Pharmaceutical Aspects of the Manufacture and Sale of Biological Preparations

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HISTORICAL INTRODUCTION.

The idea is a comparatively recent one in the history of medicine that many diseases are due to the presence of distinct germs, or microbes, and that the bacteriologist can, in many cases, grow pure cultures of these germs which may be so weakened by continued artificial culture that they are safely administered to animals, thus rendering them immune to the diseases.

The application of the principle involved in the foregoing process is, however, in at least one instance, much older than the idea itself.

Edward Jenner in the latter part of the 18th century, while working as an apprentice to a country physician, had his attention called to the fact that those people in the dairies who had contracted cow-pox (vaccinia) were thereby rendered immune to attacks of smallpox. This was the first fruitful observation of the principle of serum therapy.

Jenner's first observations were made in 1775, but it was not until 1796 that he found an opportunity to actually make experiments in vaccination as he called the process of innoculating against smallpox with cow-pox. In 1798 his investigations were first published.

Jenner's work and success are too well known to call for further comment. Notwithstanding the success of small-

pox vaccination and its almost instant extended use, it is not at all likely that Jenner conceived of smallpox, to say nothing of numerous other diseases, as being due to specific germs or organisms. The development of this theory of disease was left for Louis Pasteur.

Pasteur began his researches while still a pupil of Dumas. Prompted by the queries of a German manufacturer of, "tartrate of lime," Pasteur began a series of investigations about 1860, which led to the discovery of the organism which is the cause of fermentation in this product. Similar results were obtained in the work carried on to determine the cause of fermentation in beer and wines. The organism which causes fermentation was called a germ and the discovery of the fact that fermentation is due to definite organisms began a new era in medicine, namely that of "germ disease."

Pasteur next undertook a new line of investigation prompted by the invasion of France by the silk worm plague. Pasteur made a trip to the seat of the trouble and succeeded in isolating and identifying the germ which was the cause of this disease. The only means of combatting the disease was to isolate the contaminated worms, when the plague soon became extinct. In connection with his study of the silk worm plague Pasteur investigated anthrax or splenic fever and succeeded in isolating the germ and preparing a successful vaccine with which to fight the disease. In 1884 Pasteur's crowning achievement, the isolation of

the parasite of hydrophobia and the preparation of a successful vaccine was accomplished.

Robert Koch was a country physician in Wollstein, Germany, when he became interested in the work of Louis Pasteur . The discovery of germ life caused Koch to concentrate his energies upon this line of work. It was in 1876 that he first obtained pure cultures of the bacillus of anthrax but he was unable to find a method of preventive innoculation until seven years later. He was employed by the government in the fight against Asiatic cholera, but before leaving on an expedition to Africa, he announced his most startling discovery, the isolation of the bacillus of tuberculosis. His work in Africa then took up most of his time and it was not long before he discovered the comma which causes cholera. He next undertook to prepare a serum for the treatment and the prevention of this disease. The old method of growing cultures was resorted to but resulted in failure on account of the rapid rate of growth of the bacillus of Asiatic cholera for a few days, and then its equally fast disappearance. It was therefore not until 1891 that Hoffkine obtained pure cultures of the bacillus by inoculating rabbits. In this way he prepared a serum with which to combat the disease.

Koch's discoveries were now so universally known that much surprise and disappointment were experienced when it was learned that the method and agent employed by him, in

1890, against the bacillus of tuberculosis was a failure.

Koch next turned his attention to the disease known as rhinderpest, prevalent in South Africa, and found means of combatting it.

It may be well here to discuss briefly the discovery of at least three more of the important discoveries in serum therapy, namely:

1. Diphtheria antitoxin.

2. Tetanus antitoxin.

3. Typhoid fever serum.

The first is well known to all who have ever heard of diphtheria or seen the terrible results of this plague. The announcement that an antitoxin had been discovered which would prevent diphtheria created as much enthusiasm as Koch's discovery of the tuberculosis bacillus. This discovery, like most other recent ones, was the logical outcome of a series of experiments, performed independently, by Roux of Paris and Behring of Berlin. Klebs, in 1883, discovered the germs of diphtheria in the throats of patients suffering from the disease. The following year Loeffler isolated the germ and produced it in a pure culture with which he inoculated animals and succeeded in producing in them a disease similar to diphtheria. With this as a guide, and with the knowledge gained from the work of Pasteur, that it was possible to immunize one animal by injecting blood into it from another immunized animal, the first diphtheria anti-

toxin was soon produced.

It was not until 1880, when Sternberg made his notable experiments, that the true character of tetanus was known. Sternberg proved that this disease was caused by a specific flagellate organism. His work was afterwards confirmed by Carle and Rattone. It took many years to show the true pathology of tetanus, due principally to the fact that the germ would not grow when exposed to the air. For this reason it was not until 1888 that any one succeeded in producing tetanus in animals by inoculating them with some of the discharge matter from the wounds of tetanic patients. Carle and Rattone accomplished thic task and the following year Kitasato obtained pure cultures of the bacillus.

The first micro-organisms of typhoid fever were observed about 1871 by Recklinghauser but it was not until the investigations by Eberth, 1880 - 1882 that any definite idea of the pathology of the disease was gained. Altho it never had been possible to produce symptoms of the disease in animals, Gaffky in 1884 succeeded in producing pure cultures in gelatin and other media. It was from these cultures that the germs, which were to be first killed and later used, were obtained.

REGULATION OF SALE OF SERUM.

Previous to 1902 there was little if any regulation of the sale and manufacture of serums and antitoxins. In many instances the local boards of health prepared the serums for use in their respective vicinities and carelessness and lack of ability on their part was the direct cause of legislation. The results of two specific instances of this carelessness are the shocking fatalities at St. Louis[1] in 1901 and at Camden, N. J. in the same year. In both places many deaths resulted from impure diphtheria antitoxin. The antitoxin had been contaminated with tetanus to which the deaths were due. Both cities had prepared their own antitoxin but the investigation which was later carried on resulted in no prosecutions.

In the city of New York[2] and the state of Massachusetts the health departments prepared and distributed their own antitoxins free of charge. This was held by some[3] to be detrimental to druggists and to honest doctors. The conditions under which the serums were obtained, especially in New york, furnished a source of complaint and this coupled with the results in Camden and St. Louis formed the direct cause for the law passed July 1, 1902, regulating the manufacture of serums, antitoxins, viruses, and vaccines.

1. Western Druggist, 24, p.
2. Jour. Amer. Med. Assoc., 37, 1260, 1539.
3. Pharmaceutical Era, 27, 222.

[PUBLIC—No. 244.]

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.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That from and after six months after the promulgation of the regulations authorized by section four of this Act no person shall sell, barter, or exchange, or offer for sale, barter, or exchange in the District of Columbia, or send, carry, or bring for sale, barter, or exchange from any State, Territory, or the District of Columbia into any State, Territory, or the District of Columbia, or from any foreign country into the United States, or from the United States into any foreign country, any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention and cure of diseases of man, unless (a) such virus, serum, toxin, antitoxin, or product has been propagated and prepared at an establishment holding an unsuspended and unrevoked license, issued by the Secretary of the Treasury as hereinafter authorized, to propagate and prepare such virus, serum, toxin, antitoxin, or product for sale in the District of Columbia, or for sending, bringing, or carrying from place to place aforesaid; nor (b) unless each package of such virus, serum, toxin, antitoxin, or product is plainly marked with the proper name of the article contained therein, the name, address, and license number of the manufacturer, and the date beyond which the contents can not be expected beyond reasonable doubt to yield their specific results: *Provided*, That the suspension or revocation of any license shall not prevent the sale, barter, or exchange of any virus, serum, toxin, antitoxin, or product aforesaid which has been sold and delivered by the licentiate prior to such suspension or revocation, unless the owner or custodian of such virus, serum, toxin, antitoxin, or product aforesaid has been notified by the Secretary of the Treasury not to sell, barter, or exchange the same.

SEC. 2. That no person shall falsely label or mark any package or container of any virus, serum, toxin, antitoxin, or product aforesaid; nor alter any label or mark on any package or container of any virus, serum, toxin, antitoxin, or product aforesaid so as to falsify such label or mark.

SEC. 3. That any officer, agent, or employee of the Treasury Department, duly detailed by the Secretary of the Treasury for that purpose, may during all reasonable hours enter and inspect any establishment

for the propagation and preparation of any virus, serum, toxin, antitoxin, or product aforesaid for sale, barter, or exchange in the District of Columbia, or to be sent, carried, or brought from any State, Territory, or the District of Columbia into any other State or Territory or the District of Columbia, or from the United States into any foreign country, or from any foreign country into the United States.

SEC. 4. That the Surgeon-General of the Army, the Surgeon-General of the Navy, and the supervising Surgeon-General of the Marine-Hospital Service, be, and they are hereby, constituted a board with authority, subject to the approval of the Secretary of the Treasury, to promulgate from time to time such rules as may be necessary in the judgment of said board to govern the issue, suspension, and revocation of licenses for the maintenance of establishments for the propagation and preparation of viruses, serums, toxins, antitoxins, and analogous products, applicable to the prevention and cure of diseases of man, intended for sale in the District of Columbia, or to be sent, carried, or brought for sale from any State, Territory, or the District of Columbia, into any other State, Territory, or the District of Columbia, or from the United States into any foreign country, or from any foreign country into the United States: *Provided*, That all licenses issued for the maintenance of establishments for the propagation and preparation in any foreign country of any virus, serum, toxin, antitoxin, or product aforesaid, for sale, barter, or exchange in the United States, shall be issued upon condition that the licentiates will permit the inspection of the establishments where said articles are propagated and prepared, in accordance with section three of this Act.

SEC. 5. That the Secretary of the Treasury be, and he is hereby, authorized and directed to enforce the provisions of this Act and of such rules and regulations as may be made by authority thereof; to issue, suspend, and revoke licenses for the maintenance of establishments aforesaid, and to detail for the discharge of such duties such officers, agents, and employees of the Treasury Department as may in his judgment be necessary.

SEC. 6. That no person shall interfere with any officer, agent, or employee of the Treasury Department in the performance of any duty imposed upon him by this Act or by regulations made by authority thereof.

SEC. 7. That any person who shall violate, or aid or abet in violating, any of the provisions of this Act shall be punished by a fine not exceeding five hundred dollars or by imprisonment not exceeding one year, or by both such fine and imprisonment, in the discretion of the court.

SEC. 8. That all Acts and parts of Acts inconsistent with the provisions of this Act be, and the same are hereby, repealed.

Approved July 1, 1902.

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CLASSIFICATION OF BIOLOGICAL PREPARATIONS.

Serums, antitoxins, vaccines, viruses, etc. are of many different kinds and are offered to the pharmacist and the physician under many different names. A study of the nature of these various preparations, however, reveals the fact that they may all be classified under two, or at most three, main heads.

I. A serum is the blood serum of an animal which has been immunized against the specific bacterial toxins, or the bacteria themselves, and contains the necessary antibodies to be directed against the toxins, or the bacteria themselves, upon injection into the body. Under this heading may be listed:

1. Serum products.
2. Antitoxins.

II. Vaccine (vacca, a cow) was the term used by Jenner to designate the cow pox virus which he used for protective inoculation against smallpox. Later Pasteur applied the same term to suspensions of dead or attenuated bacteria. Under this head may be listed:

1. Vaccine products.
   a. Vaccine virus.
   b. Mixed vaccine.
   c. Phylacogens.

2. Bacterins.

a. Killed bacteria.

III. Sero-bacterins are preparations obtained by first immunizing healthy animals and using the serum of such animals to treat the bacteria of specific diseases. They are, in fact, combinations of serums and vaccines.

PREPARATION OF BIOLOGICAL PRODUCTS.

While the preparation of viruses, serums and antitoxins is no part of the province of pharmacy, or of pharmaceutical chemistry, it is a matter of so great interest that it has seemed proper to outline briefly here the method of preparing two of the most important of these products.

Diphtheria antitoxin[1] is obtained in the laboratory by growing diphtheria bacilli on veal broth. The toxin is then injected into horses, by increasing doses, until an average maximum dose is reached. The tissues of the horse form an antitoxin in the process of combatting the toxin. When the maximum concentration of antitoxin is formed, generally after several months of inoculation with the toxin, the required amount of blood is withdrawn from the jugular vein and allowed to separate from the clot. The serum is now filtered, purified, and lastly standardized. The standardization is accomplished by using a standard antitoxin, furnished by the government laboratories, experimentation being performed upon guinea-pigs. After the strength of the product is ascertained, the antitoxin is put in sealed packages for use.

Vaccine virus[2], commonly called smallpox vaccine, is prepared by first collecting the crusts from healthy

1. Mulford Working Bulletin, p. 1513.
2. Parke and Williams, Pathogenic Micro-organisms, p.568

children about nineteen days after successful vaccination, cutting these up , and emulsifying them with boiling water to a mucilagenous paste. This seed is then inoculated into a six inch area on the abdomen of a calf, the rest of the animal being vaccinated in the usual way. The pulp from the special area is collected and mixed with glycerin. After being tested, this virus is used in a dilution of 1:12 1/2 parts of salt solution for vaccinating rabbits. Five days after these have been inoculated the pulp is removed and mixed with a sterile mixture. This pulp, after purification, is used to vaccinate calves. The crusts of these final inoculations are removed, and after being emulsified with sterile water and glycerin in a special vaccine mill, the product is put into glass vials for issue.

The preparation of these two products, representing as they do the two principal types of biologicals, will serve as examples of the methods employed in the manufacture of this important class of medicinal agents. In the main the methods of preparing other members of each class differ from these only in details.

BIOLOGICAL PRODUCTS.

ESTABLISHMENTS LICENSED FOR THE PROPAGATION AND SALE OF VIRUSES, SERUMS, TOXINS, AND ANALOGOUS PRODUCTS.[1]

The following table contains a list of the establishments holding licenses issued by the Treasury Department in accordance with the act of Congress approved July 1, 1902, 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 licenses granted to the following establishments for the products mentioned do not imply an indorsement of the claims made by the manufacturers for their respective preparations. The granting of a license means that inspections of the establishment concerned and laboratory examinations of samples of its products are made regularly to insure the observance of safe methods of manufacture, to ascertain freedom from contamination, and to determine the potency of diphtheria antitoxin, tetanus antitoxin, and vaccine virus, for which potency standards or tests have been established.

AMERICAN ESTABLISHMENTS.

No. of license.	Name.	Products.
1	Parke, Davis & Co., Detroit, Mich.....	Antidysenteric serum; antigonococcic serum; antimeningococcic serum; antirabic virus; antistreptococcic serum; antituberele serum; cholera vaccine prophylactic; diphtheria antitoxin; erysipelas and prodigiosus toxin; normal horse serum; tetanus antitoxin; thyroidectomized horse serum; tuberculin B. E., tuberculin B. F., tuberculin old, tuberculin T. R.; vaccine virus; bacterial vaccines made from acne bacillus, acne diplococcus, colon bacillus, Friedlander bacillus, gonococcus, influenza bacillus, meningococcus, micrococcus catarrhalis, paratyphoid bacillus A, paratyphoid bacillus B, pertussis bacillus, pneumococcus, pseudodiphtheria bacillus, staphylococcus albus, staphylococcus aureus, staphylococcus citreus, streptococcus pyogenes, and typhoid bacillus; and modified bacterial derivatives prepared from colon bacillus, diphtheria bacillus, gonococcus, paratyphoid bacillus A, paratyphoid bacillus B, pneumococcus, pyocyaneus bacillus, staphylococcus albus, staphylococcus aureus, staphylococcus citreus, streptococcus pyogenes, and typhoid bacillus.

[1] Reprint from the Public Health Reports, vol. 31, No. 15, Apr. 14, 1916, pp. 943-948.

AMERICAN ESTABLISHMENTS—Continued.

No. of license.	Name.	Products.
2	H. K. Mulford Co., Philadelphia, Pa...	Antianthrax serum; antidysenteric serum; antimelitensis serum; antimeningococcic serum; antipneumococcic serum; antirabic virus; antistreptococcic serum; diphtheria antitoxin; normal horse serum; pollen vaccine; tetanus antitoxin; tuberculin B. E., tuberculin B. F., tuberculin old, tuberculin T. R.; vaccine virus; bacterial vaccines prepared from acne bacillus, cholera vibrio, colon bacillus, diphtheria bacillus, dysentery bacillus, gonococcus, influenza bacillus, meningococcus, micrococcus catarrhalis, micrococcus neoformans, paratyphoid bacillus A, paratyphoid bacillus B, pertussis bacillus, plague bacillus, pneumococcus, pseudodiphtheria bacillus, pyocyaneus bacillus, staphylococcus albus, staphylococcus aureus, streptococcus pyogenes, and typhoid bacillus; and sensitized bacterial vaccines prepared from acne bacillus, cholera vibrio, colon bacillus, gonococcus, influenza bacillus, meningococcus, micrococcus catarrhalis, paratyphoid bacillus A, paratyphoid bacillus B, pertussis bacillus, pneumococcus, pseudodiphtheria bacillus, staphylococcus albus, staphylococcus aureus, streptococcus pyogenes, and typhoid bacillus.
3	Dr. H. M. Alexander & Co., Marietta, Pa.	Antirabic virus; antityphoid vaccine; diphtheria antitoxin; normal horse serum; tetanus antitoxin; tubercle bacillus extract Dixon, tubercle bacillus suspension Dixon, tuberculin B. E., tuberculin B. F., tuberculin old, tuberculin T. R.; and vaccine virus.
6	The Slee Laboratories, Swiftwater, Pa..	Antistreptococcic serum; diphtheria antitoxin; normal horse serum; tetanus antitoxin; and vaccine virus.
8	The Cutter Laboratory, Berkeley, Cal..	Antimeningococcic serum; antipneumococcic serum; antirabic virus; antistreptococcic serum; diphtheria antitoxin; normal horse serum; tetanus antitoxin; tuberculin B. E., tuberculin B. F., tuberculin old, tuberculin T. R.; vaccine virus; and bacterial vaccines prepared from acne bacillus, colon bacillus, Friedlander bacillus, gonococcus, micrococcus catarrhalis, pertussis bacillus, pneumococcus, pseudodiphtheria bacillus; staphylococcus albus, staphylococcus aureus, staphylococcus citreus, streptococcus pyogenes, and typhoid bacillus.
14	Bureau of Laboratories, Health Department, New York City.	Antigonococcic serum; antimeningococcic serum; antipneumococcic serum; antirabic virus; antistreptococcic serum; diphtheria antitoxin; normal horse serum; tetanus antitoxin; old tuberculin; vaccine virus; and bacterial vaccines prepared from glanders bacillus, gonococcus, pertussis bacillus; pneumococcus, staphylococcus albus, staphylococcus aureus, streptococcus pyogenes, and typhoid bacillus.

AMERICAN ESTABLISHMENTS—Continued.

No. of license.	Name.	Products.
16	National Vaccine and Antitoxin Institute, Washington, D. C.	Diphtheria antitoxin; normal horse serum; tetanus antitoxin; vaccine virus; and bacterial vaccines prepared from colon bacillus, Friedlander bacillus, gonococcus, micrococcus catarrhalis, micrococcus tetragenus, paratyphoid bacillus A, paratyphoid bacillus B, pneumococcus, pseudodiphtheria bacillus, pyocyaneus bacillus, staphylococcus albus, staphylococcus aureus, staphylococcus citreus, streptococcus pyogenes, and typhoid bacillus.
17	Lederle Antitoxin Laboratories, Pearl River, N. Y.	Antigonococcic serum; antimeningococcic serum; antipneumococcic serum; antirabic virus; antistreptococcic serum; diphtheria antitoxin; normal horse serum; pollen vaccine; tetanus antitoxin; vaccine virus; and bacterial vaccines prepared from acne bacillus, cholera vibrio, colon bacillus, Friedlander bacillus, gonococcus, influenza bacillus, meningococcus, micrococcus catarrhalis, paratyphoid bacillus A, paratyphoid bacillus B, pertussis bacillus, plague bacillus, pneumococcus, staphylococcus albus, staphylococcus aureus, staphylococcus citreus, streptococcus pyogenes, and typhoid bacillus.
19	Serum Division, Memorial Institute for Infectious Diseases, 637 South Wood Street, Chicago, Ill.	Diphtheria antitoxin.
23	Bacterio - Therapeutic Laboratory, Asheville, N. C.	Watery extract of tubercle bacilli (von Ruck): modified tubercle bacillus derivative (von Ruck).
30	Dr. G. H. Sherman, 419 St. Aubin Street, Detroit, Mich.	Bacterial vaccines prepared from acne bacillus, colon bacillus, Friedlander bacillus, gonococcus, influenza bacillus, meningococcus, micrococcus catarrhalis, paratyphoid bacillus A, paratyphoid bacillus B, pertussis bacillus, pneumococcus, pseudodiphtheria bacillus, staphylococcus albus, staphylococcus aureus, staphylococcus citreus, streptococcus pyogenes, nonvirulent tubercle bacillus, and typhoid bacillus.
40	Hygienic Laboratory, California State Board of Health, Berkeley, Cal.	Antirabic virus; and sensitized typhoid vaccine.
43	The Abbott Laboratories, Abbott Alkaloidal Co., Chicago, Ill.	Bacterial vaccines prepared from acne bacillus, colon bacillus, Friedlander bacillus, gonococcus, pneumococcus, staphylococcus albus, staphylococcus aureus, streptococcus pyogenes, and typhoid bacillus.
46	New York Pasteur Institute, 361 West Twenty-third Street, New York City.	Antirabic virus.
49	Dr. W. T. McDougall, 707 Parallel Avenue, Kansas City, Kans.	Do.
50	St. Louis Pasteur Institute, 803 North Garrison Avenue, St. Louis, Mo.	Do.
51	The Upjohn Co., Kalamazoo, Mich.....	Bacterial vaccines prepared from colon bacillus, Friedlander bacillus, gonococcus, influenza bacillus, micrococcus catarrhalis, micrococcus tetragenus, paratyphoid bacillus A, paratyphoid bacillus B, pertussis bacillus, pneumococcus, pseudodiphtheria bacillus, staphylococcus albus, staphylococcus aureus, staphylococcus citreus, streptococcus pyogenes, and typhoid bacillus.

AMERICAN ESTABLISHMENTS—Continued.

No. of license.	Name.	Products.
52	E. R. Squibb & Sons' Research and Biological Laboratories, New Brunswick, N. J.	Antigonococcic serum; antimeningococcic serum; antirabic virus; antistreptococcic serum; diphtheria antitoxin; leucocyte extract; normal horse serum; tetanus antitoxin; and bacterial vaccines prepared from acne bacillus, colon bacillus, gonococcus, meningococcus, pertussis bacillus, pneumococcus, pyocyaneus bacillus, staphylococcus albus, staphylococcus aureus, staphylococcus citreus, streptococcus pyogenes, and typhoid bacillus.
53	Laboratory of Clinical Pathology, 1208 Wyandotte Street, Kansas City, Mo.	Antirabic virus.
54	Dr. James McI. Phillips, 2057 North High Street, Columbus, Ohio.	Do.
56	Eli Lilly & Co., Indianapolis, Ind.	Antirabic virus, antistreptococcic serum, diphtheria antitoxin; normal horse serum; normal sheep serum; tetanus antitoxin; vaccine virus; and bacterial vaccines prepared from acne bacillus, colon bacillus, Friedlander bacillus, gonococcus, influenza bacillus, meningococcus, micrococcus catarrhalis, paratyphoid bacillus A, parstyphoid bacillus B, pertussis bacillus, pneumococcus, pyocyaneus bacillus, staphylococcus albus, staphylococcus aureus, staphylococcus citreus, streptococcus pyogenes, and typhoid bacillus.
57	American Biological Co., 600 F Street, Washington, D. C.	Bacterial vaccines prepared from acne bacillus, gonococcus, staphylococcus albus, staphylococcus aureus, streptococcus pyogenes, and typhoid bacillus.
58	Swan Myers Co., 219 North Senate Avenue, Indianapolis, Ind.	Bacterial vaccines prepared from colon bacillus, Friedlander bacillus, gonococcus, micrococcus catarrhalis, pertussis bacillus, pneumococcus, staphylococcus albus, staphylococcus aureus, streptococcus pyogenes, and typhoid bacillus.
59	International Laboratories, 65 Irving Place, New York City.	Leucocyte extract (rabbit).
60	Greeley Laboratories, Inc., 655 Huntington Avenue, Boston, Mass.	Bacterial vaccines prepared from acne bacillus, colon bacillus, gonococcus, micrococcus catarrhalis, pertussis bacillus, pneumococcus, pseudodiphtheria bacillus, pyocyaneus bacillus, staphylococcus albus, staphylococcus aureus, staphylococcus citreus, streptococcus pyogenes, and typhoid bacillus.
61	Stafford Biological Laboratories, Smith Building, Detroit, Mich.	Bacterial vaccines prepared from acne bacillus, colon bacillus, Friedlander bacillus, gonococcus, influenza bacillus, micrococcus catarrhalis, pertussis bacillus, pneumococcus, pseudodiphtheria bacillus, staphylococcus albus, staphylococcus aureus, staphylococcus citreus, streptococcus pyogenes, and typhoid bacillus.
62	Dr. George Ives Clinical Laboratory, 213 Wall Building, St. Louis, Mo.	Bacterial vaccines prepared from staphylococcus albus, staphylococcus aureus, staphylococcus citreus, and streptococcus pyogenes.

TABLE OF BIOLOGICAL PREPARATIONS.

In the following table the biological preparations of four of the principal manufacturers are listed, together with the style of container in which each preparation is dispensed.

Key to table.

a.- Syringe container.

b.- Bulb and ampoule containers.

c.- Vial container.

d.- Bottle container.

Parke, Davis & Co.

	a	b	c	d
Diphtheria antitoxin	"			
Tetanic "	"	"		
Anti anthrax serum				
Anti dysenteric "				
Anti gonococcic "		"		
Anti meningococcus serum	"			
Anti pneumococcus "				
Anti staphylococcus "				
Anti streptococcus "	"	"		
Old tuberculin "				
New tuberculin " T. R.		"		
Tuberculin Deny's B.F. serum				
Tuberculosis serum vaccine				
Acne bacillus vaccine	"	"	"	"
Cholera "				
Colon bacillus "	"	"	"	"
Influenza mixed "	"		"	
Anti rabic "				
Furunculosis "	"	"	"	"
Gonococcus "	"	"	"	"
Meningococcus "	"	"		
Pertussis bacillus vaccine	"	"	"	"
Plague bacillus "		"		
Pneumococcus "	"	"	"	"

H.K. Mulford Co.				Eli Lilly & Co.			
a	b	c	d	a	b	c	d
"				"			
"				"			
"							
"		"					
"		"				"	
"		"					
"		"		"		"	
						"	
						"	
				"			
"	"	"		"		"	
"							
"		"		"		"	
		"					
"	"	"		"		"	
"	"			"		"	
				"		"	
"	"	"		"		"	

Abbott Laboratories

a	b	c	d
"			
"		"	
		"	
		"	"
		"	"
		"	"
		"	"

	Parke, Davis & Co.			
	a	b	c	d
Pyocyaneus bacillus vaccine				
Pyorrhea Alveolaris "	"	"	"	"
Staphylococcus "	"	"	"	"
Streptococcus "	"	"	"	"
Typhoid "	"	"		
Vaccine virus		tubes		
Catarrhal combined "				
Van-Cott " "	"	"	"	"
Urethritis "	"	"	"	"
Scarlet fever "				

Note,- Tuberculin "Old", and "New", and "B.E." is put out by P. D. & Co, in disc form.

H. K. Mulford Co.

a	b	c	d
"	"	"	
"	"		
"	"	"	
"	"	"	
	"		

Eli Lilly & Co.

a	b	c	d
"		"	
"		"	
"		"	
"		"	
capillary tubes			
"		"	
"		"	
"		"	

Abbott Laboratories

d

a	b	c	d
		"	"
"		"	"
"		"	"
"		"	
		"	"
		"	"

ADMINISTRATION.

Vaccines are usually injected subcutaneously. The best method is to pick up a fold of the skin between the finger and the thumb and then push the needle well down into the center of the fold and slowly inject the fluid.

Serums are usually administered by subcutaneous injection into the tissue of the back, abdomen or buttocks. Intramuscular injection into the muscles of the buttocks insures a more rapid absorption of the serum and probably causes the patient no more pain. In severe cases the serum is given intravenously.

Antimeningococcic serum is given subdurally in order to bring it into direct contact with the infected membranes.

KEEPING QUALITIES OF BIOLOGICAL PREPARATIONS.

Antitoxins and serums, if properly protected from heat and light will retain their potency for a long time. Boehncke[1] made an intensive study of the keeping qualities of diphtheria antitoxic serums and found that serums which had been kept in an ice box without special precautions showed no loss of potency under four years.

It is recommended that all serums be kept in the dark at a uniform temperature of from 35° to 50° F.

Vaccines undergo decomposition very slowly when they are kept in a dark, cool place and the immunizing quality of many is improved upon standing.

Vaccine virus should not be kept long before being used as it deteriorates very readily unless properly kept.

1. Lilly, Biological Therapy, p. 12.

GLOSSARY.

Agglutin,- The substance in a serum which causes the coagulation of the bacteria.

Antitoxin,-The name given to the substance in a serum which nullifies the toxin of a disease.

Bacillus,- The rod form of bacteria.

Bacteria,- Extremely minute unicellular micro-organisms which reproduce with exceeding rapidity and grow without the aid of chlorophyll.

Bacteriolysins,- Substances in the blood serum which break up bacteria, killing them and making them soluble.

Comma,- A bacteria of curved shape said to be present in cholera.

Culture,- The artificial development of microorganisms, especially bacteria, in specially prepared media.

Flagellate,- Whip shaped.

Globulin,- A term referring to the concentrated form of serum. When ammonium sulphate is added to a serum the immune bodies are precipitated out together with certain globulins These antitoxin carrying bodies are redissolved in salt solution and form the glob-

ulin serum .

Immunity,- Resistance offered to bacterial infection.

Innoculation,- The introduction of bacteria or other organisms into surroundings suited for their growth.

Organism,- Any living body.

Parasite,- Any plant or animal living in, on, or with some other living organism at whose expense it obtains its food, shelter, or some other advantage.

Pathogenic organisms,- Those organisms which cause disease.

Bacteriotropins,- Substances in blood serum which reduce the resistance of the bacteria of diseases facilitate phayocytosis.

Pathology,- The science treating of diseases their cause, nature, progress, and manifestations.

Phayocytosis,- The taking up or engulfing of foreign substances by certain cells(phayocytis) for digestion.

Phylacogens,- Mixed vaccines prepared by P. D. & Co. according to the formula of Dr. C. F. Schafer.

Prophylactic agents,- Those agents used for protective innoculation against disease when they do not confer immunity after the disease has been contracted.

Sero bacterins,- Preparations obtained by first immunizing healthy animals and using the serum of such animals to treat the bacteria of the specific disease. They are really a combination of serum and vaccine, hence the name.

Serum therapy,- The treatment of disease by the injection of blood serum from immunized animals.

Subcutaneous,- A form of innoculation in animals in which the bacteria are injected by means of a hypodermic needle under the skin, or are introduced by a platinum loop into a pocket made by an incision.

Subdurally,- Under the membrane lining the cavity of the cranium.

Toxin,- A poisonous product of decomposition in a few substances belonging to the group of alkaloid like bodies known as ptomaines, basic compounds, having a more or less definite chemical composition.

Vaccines,- Suspensions of dead or attenuated bacteria. Specifically, smallpox vaccine.

Mixed vaccines,- Preparations of different kinds of vaccines for the treatment of mixed infections.

Virus,- A principle, unknown in its nature and inappreciable by the senses, which is the agent for the transmission of infectious diseases.

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