharmaceutical Association.

PHARMACY IN ITS HIGHER DEVELOPMENT.

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This paper deals with the subject of BIOLOGICS. It is not intended as a technical treatise but is rather designed for the commercial pharmacist—the man who handles these products for revenue—and to whose interest it is that he become conversant with the various products, mode of preparation, uses, and their proper preservation.

In the United States biological products are generally produced by the large pharmaceutical houses operating special laboratories under Government license. They are marketed through the medium of the drug trade which is the legitimate channel for their distribution. The average pharmacist however fails to appreciate the intimate relationship between these advanced therapeutic agents and those which have heretofore occupied his active attention and as a consequence is neglectful of an opportunity to materially advance his professional status. In-

deed, the intelligent handling of these products offers an exceptional opportunity to the pharmacist to elevate his calling to a higher plane.

In this field he need not fear the department store, nor the mail-order house, nor the professional price-cutter, for these products cannot appeal to the laity to be employed in self-medication.

Nor do these products appeal to the unprogressive and slothful physician. Their effective application is founded upon accurate clinical and bacteriological diagnosis. How many of your medical friends possess microscopes and are able to differentiate the various pathogenic (disease-breeding) organisms?

The alert physician is quick to perceive the advantages of a scientific and specific therapy that draws the populace away from the evils of self-drugging. He is also able to estimate the value of keeping his patients under close observation and the psychical effect of a cleansed skin and a needle puncture.

Then each individual is "a law unto himself." *A teaspoonful three times a day after meals* is a useless slogan when it comes to the administration of biologics. The indications, dosage and mode of administration are largely matters of individual observation and personal idiosyncrasy. There is no known means by which an individual's resistance or recuperative power may be gauged beforehand, and when a substance is introduced direct into the circulation there is not an ever-watchful and long-suffering stomach to stand guard over the vital organs. So one must needs be careful. There is no such thing as drawing hard and fast rules in the administration of these products. A physician before administering the second dose must know as accurately as possible, the beneficial or untoward effects of the first. This necessitates his having clinical experience and some knowledge of laboratory diagnostic measures.

Therefore, since so much is dependent upon the administration of these products, it is readily apparent how important are these products themselves. It is the pharmacist's business that these products he handled with a care bordering upon reverence and when he has grasped some of the fundamentals governing their production, he will so handle them.

The science of bacteriology is the basis upon which biologics production rests. Their actual production however, is dependent upon the application of processes that are distinctly pharmaceutical. There is scarcely a pharmaceutical process one can mention that has not its application in the biological laboratory.

Maceration, filtration, digestion, distillation, evaporation, sterilization, desiccation, levigation, dialysis, precipitation, and physiological assay are some of the processes that occur to the writer offhand. These are common pharmaceutical procedures in the biological laboratory. The fact that more refined methods are employed such as vacuum evaporation and filtration, filtration through porcelain, steam and dry-air sterilization, centrifugalization, and other methods requiring special apparatus, does not alter the fact that the processes are essentially pharmaceutical.

Another striking parallel is found in the finished product. *Pills*—veterinary Blackleg Vaccine in pill form; *Triturations*—Blackleg Vaccine in the form of accurately divided powders; *Tablets*—Calmette's Tuberculin Ophthalmic Test tablets and the Bacterial Vaccines and Tuberculins in tablet form. *Capsules*—Moro's Tuberculin Ointment, which appears also in collapsible tubes. This also

is a true *Ointment* composed of 50% Koch's Old Tuberculin incorporated with Lanolin. Then there are *Mixtures*—the Bacterial Vaccines; *Emulsions*—Tuberculin Bacillen Emulsion, which is more properly a suspension; and *Extracts*—which instead of containing the soluble elements extracted from vegetable drugs, contain substances evolved by bacteria in their growth in artificial culture media. And it might here be added that from their physiological effects there would seem to be an intimate chemical relationship between certain bacterial toxins and some very poisonous vegetable principles—as *ricin* and *abrin*.

Bacteriology, is a science which should have a place in the curriculum of every college of pharmacy. Problems of sterilization, fermentation, and the role of bacteria in disease, might well demand the pharmacist's careful consideration.

It was not until the 8th Revision of the United States Pharmacopeia that this class of products came into official recognition.

Antidiptheric Serum is the pioneer in this respect. Tetanus Antitoxin and Vaccine Virus have been accepted for inclusion in the next—the 9th Revision of the U. S. P. In the past decade these products have multiplied to an astonishing extent. Millions of dollars are now invested in their production and dispensing pharmacists have even taken to specializing in their production in this field.

In describing the various products found upon the market this paper will deal first with those products official, or about to become official in the U. S. P. Second; those products which have been passed by the Council on Pharmacy and Chemistry of the American Medical Association and included in NEW AND NON-OFFICIAL REMEDIES, 1912, and lastly those products which are of more recent origin and which for some reason are not officially recognized. Following a description of these products the writer will compare the different classes of bacterial derivatives.

Serum Antidiphthericum—Diphtheria Antitoxin is official in the 8th Revision of the U. S. P. It is described as "a fluid separated from the coagulated blood of a horse immunized through the inoculation of diphtheric toxin." It is recognized also in the French, German and Spanish Pharmacopeias. It is marketed in the forms of *Serum, Globulin* or *Concentrated,* and *Globulins, Dry.* The Serum only is official.

The process of preparing diphtheria antitoxin is characteristic of the preparation of serums in general so will be dealt with in detail.

The initial process is the securing of a pure culture of diphtheria bacilli from a throat infected with the disease. A pledget of sterilized cotton mounted on a swab is applied to the diseased tissue and then smeared on a slant of Loeffler's blood-serum media contained in a test tube. This is placed in an incubator kept at the body temperature for twelve or more hours when numerous, roundish, pin-point colonies will have formed upon the surface. Among these will be found pure cultures of the Klebs-Loeffler diphtheria bacillus. From these pure cultures other tubes are planted which serve to inoculate large flasks of specially prepared bouillon. The flasks are then placed in an incubator where in the course of five or seven days countless millions of diphtheria germs are grown, giving rise to large quantities of virulent diphtheria *toxin*. This toxin is an exceedingly toxic substance and is principally responsible for the destructive effects of the diph-

theria disease. Trikresol is then added to the contents of the flasks to kill the germs and the product is then filtered through a Berkefeld—an unglazed porcelain—filter, filtration being facilitated by the employment of vacuum pressure.

The filtrate freed from germs contains the soluble products elaborated by the growing and multiplying germs and is known as *diphtheria toxin.* This toxin is standardized by inoculating guinea pigs of 250 grams weight with graduated quantities of toxin. The smallest quantity proving fatal to the guinea pig within a period of four days is called the minimum lethal does and this is employed as a basis for inoculating the larger animals.

Now comes the production of the antitoxic serum. Perfectly sound horses are injected subcutaneously with gradually increasing quantities of the toxin, beginning with one or more lethal guinea pig doses and increasing, as the animal acquires immunity to the toxin, to perhaps a hundred thousand times that quantity —in volume approximately 0.1 cc. to 250.0 or 500.0 cc. of the toxin. The injections are given at intervals of a few days and continue over several months—until the animal's maximum immunity is reached. As the animal develops immunity to the toxin, *antitoxin* is formed. This antitoxin is a reaction product of the living organism. The body cells are attacked by the poison, and if not destroyed, are stimulated into the over-production of *antibodies* capable of combining with and neutralizing the poison:—*Ehrlich.*

The horse is allowed to rest for a week or two during which a preliminary test is made of the antitoxic strength of his blood serum. If this comes up to requirements the animal is bled by passing a canula attached to a sterilized rubber tube, into the external jugular vein. From five to ten liters of blood is drawn off into sterile parchment-covered jars or test tubes which are set aside to allow the separation of the serum from the clot. The supernatant fluid is then siphoned off and to it is added 0.4% trikresol as a preservative. The product then filtered constitutes the *Diphtheria Antitoxin* of the market.

The physiological activity of Antitoxin is determined by the number of immunity units contained in each cc. This may vary from 200 units in poor serum to upwards of 1500 units in highgrade serum. The *unit* is the measure of *antitoxic power*—not of weight or volume. It is an arbitrary quantity based upon physicological test—the neutralization of toxin by antitoxin in the body of the guinea pig—which animal is highly susceptible to the diphtheria bacillus and its poisons.

Under the Act of Congress approved July 1, 1902, all Diphtheria Antitoxin sold in the United States is required to conform to the standard established by the U. S. Public Health and Marine Hospital Service. This standard is based on the Ehrlich Immunity Unit preserved at the Royal Institute for Experimental Therapy at Frankfort-on-the-Main. Antitoxins of foreign production are standardized and sealed in government laboratories before they are marketed, but in the United States antitoxins are tested in comparison with the Government standard unit in the laboratory of each individual producer. This standard unit is prepared and preserved with the most exacting care at the Hygienic Laboratory, Washington, D. C.

At intervals of two months about 10 cc. of the standard unit serum is distributed to each of the licensed manufacturers. This is a glycerin solution of

dried antitoxin and properly diluted contains one antitoxic unit in each cc. This standard antitoxic unit is used to standardize a laboratory test toxin which determines that amount (approximately 100 fatal guinea pig doses) which just equals or neutralizes the unit when the two are mixed together and injected into a 250 gm. (standard weight) guinea pig, the life or death of the guinea pig within a period of four days serving as indicator. The strength of all unknown antitoxins is tested against this standardized test toxin.

Thus it is seen that the process of testing antitoxin may be compared with an estimation in volumetric analysis, but instead of a chemical this is a physiological test. The body of the guinea pig is the container in which the titration is made, its life functions are the indicator, and its life or death the end reaction.

Globulin Antitoxin—Antidiphtheric Globulins or Concentrated Antitoxin—represents in a concentrated form the antitoxic elements of the natural serum. The Gibson method for extracting the globulins from the serum is most commonly employed. It is briefly as follows. (It will be observed that starting with the serum above described, the preparation of globulin antitoxin is entirely a chemical and pharmaceutical process.)

A quantity of antitoxic serum is added to an equal volume of a saturated solution of ammonium sulphate. A heavy, flocculent, waxy precipitate of the serum globulins results which is separated from the serum-albumin, nucleo-proteids and other inert substances by filtration. The precipitate, containing most of the antitoxin of the serum, is added to a saturated solution of sodium chloride in which the antitoxic—or pseudo-globulin, goes into solution leaving behind the insoluble euglobulins. These are separated by filtration, the filtrate containing an antitoxin of the serum taken. The antitoxic globulin is then precipitated from the salt solution by the addition of acetic acid. The resulting heavy, flocculent precipitate is separated by filtration and dried between layers of absorbent filter paper. The white, waxy mass is then placed in a bag of dialyzing parchment and dialyzed in running water for several days during which the mass gradually liquefies to a fluid resembling the original serum. This is neutralized with sodium hydroxide and the dialysis continued until it is freed from all adhering salts, etc.

This fluid is from one-half to one-third less the original volume of the serum, and contains most of the antitoxin originally contained. Sodium chloride then restores the normal salt content and a preservative is added. Finally, the globulin antitoxin is filtered through paper, then through a Berkefeld filter, and tested in the same manner as is the U. S. P. antitoxin.

lin Antotoxin which is intended for the extemporaneous preparation of the fluid

This product still further concentrated and dried *in vacuo,* is the *Dried Globu*-antitoxin by dissolving the substance in sterile, distilled water.

Tetanus Antitoxin is proposed for inclusion in the 9th Revision of the U. S. P. It is official as *Serum Antitetanicum* in the Belgian, French and Swiss Pharmacopeias. Both liquid and desiccated preparations are recognized by the French Pharmacopœia. Like Diphtheria Antitoxin, it occurs on the market in the Serum, Globulin, and Dried forms.

Tetatnus Antitoxin is described as—*the blood serum of horses immunized to the toxin of the tetanus bacillus.*

The antitetanic serum sold in interstate commerce in the United States should conform to the standard established by the U. S. Public Health and Marine-Hospital Service. This standard is defined as follows—"The immunity unit for measuring the strength of tetanus antitoxin shall be ten times the least quantity of antitetanic serum necessary to save the life of a 350-gram guinea pig for ninety-six hours against the official test dose of a standard toxin furnished by the Hygienic Laboratory of the Public Health and Marine-Hospital Service."

Antitetanic Serum Dried is employed as a dusting powder in the treatment of infected wounds.

The two serums described above are classified as *antitoxic sera.* Another group embracing a considerable number of products are the *anti-bacterial sera.* In the preparation of these, instead of employing the bacterial *toxins* in inoculating the animals, the respective bacteria themselves are employed in the forms of virulent, attenuated or killed cultures. These serums are directed against the bacteria present in the disease, rather than against the neutralization of their toxins. A brief summary follows. (See NEW AND NONOFFICIAL REMEDIES 1912.)

Anti-streptococcus Serum is official in the French Pharmacopeia. It is prepared by immunizing horses with virulent cultures of streptococci.

Anti-dysenteric Serum is the blood serum of horses immunized against the Shiga bacillus.

Anti-gonococcic Serum is prepared from the blood of rams immunized against both dead and living cultures of virulent gonococci.

Anti-meningococcic Serum is the blood serum of horses immunized against the meningococcus of Weichselbaum (Diplococcus intracellalaris.)

Anti-pneumococcus Serum is the blood serum of horses immunized against pneumococci.

Anti-staphylococcus Serum is prepared from the blood of horses immunized against staphylococci.

Anti-tubercle Serum is prepared by treating horses for several months with the toxic products of the tubercle germs.

Anti-typhoid Serum is a serum obtained from horses which have been injected with killed cultures of bacillus typhosus.

Normal Horse Serum is obtained from normal animals as distinguished from that obtained from horses undergoing the process of immunization for the process of immunization for the production of curative sera. It is employed to check hemorrhage and acts by increasing the coagulative power of the blood. Normal serum from other animals has also been employed for this purpose.

Two very interesting examples of serums obtained by inoculating animals with substances not of bacterial origin are seen in Hay Fever Serum and Snake Bite Serum.

Hay Fever Serum (Pollantin) Dunbar's Serum—is obtained from the blood serum of horses which have been immunized with pollen toxin. It is therefore an antitoxic serum corresponding to the toxins or poisonous proteids obtained

from ragweed and plants of the *Gramineae*. It is employed as a local application to counteract the effects of pollen toxin in Hay Fever.

Serum Antivenimeux—Antivenomous serum is obtained from horses immunized against the venom of snakes. It is employed against the poison of venomous reptiles as the viper, rattlesnake, ets.

Of the VIRUSES there are two of immediate interest to the pharmacist—*Vaccine Virus* and *Antirabic Vaccine*. The former is proposed for inclusion in the U. S. P. 9th Revision.

Vaccine Virus—Smallpox Vaccine is perhaps the oldest and most extensively employed of this class of products. It is the material obtained from the skin eruptions of calves affected with vaccinia-cowpox, and is employed for the vaccination of human beings against smallpox. The organism which presumably gives rise to this disease has not been isolated, which fact necessitates the employment of the material (or virus) as an immunising agent.

In the preparation of Vaccine Virus, the process of vaccinating or inoculating the calf and the subsequent curettage of the vesicles in the gathering of the lymph, is essentially a surgical procedure. The grinding of the "pulp," its incorporation with glycerin and the manipulations leading up to the finished product, are pharmaceutical processes, though exception may perhaps be taken to the bacteriological methods employed to determine the presence of contaminating organisms or chemical poisons.

Antirabic Vaccine is an emulsion of the cords of rabbits that have died as a result of the subdural injection of fixed rabies virus. The fixed virus is obtained by the passage of rabies virus through a long series of rabbits until the animals die after a uniform period of incubation. The cords are removed from the rabbits and dried over potassium hydroxide for a period of from two to fifteen days. The fixed virus in general use is of the strain employed by the U. S. Hygenic Laboratory, Washington, D. C.

As prepared for administration, each section of cord of the requisite attenuation is ground up with glycerin and salt solution into an "emulsion," the cords of gradually increasing virulence injected subcutaneously into the infected subject as a prophylactic against rabies. The object is to gradually produce an immunity to the rabies virus before the "street virus" takes effect.

Another important class of biological products are the *Bacterial Vaccines* or *Bacterins*. These are suspensions of killed pathogenic bacteria in physiologic salt solution to which phenol or trikresol has been added as a preservative. They are standardized to represent an approximate number of bacteria to the cubic centimeter.

The Bacterial Vaccines may be "stock" vaccines, or "autogenous" vaccines. Stock vaccines may be "specific"—composed of one organism only—or, "mixed" or "polyvalent" which are vaccines representing different strains of one organism, or strains of a number of different organisms.

Autogenous vaccines are prepared from the organisms giving rise to an infection in an individual case, and are employed in that case only. The preparation of such vaccines sometimes becomes necessary because of the peculiar nature of an infection. Pharmacists do not often have occasion to handle this special

work. The stock vaccines are designed to cover a broad range by embracing in their composition as many diverse strains of the organisms represented, as possible.

The bacterial vaccines or bacterins comprise a very large class of biological products. They are composed of one species of organism only, or two or more organisms, the name of the product designating its composition. Thus—Acne Vaccine is a suspension of the *Bacillus acnes.* Staph-Acne Vaccine contains in addition to the Bacillus acnes, various strains of *Staphylococcus;* etc.

One product of this group—*Typhoid Vaccine* has come into very extensive use as a prophylactic measure against typhoid fever. Its use is now compulsory in the U. S. Army and Navy, and has become a routine measure in several European military organizations. Its use has practically eliminated typhoid fever from the military camps.

The most recent development in this field is a new class of bacterial derivatives termed *phylacogens.* These are distinct from the Bacterial Vaccines in that they contain none of the bacterial cell substance. They are sterile aqueous solutions of the metabolic substances or derivatives generated by bacteria grown on artificial culture media. The bacteria, first killed, are removed by filtration through porcelain. A considerable variety of pathogenic bacteria are employed in their preparation, the different organisms being present in about equal proportions. A basic phylacogen is first prepared and is known as *Mixed Infection Phylacogen.* The specific phylacogens are prepared by adding to this basic material an equal proportion of the filtrate obtained by growing and treating the organism considered to be predominant in the pathological condition. For example; in the preparation of *Rheumatism Phylacogen,* a strain of Streptococcus—*Micrococcus rheumaticus*—is grown and treated like the several organisms entering in- from this product added to the Mixed Infection Phylacogan. There are also marketed Gonorrhea Phylacogan and Erysipelas Phylacogen.

Another group embracing some four-score of products are the *Tuberculins.* These are employed in the diagnosis and treatment of tuberculosis. Some of these products are employed very extensively. They will be treated upon in another paper.

There are also the various tests for syphilis, typhoid fever, and cholera, and the various products for veterinary use which time and space do not permit the writer to enumerate.

There are however three distinct classes of biologic products—Serums; those products derived from the blood of animals. Viruses; those products in which the infective material itself is employed; and the Bacterial Vaccines, which contain the dead organisms in suspension.

In closing, the writer will quote from NEW AND NONOFFICIAL REMEDIES 1912; published by the AMERICAN MEDICAL ASSOCIATION.

"The vaccines, viruses and serums constitute one of the most important groups of drugs with which the physician has to deal. Some preparations of this group are specific cures for certain diseases; others are invaluable in prophylaxis and diagnosis. The great importance of exercising some degree of governmental control over these products was recognized by the passage by Congress in 1902,

of a law entitled "An Act to Regulate the Sale of Viruses, Serums, Toxins and Analogous Products in the District of Columbia, to Regulate Interstate Traffic in Said Articles, and for Other Purposes." The law provides for the licensing of U. S. Public Health and Marine Hospital Service to have an inspection made of its necessary for an establishment desiring it to request the Surgeon-General of the U. S. Public Health & Marine Hospital Service to have an inspection made of its laboratories, methods, products, etc. This inspection is made by an officer of that service, and consists in a careful examination of the stables, laboratory, facilities, methods, animals, collection of the serum, standardization, and tests for potency, purity, and amount of preservative employed. Samples of the products from licensed manufacturers are bought on the open market and examined at frequent intervals in the Hygenic Laboratory of the P. H. and M. H. Service. The inspection of the laboratories is repeated at least once a year and if unsanitary conditions are found, or if the products are not what they are claimed, the license is suspended.'

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DESTRUCTION OF FLIES BY FORMALDEHYDE.

A very conclusive test of the efficacy of formaldehyde is claimed to have been made by a writer in the Economic Entomology, according to a report in the Veterinary Record. The mixture used was one of formalin, 1 oz.; milk, 8 oz.; water, 8 oz., and was used by placing it in shallow plates with a piece of bread in the middle of each plate. Six plates of the mixture were placed in the passage-way between the stalls in a large calf barn. This passage-way was about six feet wide and thirty feet long. The mixture was exposed at 12 o'clock noon and left until 8 o'clock the next morning. The dead flies when swept up measured three quarts, and half as many had died in the stall on each side. Between forty and fifty thousand flies were killed in twenty hours by this experiment.—*Pharmaceutical Journal and Pharmacist.*