By the M. L. D. method, Brauns and Closson found an average toxicity for their product of 0.00096 mg. per Gm. of frog as compared with our figure of 0.00045 mg. per Gm. for the Jacob's product, thus emphasizing again the discrepancy between our figures and those of Brauns and Closson.

CONCLUSIONS.

Strophanthin exists on the market to-day in at least two strengths differing greatly from each other in toxicity, one being practically twice as strong as the other. It seems justifiable, therefore, and indeed absolutely necessary to insert in the description of Strophanthin in the next revision of the Pharmacopœia a statement regarding its physiological activity.

The ouabains on the market appear to be of uniform activity and practically twice as strong as strophanthin.

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REPORT ON THE AVAILABILITY OF CERTAIN NEW BIOLOGICALS.

BY J. C. PEACOCK.*

Since the definite service of pharmacy is to provide and dispense remedial agents, it seems appropriate to report to this Section on the availability of new materia medica as the same comes into the market.

New biological products mean new medical progress, for the ability to combat and control disease has steadily gathered strength with the practical application of succeeding discoveries in this field; and pharmacists who are endeavoring to keep up with the onward march of the medical sciences are desirous of getting a better working knowledge of this class of remedies.

The mystery in which the packages of biological agents have been all too generally enveloped can be dispelled by a better comprehension of the nature of these preparations which are so intimately associated with the treatment of disease and the protection of health.

In a paper entitled "Biologicals Viewed as Pharmaceuticals" which this writer presented last year to the Section on Practical Pharmacy and Dispensing, the suggestion was made to look upon biologicals just as other pharmaceuticals are regarded; that is, to consider them with respect to their proximate composition, as preparations of the active factors or influences which they represent, in the same way that galenicals are thus thought of by the pharmacist, as he dispenses the latter.

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* Presented to the Scientific Section, A. PH. A., Portland, Maine meeting, 1928.

The medical profession is taking the lay public more and more into its confidence on health matters and means of dealing with disease; consequently when such remedies as new biological products become commercially available the fact may well be heralded by this and other pharmaceutical associations to the pharmacist who in turn can relay this news to physician patrons and lay customers.

Such program of information must always be one of the practical services to be encouraged and promoted by organized pharmacy; for the publicity essential to the success of its votaries is constantly asking for the better education of all concerned with the remedies to be used.

Since the last meeting of this ASSOCIATION the following biologicals have been developed to the stage of commercial availability:

Diphtheria Toxoid; Perfringens (Gas Gangrene) Antitoxin; Johnin; Antivenin, Bothropic—Tropical American Anti-Snake-Bite Serum; Antivenin (Veterinary)—North American Antivenin for veterinary use; Streptococcus Cardioarthritidis Antigens and Anti-Serums; Antibrucella Serum, Polyvalent (Antimelitensis Serum or Malta Fever Serum); Tetanus Antitoxin, Bovine; and Diphtheria Toxin-Antitoxin Mixture made with goat serum.

This report is intended only to inform the pharmacist on such practical considerations of the above-mentioned products as those of designation, synonymous names, indication, nature, action, strength, style and size of container, dosage, method of administration and related aspects.

The circulars of directions which accompany these products will be found of much practical help in the administration of them.

Cataloging these new biologicals in the order in which they have appeared in the market, they are as follows:

Diphtheria Toxoid (Anatoxine-Ramon) is a non-toxic modified diphtheria toxin used for active immunization against diphtheritic infection. It is prepared by the action of formaldehyde on diphtheria toxin which has been made in the usual way. By this treatment, the toxin loses all of its toxic or poisonous character as ordinarily determined by guinea-pig inoculation, but retains its immunizing or antigenic powers.

The toxoid is diluted with salt solution to reduce undesirable local reactions which a full strength solution would characteristically produce.

To avoid possible confusion with the term Antitoxin, Diphtheria Anatoxine, as it is called in Europe, is known as Diphtheria Toxoid in America. The products are identical.

Toxoid differs from Toxin-Antitoxin Mixture, in that the former is diphtheria toxin *Modified* by the action of formaldehyde, while the latter is diphtheria toxin *Neutralized* by Diphtheria Antitoxin. Toxoid is therefore free from serum proteins, which is its obvious advantage over Toxin-Antitoxin Mixture.

In France especially, Toxoid has found extensive use on account of this freedom from horse serum protein and because of the observation that active immunity is produced in three to eight weeks or in about one-fourth the time required for Toxin-Antitoxin Mixture; also, because fewer doses are needed.

Diphtheria Toxoid is given subcutaneously, preferably in the back between the shoulder blades in two doses of 1 cc. each, with an interval of 3 weeks.

Diphtheria Toxoid is supplied in packages of two 1-cc. ampul vials, enough for

one immunization; and in packages of twenty 1-cc. ampul vials, enough for ten immunizations. In each package of Diphtheria Toxoid there is included an ampul vial with Green Label marked "Diluted Diphtheria Toxoid for the Reaction Test," and containing Diphtheria Toxoid diluted 1 to 20 with salt solution.

It is believed that the duration of immunity is equally long for Toxoid as for Toxin-Antitoxin.

Perfringens Antitoxin (Anti-Gas-Gangrene Serum) is an antitoxic serum prepared from the blood plasma of horses highly immunized against the toxin of *Bacillus Perfringens*, or *Bacillus Welchii*, which is recognized as the primary cause of gas gangrene.

In 1917, Bull and Pritchett prepared Perfringens Antitoxin that gave good results. Consequently this serum is sometimes asked for under the name of Bull or Bull's Serum. Continued work has improved this product until now an unconcentrated antitoxin may be had containing one antitoxic unit per cc. of serum. The U. S. Hygienic Laboratory has set that strength as a minimum standard for Perfringens Antitoxin.

One unit is the amount of antitoxin necessary to neutralize 1000 M. L. D. of Welch toxin. M. L. D. is the minimum lethal dose of toxin that will kill a 300-Gm. pigeon.

This standard antitoxin is produced in commercial quantity and is offered in the unconcentrated form in 100-cc. bottles including at least one antitoxin unit per cc.; and at times may be had in bottles of 50 cc. containing at least two antitoxic units per cc.

Perfringens Antitoxin is concentrated by the usual methods of globulinization until five times as strong as the unconcentrated. This refined product is marketed in syringes containing 20 cc. of concentrated antitoxin containing at least five antitoxic units per cc. or 100 units.

An initial dose of 40 to 100 units intramuscularly, followed at once in severe cases by another 40 to 50 units intravenously is usually employed. Thereafter, 40 to 80 units, intramuscularly, each day as indicated. The concentrated antitoxin is preferable because of its smaller volume. Surgical consideration may be necessary in some cases in which Perfringens Antitoxin is indicated. In doses of 25 or more units, this antitoxin is much used as a prophylactic with or without surgical procedure.

Johnin is an agent for the diagnosis of Johne's disease or chronic infectious dysentery in cattle.

The organism causative of this disease is now known as *Mycobacterium paratuberculosis*. It is an acid-fast organism entirely distinct from the tubercle bacillus, although resembling the latter in its staining properties.

A very full account of this diagnostic agent, by Dr. H. K. Wright of the Veterinary Department of the Mulford Laboratories, will be found in the April 1928 issue of the *Journal of the American Veterinary Medical Association.*

The history of the development of Johnin, together with method of preparation, statement of dosage and technique of application, as also mention of the symptoms suggesting its use, reports of field tests on known-infected herds and an interpretation of its effects and practical value, are given in full and careful detail.

While private veterinary practitioners are interested in this disease, the state

veterinarian, or state livestock sanitary official, is particularly concerned, since an attempt is being made to eradicate the disease along the same lines as bovine tuberculosis through the coöperation of the state and national governments. Only qualified veterinarians should administer Johnin. It is supplied in vials of 25 cc. (5 tests) and 100 cc. (20 tests).

Antivenin (Bothropic), Tropical American Anti-Snake-Bite Serum, is a purified and concentrated serum globulin obtained from the blood of horses which have been highly immunized against the venom of tropical American serpents of the genus Bothrops, especially against that of the "Fer-de-lance" (or *Barba amarilla* —Yellow Beard) (*Bothrops atrox*), the most dangerous snake of the mainland of tropical America from Mexico to Venezuela, and against the venom of the Horned Palmed Viper and Hog Nosed Viper.

A year ago the availability of Antivenin Nearctic, a polyvalent North American Anti-Snake-Bite serum was reported to this ASSOCIATION, and on November 10, 1927, Antivenin Bothropic, the corresponding specific serum against the venom of these common tropical American snakes was licensed for manufacture and sale.

A minimum standard has been established requiring that each cc. of Antivenin (Bothropic) neutralizes 1 mg. of venom of the "Fer-de-lance" (*Bothrops atrox*).

Antivenin (Bothropic), like North American Anti-Snake-Bite serum, is supplied in 10-cc. syringe packages, which is an average dose, with the same dating of five years, and in every other respect is comparable to North American Anti-Snake-Bite serum. The package is furnished with directions in both the English and Spanish languages.

Antivenin (Bothropic) is specific medication and therefore like Antivenin (Nearctic) makes non-specific treatment entirely unnecessary.

Antivenin (Veterinary).—North American Antivenin for the treatment of snake bite in animals. This product which is unconcentrated North American Anti-Snake-Bite serum is derived from the blood of horses artificially immunized against the venoms of the poisonous North American serpents of the zoölogical family Crotalidae, including rattle-snakes, the copperhead and the moccasin. In contradistinction to Antivenin for human use, which is concentrated, Antivenin (Veterinary) is unconcentrated.

Since the announcement of Antivenin Nearctic something over a year ago, Antivenin, Veterinary, has been made available for use on animals.

While the human antivenin is entirely suitable for use on animals, it has been practicable to furnish an unconcentrated Antivenin at a greatly reduced price, thereby putting this specific remedy as insurance against loss into the hands of stock owners and others interested in saving the lives of animals that are bitten by poisonous snakes in Canada, the United States and North-Central Mexico.

This service will apply to valuable hunting and other dogs as well as to live stock in general.

Antivenin (Veterinary) is prepared in the same manner and with the same exacting care as Antivenin for human use. Antivenin (Veterinary) is supplied unconcentrated in vials of 50 cc., representing the quantity necessary for an average dose. Although unconcentrated, this serum is accurately standardized and is rich

in the specific protective substances. Veterinary Antivenin is injected either subcutaneously or intravenously.

This dosage may be repeated within a few hours or at once in severe cases. Antivenin should always be administered as soon as possible after the bite, and the smaller the animal bitten the larger the dose and the quicker the administration should be.

Antivenin (Veterinary) may safely be used on humans, administering 50 cc. as a full dose, if the concentrated serum for human use is not available.

Like other antivenins, Antivenin (Veterinary) is not subject to return or exchange. It carries a five-year expiration date, and, when stored in a reasonably cool place, may be used at any time up to this date with the full assurance that it has not suffered any appreciable loss in potency.

Anti-Rheumatic Fever Products or Streptococcus Cardioarthritidis Products.—These are usually designated by the abbreviated term "S. C. A." for the identification of the Anti-sera and the soluble antigen prepared from the streptococcus cardioarthritidis.

These biologicals have resulted from the study of this organism by Dr. J. C. Small, he having constantly found this organism in the throat of rheumatic patients and associated with chorea.

S. C. A. Products are produced under authorization of the Rheumatic Fever Committee of Philadelphia in addition to the usual Government license.

Antistreptococcus Cardioarthritidis Serum, Concentrated (S. C. A. Serum, Equine) as used in the treatment of chorea and acute rheumatic fever, its complications and sequelae is produced in the horse's blood in a similar manner to diphtheria antitoxin. It is supplied in packages of one 10-cc. syringe with extra needle permitting dosage of 5 to 10 cc., which is injected intramuscularly. If needed, these amounts may be given two or three times at intervals of twelve to twenty-four hours.

S. C. A. Serum (Bovine) is an unconcentrated antistreptococcus serum, cardioarthritidis, which is supplied to patients who are sensitive to equine serum. This form is packaged in 20-cc. syringe.

These serums are used in treatment of acute attacks of rheumatic fever. S. C. A. Products are specific for streptococcus cardioarthritidis only, and no definite benefit can be expected in conditions due to other organisms.

In addition to the two forms of serum, Streptococcus Cardioarthritidis Soluble Antigen (S. C. A. Soluble Antigen) is offered for the treatment of sub-acute and chronic rheumatism and as a supplement to the serum. This antigen is a bacteria-free filtrate prepared from suspensions of the micro-organisms in normal saline solution. It contains the substance responsible for the reactions and in a definite concentration, which may be diluted as required. This product is used for active immunization in dilutions of 1:100 million, 1:10 million and 1:1 million. These are known as Dilutions 0, 1 and 2, and are packaged in 5-cc. vials with rubber caps to permit the withdrawal of the necessary dosage.

To prevent relapses, S. C. A. Soluble Antigen Dilution 0 is given to build up an active immunity, and should be started while the passive immunity is still high (on the third day following the last serum injection). In cases where the

serum is not used the Soluble Antigen may be used alone. Treatment is started with Dilution 0 and followed by Dilutions 1 and 2.

The antigen is also used as a diagnostic agent for the identification of patients suffering from chronic rheumatism, by subcutaneous injection.

Antimelitensis Serum (Antibrucella Serum Polyvalent; *Melitensis* and *Abortus*) for the treatment of Undulant or Malta Fever.

Recent investigations have established the close relationship of the causative organism of Malta Fever (*Micrococcus melitensis*) to the *Brucella Abortus* of Bang (the organism of bovine contagious abortion which has been proved to be infectious for human beings).

A serum formerly supplied under the name of Anti-Malta-Fever Serum was prepared against *Brucella melitensis* only. In the production of the present Antimelitensis-Serum or Antibrucella Serum, hyper-immunization of cattle is effected by treatment with the two types, Brucella melitensis and Brucella abortus. In immunizing cattle, the two types are kept separate, so that *antimelitensis* and *antiabortus* serums are prepared and obtained separately. These serums are then mixed in equal proportions, so that the resulting product is a polyvalent Antimelitensis-Serum which contains antibodies for both types of organisms.

Physicians may not think of the possibility of meeting Malta Fever, but typhoid or paratyphoid will be considered. Having these in mind, they will send blood for a Widal test. Experience indicates that in all such cases an examination for Malta Fever should be done.

Antimelitensis Serum Polyvalent is supplied in packages of 50-cc. double-end vials with injection outfit.

The average dose, injected intravenously, is 50 cc. to 100 cc., repeated in 12 to 24 hours, if necessary.

It is a bovine serum and can, therefore, be administered safely to individuals who have previously received the injection of serum from horses, or who may naturally be sensitive to horse serum. Individuals who are known to be sensitive to bovine serums must first be desensitized by the usual methods.

Tetanus Antitoxin, Bovine, is now obtainable for use on patients who have had a previous injection of horse serum, or who may be otherwise sensitive to equine protein, thus enabling the administration of Tetanus Antitoxin as an immunizing agent under these conditions.

Tetanus Antitoxin, Bovine, is considerably higher in price than that of equine origin owing to the fact that the production of the bovine product is very much smaller per animal and consequently exceeds in cost Tetanus Antitoxin that is regularly produced in larger amounts in horses.

The product so far available is concentrated or globulinized and put up in the 1500-unit syringe package, making it the counterpart of the equine antitoxin which is so commonly used in this form and strength for prophylaxis. Like the equine product, each package of Tetanus Antitoxin, Bovine, is finished with an excess of antitoxin units to allow for a two years' dating.

Diphtheria Toxin Antitoxin Mixture (Goat) is a mixture of $^1/_{10}$ L plus dose of toxin per cc. made with Diphtheria Antitoxin cultivated in the blood serum of the goat instead of from usual Diphtheria Antitoxin obtained from the serum of immunized horses.

In all other respects this Toxin-Antitoxin Mixture is the exact counterpart of the usual Diphtheria Toxin-Antitoxin of this strength and it is used in the same dosage, and method of administration for active immunization.

This product offers opportunity for immunization of all subjects hypersensitive to horse serum protein.

PHYTOCHEMICAL NOTES.*†

No. 102. THE NON-HEPTANE CONSTITUENTS OF JEFFREY PINE.

BY P. A. FOOTE.

Early in 1927 an understanding was reached with Dr. Graham Edgar of the Ethyl Gasoline Corporation of Yonkers, N. Y. in accordance with which a large amount of Jeffrey Pine oil was to be sent to the Wisconsin Pharmaceutical Experiment Station for rectification of its principal constituent, the heptane. The non-heptane constituents were to be used for further investigation of these substances whereas the heptane fraction was to be forwarded to Yonkers for the study of the standardization of gasoline as fuel in internal combustion engines. The Jeffrey Pine oil was produced in California during the summer of 1927 as a coöperative enterprise between the Ethyl Gasoline Corporation, the local representative of the Bureau of Forestry and a third party, the California Chemical Company. The material, four drums of about 50-gallon capacity each, was received in the fall of the same year.

Through the kindness of Professor O. Kowalke, the Walter Lummus 20-gallon copper, steam-jacketed alcohol rectifying still of the Chemical Engineering Department was used. It is equipped with a 6-ft. 12-section column and dephlegmator, the latter being unnecessary for this work. The details of this fractionation have been recorded in a report submitted to Dr. Edgar, hence need not be repeated here. The densities of the numerous fractions revealed that great care had been exercised in excluding contamination with Western Yellow Pine. For the purposes of this paper it may suffice to record the summary of materials obtained, *viz.:*

I. An aqueous cohobate.
II. Oily fractions distilling below the boiling point of *n*-heptane.
III. The heptane fractions forwarded to the Ethyl Gasoline Corporation.
IV. Oily fractions distilling above the boiling point of *n*-heptane after the removal of aldehydes by shaking them with a concentrated solution of sodium acid sulphite.
V. The oily aldehydes regenerated from the sodium acid sulphite addition products.

Isolation and Identification of the Aldehydes.—From the numerous fractions distilling over above the boiling point of *n*-neptane the aldehydes were removed by shaking them with a concentrated solution of sodium acid sulphite. The solid addition product was separated with the aid of a force filter and the drained solid washed with petroleum ether. The aldehydes were regenerated with sodium car-

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* From Scientific Section, A. PH. A., Portland meeting, 1928.

† From the laboratory of Edward Kremers.