hold the fragments in place while bony union is being established. Of course, in an infected fracture the intramedullary bone graft cannot be used and external splints may fail to maintain alignment. It should be remembered that the Lane plate can be removed with the greatest ease if infection should require the removal of the internal splint, whereas, it is difficult to remove an intramedullary bone peg. Too great caution cannot be observed in the use of bone pegs following war fractures, since even months may elapse after complete external healing has occurred and yet the trauma incident to an open operation will reawaken a dormant infection. Hence the prudence of relying on osteotomy with extension and counterextension more often than is common practice in the correction of old badly healed war fractures. I have used the Groves wire cradle splint for fractures of the femur many times. I do not believe there is a better femur fracture splint for use in war or civil practice. It might be described as a Hodgen splint supported below by posts instead of being suspended from above. The surgeon can work over or under it. It admits of easy access to every part of the leg or thigh while extension is being carried on. When the Steinmann pin or any sort of ice tongs device is used this wire cradle splint is especially satisfactory. The weight and pulley are attached to the splint itself, maintaining pull in any direction with mathematical accuracy. I believe the Groves cradle splint to be one of the most valuable developments of war surgery.

DR. MORRIS K. SMITH, New York: The treatment of gunshot fractures of the humerus, as carried out on the service of Colonel Blake at the American Red Cross Military Hospital No. 2 in Paris, permits the maintenance of joint and muscle function. Points which I wish to emphasize particularly are: (1) the method permits of control by the surgeon of the position of the fragments; (2) union takes place rapidly; (3) disability is reduced to a minimum by mobilization of joints and exercise of muscles. Records are particularly difficult to keep under the condition of active war surgery. However, in the case of fifteen American patients the time of beginning union was noted averaging twenty-four days, and in twenty-six the time of consolidation averaged forty days. As our patients were, in general, evacuated early, we are unable to give much data as to the time of functional cure. We have treated a small number of simple fractures by this method and they have done excellently.

DR. RALPH T. KNIGHT, Minneapolis: The interesting part about the treatment of war fractures is that the principles have been and will be used extensively in fractures of civil practice. The point I wish to call especial attention to is the possibility and importance of mobilization of the knee joint during the treatment of all fractures of the femur and the bones of the lower leg. It has been shown conclusively and consistently by Colonel Blake that it is not necessary to immobilize the fragments completely in order to obtain the nicest union and return of function; and it is possible to obtain sufficient immobilization of fragments still leaving the knee free to be moved by the patient with proper apparatus.

Practice with Sickness Insurance in Germany.—The *Nederlandsch Tijdschrift* states that a regulation has been adopted by the sickness insurance companies at Hamburg—mainly through the efforts of Professor Pfeiffer—which he thinks should be imitated by the companies throughout the whole country. The insured pay as their premiums 4 per cent. of their wages. Of the amounts thus paid in, the companies pay out 23 per cent. for medical care, the house physicians receiving three fourths of the whole and specialists one fourth. For any extra attendance at night or in emergencies physicians not under contract with the company are to be called on. The payments are to be according to the work done and this is estimated by a commission composed of physicians and representatives of the business office of the companies. The insured have free choice among the physicians under contract with the company. The agreement is to be in force for two years. The details were given in the *Münchener medizinische Wochenschrift*, No. 29.

AMERICAN-MADE SYNTHETIC DRUGS—II

EXAMINATION OF PROCAIN (NOVOCAIN), BARBITAL (VERONAL), PHENETIDYL-ACETPHENETIDIN (HOLOCAIN), CINCHOPHEN OR PHENYLCINCHONINIC ACID (ATOPHAN), MANUFACTURED UNDER FEDERAL TRADE COMMISSION LICENSES *

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Before European hostilities, the United States was so dependent on Germany for synthetic drugs that the dependence was considered a necessity; this was strikingly manifested by the precipitous rise in prices immediately after the embargo was declared against Germany. Since then the shortage of German-made synthetics has caused two important results: 1. The physician can do without most of the German drugs, because the pre-war demand had been stimulated artificially. 2. Those few synthetics, which were in great need, are being rapidly replaced by the American-made drugs.[1] In connection with the second result, the Chemical Laboratory of the American Medical Association has endeavored to contribute its services.

In September, 1917, it was announced[2] that the A. M. A. Chemical Laboratory would make studies of American-made synthetics. Just prior to this announcement, the National Research Council established a committee on synthetic drugs[3] "to facilitate the manufacture of synthetic drugs in this country and thus to relieve shortage and reduce the exorbitant prices which have resulted from the war."[4] Also during this time Congress was considering the "trading with enemy" act, first known as the Adamson bill—the purpose of which was to confer authority on the President to license American firms to use U. S. patents owned by German subjects. The act became law, September 28; the Federal Trade Commission was designated by the President to carry out the provisions of the law as it referred to enemy-owned patents. As a result of a conference, Oct. 30, 1917,[5] with various agencies, the Federal Trade Commission decided to consider licenses for manufacturers of synthetic drugs, *after* recommendations had been made by the Committee on Synthetic Drugs of the National Research Council; this committee in turn invoked the aid of the A. M. A. Chemical Laboratory in testing the manufacturer's products. The essence of the laboratory's work up to July 1, 1919, is reported in this paper.

* From the Chemical Laboratory of the American Medical Association.

* The first article of this series dealt with the purity of acetylsalicylic acid. Leech, P. N.: Examination of American-Made Acetylsalicylic Acid, J. Indust. & Engin. Chem., April, 1918, p. 288. "What's in a Name?" ibid., p. 255. Acetylsalicylic Acid, or "What's in a Name?" Editorial, J. A. M. A. **70**: 1097 (April 13) 1918.

1. Stieglitz, Julius: Synthetic Drugs II, J. A. M. A. **70**: 688 (March 9) 1918. Leech, P. N.: The Vindication of the American Chemist; Synthetic Drugs, Chicago Chem. Bull., January, 1918, p. 230.

2. The Quality of American-Made Synthetics, J. A. M. A. **69**: 1018 (Sept. 22) 1917.

3. This committee is composed of Julius Stieglitz, chairman, professor of chemistry, University of Chicago; W. A. Puckner, secretary of the Council on Pharmacy and Chemistry, American Medical Association, and Moses Gomberg, professor of chemistry, University of Michigan.

4. Stieglitz, Julius: Shortage of Synthetic Remedies, J. A. M. A. **69**: 400 (Aug. 4) 1917.

5. Foreign Patents to Be Open to American Manufacturers, J. A. M. A. **69**: 1550 (Nov. 3) 1917.

THE NAMING OF LICENSED DRUGS

"Partly in order to help insure to licensees a market for their products after the war, in larger part inspired by the idea of encouraging the establishment of a permanent American industry in these important articles, the [Federal Trade] Commission wisely decided that American houses should be put on the same footing as competing foreign houses for after-the-war competition, by imposing on all licensees the obligation to use *new official names* for the articles, names which after the war will be open to all competitors, domestic and foreign."[6]

The new American names are:

Arsphenamin,[7] (contracted from the scientific name arsenphenolamin) for salvarsan, arsenobenzol, diarsanol, arsaminol.

Barbital (contracted from the scientific name diethyl-barbituric acid) for veronal.

Barbital-sodium (the sodium salt of barbital) for "veronal-sodium" and "medinal."

Cinchophen for atophan or phenylcinchoninic acid (the U. S. P. IX name).

Procain for novocain hydrochlorid (from "pro" and "(co)caine").

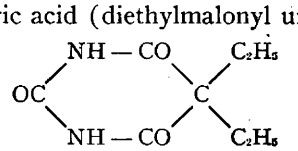
Procain nitrate for novocain nitrate.

EXAMINATION OF SYNTHETIC DRUGS

In testing chemically the products which had been submitted to the Federal Trade Commission, the aims were that the product should conform to a high degree of purity; at the same time the candidate for license should not be inflicted with undue hardships in making the product, such as an unnecessarily high degree of purity. It was insisted that the purity of the drugs should be equal to, if not greater than, that of the respective former German-made products, in order to uphold the name and reputation of the American manufacturers in the after-the-war competition. Consequently, in the chemical work the American product was always examined parallel with the German-made product, authentic samples of the latter of which the laboratory had in its possession. Whenever possible, the tests described in books of standards were carried out.

BARBITAL (VERONAL)

Barbital was introduced into medicine under the proprietary name "veronal," and was manufactured in Germany by Friedr. Bayer & Co., Leverkusen, and E. Merck & Co., Darmstadt, Germany. Barbital is described in New and Nonofficial Remedies 1919[8] as diethylbarbituric acid (diethylmalonyl urea).



It is official in the British Pharmacopeia under the name "barbitone," and in the German Pharmacopeia as "acidum diethylbarbituricum." Barbital "may be prepared by the interaction of esters of diethylmalonic acid with urea in the presence of metallic alcoholates. . . . It is also obtained by condensation of diethylcyanacetic ester with urea by means of sodium alcoholate." Barbital is used in medicine chiefly as a hypnotic.

The different brands of barbital which were submitted to the laboratory were subjected to the tests given in the books referred to above.[9] The products were:

1. Barbital (Abbott) Sample A, to Federal Trade Commission.
2. Barbital (Abbott) Sample B, to Federal Trade Commission.
3. Barbital (Abbott) Sample C, to Red Cross.
4. Barbital (Antoine Chiris), to Federal Trade Commission.
5. Barbital (V. Halter), to Federal Trade Commission.
6. Barbital (Rector Chemical Company) to Federal Trade Commission.
7. Diethylbarbituric acid (Merck), to Council.
8. "Veronal," manufactured by Farb. vorm Fried. Bayer & Co., Germany.

All responded satisfactorily to the tests. In Table 1 are given the respective melting points and percentages of ash found. (The melting point of a mixture of the sample with the original "veronal" was always taken.)

TABLE 1.—MELTING POINT

		Ash			Ash
1	188.5–189.0	0.01	5	188.0–188.5	0.01
2	188.5–189.0	0.01	6	188.0–188.5	0.01
3	188.0–188.5	0.01	7	188.0–188.5	0.01
4	188.0–188.5	0.04	8	188.0–188.5	0.02

Barbital does not seem to form an insoluble salt with chlorplatinic acid; nor an ether-insoluble hydrochlorid or oxalate; nor an insoluble barium salt. It does not respond to many urea tests, and is not affected by urease as would be expected in light of the extensive investigations made on this enzyme by Van Slyke and Cullen.

As barbital is also sold in the form of tablets or mixtures, a reliable method for its quantitative determination in the presence of other substances is needed. Some experiments in this direction were made, but the press of other work did not permit their continuation. When time permits, this work will be resumed.

At the time of writing this article, licenses for manufacture had been granted by the Federal Trade Commission to the Abbott Laboratories, to Antoine Chiris Company, and to the Rector Chemical Company.

BARBITAL SODIUM (MEDINAL OR VERONAL-SODIUM)

Barbital sodium, formerly sold under the proprietary names "veronal-sodium" and "medinal," is, as the former name suggests, the sodium salt of diethylbarbituric acid. Its therapeutic advantages are stated to be that more rapid results are obtained because of its increased solubility over barbital alone.[10] Barbital sodium should yield, according to theory, 11.19 per cent. of sodium and 89.31 per cent. of diethylbarbituric acid. A number of years ago, when "veronal-sodium" and "medinal" were being introduced, Puckner and

6. For an interesting discussion, see Stieglitz, Julius: Synthetic Drugs, J. A. M. A. **70**: 536 (Feb. 23); 688 (March 9); 923 (March 30) 1918. Bracken, L. L.: Federal Trade Commission Requests Use of Official Names, ibid. **70**: 558 (Feb. 23) 1918.

7. The testing and standardizing of arsphenamin is being done by the Hygienic Laboratory, U. S. Public Health Service. For chemical tests see reprint 472, Public Health Reports. For a review of the patent literature see article by H. F. Lewis, J. Indst. Engin. Chem., Feb. 1, 1919, p. 141.

8. New and Nonofficial Remedies, 1919, published by The Council on Pharmacy and Chemistry of the American Medical Association, p. 82.

9. The pharmaceutic monograph on barbital has been omitted. It was published in the 1918 edition of the Annual Reports of the Chemical Laboratory of the American Medical Association.

10. New and Nonofficial Remedies, 1918, p. 96.

Hilpert[11] found that these products yielded results corresponding closely to the theoretical amounts of sodium and diethylbarbituric acid. A recent examination of veronal-sodium, Merck, made for the Council on Pharmacy and Chemistry, showed it to be of the same composition as that previously reported.

Only one firm's product has been submitted to the laboratory through the Committee on Synthetic Drugs,

TABLE 2.—EXTRACTION OF A SAMPLE OF BARBITAL SODIUM

	Length of Time	Diethylbarbituric Acid per Cent.	
a.	Immediately	75.5	
a¹.	¾ hour	82.0	
b.	Immediately	82.0	
c.	1½ hours	80.5	
d.	4 hours	82.82	
e.	4 hours	83.56	
f.	4 hours	83.41	
g.	45½ hours	84.89	
h.	45½ hours	84.73	
Theory	.....	89.31	
Veronal-Sodium	(Puckner and Hilpert)	89.01	(average)
Medinal	(Puckner and Hilpert)	88.95	(average)

but because of the unsatisfactory results, it was not recommended for license, nor, as far as we are aware, has the firm investigated its anomalies.[12] The amount of moisture in this specimen was 0.04 per cent. It yielded 10.94 and 10.97 per cent. of sodium. Puckner and Hilpert found 11.02 per cent. of sodium in "medinal," and 11.01 per cent. of sodium in "veronal-sodium." The theoretical amount, according to the formula given for medinal by the proprietors $(C_2H_5)_2$ CCONNaCONHCO is 11.19 per cent. When an aqueous solution of barbital sodium was acidified, and the diethylbarbituric acid extracted with ether, it was found that the amount of freed acid extracted varied directly with the length of time after acidification.

It is possible that in preparing the sodium salt of diethylbarbituric acid, the ring opens up, forming a compound not so easily affected by dilute mineral acids.

PHENETIDYL-ACETPHENETIDIN HYDROCHLORID[13] (HOLOCAIN HYDROCHLORID)

Phenetidyl-acetphenetidin hydrochlorid was introduced in the United States under the name "holocain hydrochloride" by Farbwerke, vorm Meister Lucius and Bruening, Hoechst a. M. Germany; the product apparently had not been patented in this country, although it was protected in Germany under patents No. 78,868 and 80,568. New and Nonofficial Remedies, 1918, describes "holocain hydrochlorid" as ethenyl-paradiethoxy-diphenyl-amidin hydrochlorid $CH_3:(NC_6H_4OC_2H_5)(NHC_6H_4OC_2H_5)HCl$. It is used as a local anesthetic for the eye.

The standards, such as had been described, were meager and unsatisfactory. Hence when the first specimen of American-made phenetidyl-acetphenetidin was sent to the A. M. A. Chemical Laboratory through the agency of the Federal Trade Commission and the Committee on Synthetic Drugs, it was necessary for the laboratory to work out adequate standards.[14] As a result of the chemical work, a rather comprehensive monograph was drawn up, which was published in the 1918 Laboratory Reports. A summary of the products examined, with some of the chemical data, is given in Table 3. It will be seen that one specimen had a deficiency of about 2 per cent. of free base.

The melting point of the free base is given by a number of writers at 121 C. Although Kennert[15] stated it to be 117 C. and not 121 C., his findings seemingly went unheeded. It will be noted that our work shows the melting point to be in accord with that announced by Kennert.

The Federal Trade Commission has not issued any licenses for the manufacture of "holocain hydrochlorid." The John T. Milliken Company has withdrawn its application. The H. A. Metz Laboratories (Successor to Farbwerke Hoechst Company, New York) are making the product in this country.

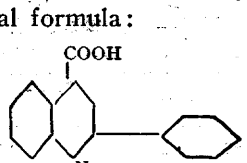
TABLE 3.—DATA ON PHENETIDYL-ACETPHENETIDIN HYDROCHLORID

Manufacturer	Appearance	Moisture	Melting Point	Phosphorus Compounds	Phenetidin*	Indol Reaction	Ash	Per Cent. Base by Weight	Per Cent. Base by Titration	Melting Point of Base	Per Cent. Platinum in Platinum Salt +
John T. Milliken Co.	White crystalline powder	5.13	191.5 to 192	Absent	Negative	Positive	0.00	89.16	89.16	116 to 117	19.02
Synthetic Products Co.	White crystalline powder	2.90	192 to 192.5	Absent	Negative	Positive	0.13	87.49	87.26	116 to 117	19.3
H. A. Metz Laboratories, Inc.	White crystalline powder	4.99	192 to 192.5	Absent	Negative	Positive	0.00	89.14	88.55	117	19.34
Farbwerke-Hoechst Co. ..... (German specimen)	Slightly pink crystal	5.09	190 to 191	Absent	Negative	Positive	0.16	89.65	89.64	116 to 117	19.00

* The phenetidin test is not very sensitive.

CINCHOPHEN (PHENYLCINCHONINIC ACID, U. S. P.; ATOPHAN)

Cinchophen (phenylcinchoninic acid) was introduced in the United States as a medicine under the proprietary name "atophan," by Shering and Glatz, New York City, who before the war were the American agents for the German manufacturers "Chemische Fabric auf Actien von E. Schering, Berlin." Phenylcinchoninic acid (2 phenyl-quinolin-4 carboxylic acid) was first described by Doebner and Gieseke[16] in 1887, who prepared it by warming together pyro-racemic acid, benzaldehyd and anilin in alcoholic solution; it has the structural formula:



The chief use of phenylcinchoninic acid is as an antiuric acid agent, especially indicated in gout.

11. Puckner, W. A., and Hilpert, W. S.: Veronal-Sodium and Medinal, J. A. M. A. **52**: 311 (Jan. 25) 1909; Rep. A. M. A. Chemical Lab., **2**: 13.

12. Since this was written, the Council on Pharmacy and Chemistry has also accepted "Barbital-Sodium Abbott."

13. No short, scientific name has been given for this substance although several are under consideration.

14. Certain chemical tests are described by E. H. Rankin, Indian J. M. Res. **4**: 237, 1916; also Chem. Abst. **10**: 524. Other references are Schmidt: Pharmaceutische Chemie **2**: 990. Beilstein II, (403). Arends, G.: Neue Arzneimittel und pharmazeutische Spezialitäten, Ed. 4, 1913, p. 271.

15. Kennert: Chem. Zentralbl. **2**: 556, 1897.

16. Doebner and Gieseke: Ann. d. Chem. (Liebigs) **240**: 291, 1887.

In 1913, the German house of Schering was made the assignee of patent 1,045,759 granted by the United States government[17] for the manufacture of phenylcinchoninic acid; at about the same time the product was admitted to the U. S. Pharmacopeia IX, under very loosely constructed standards.

Some time after the beginning of the European war the proprietary "atophan" became scarce in America. In 1917, however, Schering and Glatz, New York, placed American-made atophan on the market and submitted it to the Council on Pharmacy and Chemistry. Later, other firms began to manufacture the product and also submitted specimens. During the time it was investigating these products, the Federal Trade Commission decided that a license was needed to manufacture phenylcinchoninic acid under the patent just referred to, so that altogether the laboratory had a number of specimens to examine.

In making the examinations for the Council, the laboratory was practically confined, by virtue of the Food and Drugs Law, to limit its requirements of purity to those of the Pharmacopeia. Practically, the only tests were melting point, ash and solubility. According to the U. S. Pharmacopeia the melting point is "about 210." In New and Nonofficial Remedies, 1918, it was explained that atophan "complies with the standards for phenylcinchoninic acid, U. S. P., but melts between 208 and 212 C." The U. S. Pharmacopeia requires that no weighable ash remains on incinerating about 0.5 gm. of phenylcinchoninic acid. Considerable variations, especially in melting points, were found, as can be seen from Table 4.

By referring to this table on melting points and ash content it will be noted that the production of a better grade of products resulted after the respective firms had submitted samples to the A. M. A. Chemical Laboratory for criticism, and from a chemical standpoint, the last products examined were found to be as satisfactory as the German-made "atophan."

Solubility of Cinchophen (Phenylcinchoninic Acid.)—As methods of determining impurities, or estimating the degree of purity of phenylcinchoninic acid were not described in the U. S. Pharmacopeia, it was decided to try extraction methods.[18] This in turn led to the question of solubilities. The U. S. Pharmacopeia gives the solubility of phenylcinchoninic acid only in general terms; hence it was deemed advisable to determine its solubilities and describe them in more definite terms. The sample of phenylcinchoninic acid employed to determine the solubility was obtained by repeated recrystallization from alcohol of a commercial specimen. Solubilities were determined in water, 95.0 per cent.; alcohol, 48.5 per cent.; alcohol,[19] chloroform and ethhyl acetate.[20] Complete saturation of the solvent was attained according to the U. S. P. IX method (p. 599). The bath was maintained at a temperature of 25 C., with a range of ± 0.2 degrees. The solution was analyzed by the method of Seidell.[21] The data obtained for the solubility of phenylcinchoninic acid are given in Table 5.

The Abbott Laboratories, Chicago, have been licensed by the Federal Trade Commission to manufacture cinchophen. Other firms, however, have decided to manufacture it without the formality of obtaining a license, evidently considering the German-obtained patent not to be valid.[22]

TABLE 4.—MELTING POINTS AND ASH

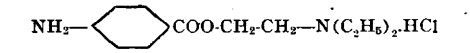
Product No.	Manufacturer	Melting Point, C.	Ash, %
1	Abbott Laboratories, Chicago	208.5-210.5	0 05
2	Abbott Laboratories, Chicago	212 -213	0.05
1	Calco Chem. Co., Bound Brook	209 -210.5	0.07
1	Morgenstern, New York	204.5-207.5	2.8
2	Morgenstern, New York	209.5-211.5	None
1	Schering and Glatz, New York	206 -208	None
2	Schering and Glatz, New York	209 -211	None
3	Schering and Glatz, New York	208.5-210	0.17
4a	Schering and Glatz, New York (1)	208.5-210	0.2
4b	Schering and Glatz, New York (2)	208.5-209.5	0.3
4c	Schering and Glatz, New York (3)	208.5-210	0.025
1	Wm. H. Sweet and Co., Columbus	204 -208	None
2	Wm. H. Sweet and Co., Columbus	209.5-211.5	0.04
1	German specimen from Schering and Glatz	210 -212	None

TABLE 5.—SOLUBILITY OF CINCHOPHEN

Solvent	Gm. per Hundred Gm. of Sat. Solution	Solubility, Parts by Weight
Distilled water	0.0160	1 in 6,216.0
95 per cent. ethyl alcohol	0.8343	1 in 119 0
Dilute ethyl alcohol	0 0875	1 in 1,142.6
Chloroform	0.1075	1 in 929.7
Ethyl acetate	1.4151	1 in 70.6

PROCAIN (NOVOCAIN)

Procain was introduced in medicine under the proprietary name "novocain," and before the war was obtainable in this country only through the Farbwerke Hoechst Company, the American representative of the German establishment, Farbwerke vorm Meister Lucius Bruening, Hoechhst a. M. Chemically it is the mono-hydrochlorid of para-amino-benzoyl-diethyl-amino-ethanol, having the structural formula:



It is prepared, according to U. S. patent No. 812,554 (issued to Alfred Einhorn, Munich, Germany) by treating para-nitro-benzoylchlorid with ethylene chlorhydrin and diethylamin with subsequent reduction of the nitro groups, the resulting product being purified by recrystallization.

Procain is employed largely in infiltration anesthesia. It is less toxic than cocain, but its anesthetic action is not sustained. This drawback is overcome by the simultaneous injection of epinephrin, and for this reason procain is often compounded with epinephrin in tablets, thus obviating the necessity of separate solutions.

When the first specimens of the American-made product were submitted through the channels of the Federal Trade Commission, it was necessary to compile a monograph.[23] This was prepared from descriptions in the available literature, mostly from tests described in New and Nonofficial Remedies, 1918, and the German Pharmacopeia V.

The submitted products were found satisfactory chemically. The toxicity determinations made by Dr. R. A. Hatcher, with the assistance of Dr. Carey

17. The validity of this patent is to be doubted.

18. Attempts were made to make salts of phenylcinchoninic acid with metals such as copper, mercury, barium and calcium, and also the chloroplatinic acid or periodid addition products. Reliable quantitative results could not be obtained.

19. This corresponds to "diluted alcohol, U. S. P."

20. The ethyl acetate was Merck's product (redistilled), stated to contain 81.6 per cent. of ethyl acetate, 10 per cent. alcohol and alcohol derivatives.

21. Seidell, A.: Bull. 67, Hyg. Lab., U. S. P. H. S., p. 11.

22. Very recently the Chemical Foundation, Inc., has undertaken to grant licenses for cinchophen. The Calco Chemical Company has obtained one.

23. The monograph appears in New and Nonofficial Remedies, 1919.

Eggleston[24] indicated that none of the specimens are to be considered dangerous when used in ordinary dosage for normal individuals. Therefore the Federal Trade Commission, on recommendation of the Committee on Synthetic Drugs of the National Research Council (aided by the A. M. A. Chemical Laboratory), issued licenses for the manufacture of procain to the Farbwerke-Hoechst Company (which license was later transferred to the H. A. Metz Laboratories), to the Abbott Laboratories, to the Calco Chemical Company and to the Rector Chemical Company.

Subsequently the products of the licensed firms were submitted to the Council on Pharmacy and Chemistry, which in turn invoked the aid of the A. M. A. Chemical Laboratory and the Cornell University Pharmacologic Laboratory. Later the Council asked the laboratory to examine the *market* supply. Altogether, therefore, a number of products were examined which were found to respond satisfactorily to the tests outlined (Table 6).

TABLE 6

Brand	Date Received	Color	Melting Point, C.*	Ash, %
Procain (Abbott), from Committee on Synthetic Drugs	12/21/17	White	154 -155	None
Procain (Abbott), submitted to Council P. and C.	1/29/18	White	153.5-154.5	None
Procain (Abbott), Gen. Pur. Off. U. S. Army	8/31/18	White	152.5-153.5	None
Procain (Abbott), Gen. Pur. Off. U. S. Army, No. 89999	9/30/18	Slight brownish tint	153 -154.5	None
Procain (Abbott), Gen. Pur. Off. U. S. Army, No. 89998	9/30/18	Slight brownish tint	153 -154.5	0.005
Procain (Abbott), Gen. Pur. Off. U. S. Army, No. 89997	10/ 8/18	Slight brownish tint	153 -154	None
Procain (Abbott), Gen. Pur. Off. U. S. Army, No. 89996	11/ 4/18	Slight brownish tint	153.5-154.5	None
Procain (Abbott), Gen. Pur. Off. U. S. Army, No. 810995	11/ 4/18	Slight brownish tint	153.5-154.5	None
Procain (Calco), from Committee on Synthetic Drugs	2/ 7/18	White	153.5-154.5	None
Procain (Farbwerke-Hoechst Co.), submitted to Council	10/24/18	White	153 -154	None
Procain (Farbwerke-Hoechst Co.), submitted to Council	12/10/17	White	153 -154.5	None
Procain (Farbwerke-Hoechst Co.), submitted to Council, market spec. "A 56"	8/ 9/18	White	153.5-154.5	None
Procain (Farbwerke-Hoechst Co.), submitted to Council, market spec. "A 57"	9/ 9/18	White	153.5-154.5	None
Procain (H. A. Metz Lab.), market spec. "A 63"	8/23/18	White	153 -154	None
Procain (H. A. Metz Lab.), market spec. "A 57"	9/23/18	White	153 -154	None
Procain (Rector), from Committee on Synthetic Drugs	12/18/17	White	153 -154.5	None
Procain (Rector), from Committee on Synthetic Drugs	5/ 2/18	White	152.5-153	None
Procain (Rector), market spec.	8/20/18	Slight brownish tint	153 -155	None
Procain (Rector), market spec.	8/23/18	Slight brownish tint	153 -155	None
Procain (Rector), market spec.	8/23/18	Slight brownish tint	153 -154.5	None

* U. S. Patent 812,554 — the novocain patent — declares that the salt melts at 156 C. Evidently based on this, both the German Pharmacopeia and past editions of New and Nonofficial Remedies give this melting point. Two specimens of German-made novocain obtained from our files, stated to be manufactured by Farbwerke-Hoechst vorm. Meister, Lucius and Bruening, Hoechst a. M., were found to melt, respectively, between 154 and 155 C. and between 153.5 and 154.5 C. when the melting point was determined according to the direction of the U. S. Pharmacopeia, ninth revision. The various specimens examined at that time melted between 153 and 155 C., and it was decided to permit this range.

An examination of some American-made procain-suprarenin tablets was also made. The procain was determined by liberation of the alkaloid with ammonia water, extraction with chloroform evaporation of the chloroform, dissolving the alkaloid in one hundredth normal sulphuric acid solution and titrating excess acid with one hundredth normal sodium hydroxid solution. The epinephrin was determined according to the method employed by Seidell,[25] with slight modifications. The tablets contained the claimed amounts of ingredients.

24. The report of these and subsequent toxicity experiments on procain appeared in the report of the Council on Pharmacy and Chemistry, J. A. M. A. **72**: 136 (Jan. 11) 1919.

25. Seidell: J. Biol. Chem. **14**: 19, 1913.

THE SYNTHETIC DRUG SITUATION

Before the war, the American physician was literally bombarded with new and wonderful (?) coal-tar synthetics, most of which were originated in Germany. In fact, it seemed that if a by-product in the manufacture of dyes could not be used for a dye per se, then a place might be found for it in the ever increasing lists of medicaments. By clever advertising and propaganda among physicians, an artificial stimulation for coal-tar drugs was created which evidently yielded lucrative financial returns. As a result of the war, it is interesting to observe that of all the synthetic drugs imported into this country from Germany and on which the American patents were controlled by the Germans (up to the time of our entrance into the war), the demand was really sufficient enough to warrant the commercial manufacture of only four of them by American firms. Of course, a larger number of *nonpatented drugs,* also imported from Germany, are now being made in sufficient quantities in this country; many of the drugs in this class were never patented or are the ones which have survived after the patent had expired, such as acetanilid, acetphenetidin, and acetylsalicylic acid.

In view of the agitation to found an institute for cooperative research as an aid to the American drug industry under the auspices of the American Chemical Society, it will be well for the medical profession to be on its guard against too enthusiastic propaganda on the part of those engaged in the laudable enterprise of promoting American chemical industry. Unless it is, it may be inflicted in the future, as in the past, with a large number of drugs that are either useless, harmful or unessential modifications of well-known pharmaceuticals. It will be well also for the chemists—those engaged in this enterprise—to be sure that the product is of therapeutic value before asking its use as a medicine. The American medical profession has learned that relatively few of the many German synthetics were really valuable or decided improvements over established drugs. If American chemists desire to retain their prestige with the medical profession, they should earnestly endeavor to see that the advantages derived from the war and from such an institute as proposed are not abused in the worthy desire to popularize chemistry both educationally and commercially. They should realize that physicians are in no receptive mood for a flood of synthetics, even though "America-made."

On the other hand, the constructive possibilities of chemistry in the service of medicine should serve as a stimulus for American research. Notwithstanding all the pharmaceutical shrubbery which Germany sent to us, still it did contain some synthetics that were worth while. As therapeutics has been benefited by these organic chemicals, it is logical to reason by analogy that there remain other synthetics to be discovered which will occupy places of equal distinction in the modern materia medica. For example, vaccines are of undoubted merit in the field of immunology, but their action is, in the end, chemical; as soon as chemical technic is refined by medicochemical research,

it is quite possible that a definite chemical agent (synthetic) will supersede the indefinite bacterial vaccines. Obviously the American chemist has the opportunity of showing his resourcefulness in aiding the public health of America and the world. In this connection, a cooperative institute devoted to purely scientific drug research, and governed in such a manner as to inspire confidence in its humanitarism and unbiased judgment, should serve a most commendable purpose. The hopes of American men of science are for a monumental research institution—cooperative with all the allied professions—and, as the *Chicago Chemical Bulletin* stated, "Stripped of all professional or commercial pettishness and not dominated by any one group of scientists." [26]

CONCLUSIONS

As for the results of the work so far, they can be summed up in two sentences.

1. American chemists are producing synthetic drugs formerly controlled by Germany, and thus have declared their independence of German chemicals.

2. Judging from the evidence at hand, we can feel assured that the quality of American synthetics will be second to none.

ALLERGY IN DRUG IDIOSYNCRASY *

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It is my purpose in this paper to call attention to some of the peculiar drug reactions occurring in man and, at the same time, to offer an explanation of them.

In a perusal of the recent textbooks on pharmacology, it was found that the word "idiosyncrasy" appears in all; but the definitions are almost as numerous as the books themselves, and in none is there any explanation for the peculiar effects of many drugs on certain people.

Given a normal person, any drug exhibited in therapeutic doses manifests a certain normal action, a side action and, in larger amounts, a toxic action, both the normal and the toxic action being more or less definitely fixed, symptomatically, for all individuals of the same species.

On the other hand, there are individuals within any species that manifest exaggerated normal and side actions from many such reasons as alterations in rate of absorption, excretion or destruction within the organism, or instability of the mechanism through which some drugs act. For example, the stimulating action of morphin, occasionally seen, is due to an exaggeration of the normal stimulating effect, which is usually marked by depression. The lessened normal action (or tolerance) is usually dependent on long-continued use of the drug. This may not be the case. The explanation of tolerance undoubtedly varies with different drugs, and a discussion of it will not be attempted here. These exaggerated normal and side actions and lessened action (or tolerance) should be included under the general heading "idiosyncrasy," and separated entirely from the abnormal actions now to be considered, and for which explanation is offered.

26. Proposed Institute for Drug Research, editorial Chicago Chem. Bull., April, 1919, p. 67.

* Read before the Section on Pharmacology and Therapeutics at the Seventieth Annual Session of the American Medical Association, Atlantic City, N. J., June, 1919.

ALLERGIC ACTION OF DRUGS

In a former paper, with Vander Veer, I was able to estimate that approximately 10 per cent. of all human beings manifest some form of hypersensitiveness. By this is meant that such persons react in a peculiar and specific way to substances that are innocuous in anything like such doses to the average individual of the race.

Coca's classification of hypersensitiveness into "anaphylaxis" and "allergy" will serve to clarify this whole field, which has been confused by the attempt to explain natural and artificial hypersensitiveness on the same basis.

Anaphylaxis is an antigen antibody reaction, artificially induced by immunologic processes. Allergy is used to express the natural hypersensitiveness of the individual not produced by immunologic processes, as the exciting agents or allergens are in many cases not capable of producing antibodies. For example, the natural hypersensitiveness of the human being to pollens, the clinical reaction to which is known as hayfever, is admittedly allergic. In experiments carried on with Coca and Flood, we could not demonstrate antibody in the individual during an attack or after injection of pollen extract by passive transfer, nor could antibody be produced in the guinea-pig itself. In other words, the extract is nonantigenic. Other substances, such as glue and certain drugs like acetylsalicylic acid, to which individuals react peculiarly, are also nonantigenic. To be sure, many of the substances to which the human being does show clinical hypersensitiveness are capable of forming antibodies. Hence the confusion between the natural hypersensitiveness or allergy and the artificial or anaphylaxis.

PROOFS OF ALLEGRIC NATURE OF DRUG REACTIONS

Inheritance.—One of the proofs of the allergic nature of abnormal drug reactions is the fact that it is established by inheritance. Natural human hypersensitiveness has been shown by Vander Veer, in collaboration with me, to be an inherited trait, and one inherited, according to the mendelian law, as a dominant characteristic. Of the fifteen cases of drug reactions which form the basis of this paper, a positive antecedent history of hypersensitiveness existed in twelve, and in the other three there were evidences of other forms of allergy, such as asthma, urticaria and hayfever, in the individual himself.

Symptomatology.—The symptoms of drug reaction or allergy are absolutely separate and apart from any normal or toxic action, and are the same as those occurring with foods, pollens and animal emanations. The symptoms are coryza, cough, bronchial spasm with urticaria in some cases, or angioneuritic edema, and frequently gastro-intestinal manifestations, with pain, vomiting and diarrhea. Occasionally, with the antipyretics, hyperpyrexia occurs or cardiac collapse and, in practically all, a marked eosinophilia, from 10 to 15 per cent. I shall speak particularly of the acetylsalicylic acid reactions, as these have been most frequently encountered thus far. Symptoms begin, as a rule, from fifteen to twenty minutes after the ingestion of 10 grains of the commercial drug. In nine of the fifteen cases, violent bronchial asthma was induced and one case was almost fatal from asphyxia. The attack lasts from eight to thirty-six hours, and in one instance was prolonged for three weeks. In only three of the cases was urticaria present. Con-