lessness, and threatened cardiac failure. After partial recovery he again relapsed with great dyspnoea, and gradually became delirious, and during a portion of the time apathetic and lethargic. The Cheyne-Stokes respiration then appeared accompanied by a pulse of 112, the temperature being normal. A cycle of respirations occupied 55 seconds there being 27 respirations. The period occupied by the rising respirations was 25 to 30 seconds by the declining respirations 15 seconds. The number in each of these phases was about the same—14, making the succession during the declining period nearly twice as rapid as during the rising period. The pause lasted from 10 to 15 seconds. In this phase there was no perceptible alteration in the rate or character of the cardiac action, and no alteration in the pupils. Coughing during the cycle, did not influence its duration, nor any of its intrinsic characters. When aroused from his somnolence, which could be easily effected, there was no change in the cycle, except that the phase of decline was lengthened by a few additional respirations, during which there were no chest movements, but air could be heard to enter the extreme lower parts of the lung in jerky momentary pumps. The pause was of course correspondingly shortened. Otherwise the pause was a period of absolute stillness, so far as respiratory sounds were concerned, but as already remarked the cardiac sounds were in no respect altered. The patient died ten days later. The breathing during the whole period was closely allied to the Cheyne-Stokes type, but at no time was it found as typical subsequent to the above observation, as at that time.

CAFFEINE AND THE QUESTION OF ITS ISOMERISM.

Read in the Section of Materia Medica and Pharmacy, at the Forty-third Annual Meeting of the American Medical Association, held at Detroit, Mich., June, 1892.

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In chemistry, caffeine is a body of distinctive molecular character, the subject of active research within the past ten years. In physiology it is bound to be of increasing interest that caffeine, the chosen adjunct of food, holds a remarkable relation to uric acid, an excretory carrier of nitrogen. In dietetics it is of wide import that the beverage plants of the world owe their effects in great measure to caffeines. In pharmacognosy it is worthy of attention that uncertain combinations of caffeines are in medicinal use. In these several studies it is desirable to settle the chemical question, whether caffeine be capable of isomerism or not.

This is not a question that has been raised by chemists; nor is there at present any chemical evidence, that I am aware of, for so much as a suggestion of the isomerism of caffeine. Pharmacologists have virtually raised this question, though they have not defined it as one of isomerism. And there is a great extent of medical opinion and lay opinion that, whatever chemists may say, the alkaloid of coffee does not produce the same effect upon the nervous system that is produced by the alkaloid of tea. If this somewhat widespread opinion, though not well defined, be well grounded, the chemist ought to be able to account for it. On one point the chemist is clear, if there be a caffeine in tea in itself not of the

same physiological effect as the caffeine in coffee, then these bodies are not chemically identical. Then, both being caffeines, that is, trimethyl xanthines, it follows that the one must be isomeric with the other. Before this point is reached, however, there is a great deal for chemical analysis to do, and something for pharmacology to do.

There are five beverage plants, growing in different quarters of the earth, all largely adopted into use by uninstructed man, as a restorative from fatigue and a stimulant with food, and each of these plants contains an abundance of the body named caffeine. The body has been found as a slight or inconstant constituent of a few other plants, all of them adjuncts of food.¹ It was found in coffee in 1821; in tea in 1827; in guarana in 1840; in the maté of Paraguay in 1843; and in the kola of South Africa in 1865. In 1838 Jobst and Müllder declared theine to be identical with caffeine. As soon as an alkaloid was found in guarana, in maté and in kola, in each instance the body was reported to be caffeine, and there have been no chemical reports to the contrary. The names, theine and guaranine, have fallen into disuse, and no other name than caffeine has been given to the body derived from maté or kola.

This one body, from five vegetable sources, is one of strongly marked chemical character. It is clearly determinate in character, more so than the most of the alkaloids are, and a body built altogether unlike them. Indeed, it is well within the control of synthetic chemistry. It is liable to be put upon the market as an artificial product. As an artificial body, if properly purified, it should be not an imitation but a veritable reproduction of the natural article. It is becoming probable, however, that this body, the chief alkaloid of five plants, is not the only one existing in them. Traces, at least, of two or more homologues of caffeine have been found in certain teas. There is need of analysis for these homologues, as lesser constituents. The presence of alkaloids accompanying caffeine, as codeine accompanies morphine, is to be put out of the way. Then there will be a clear field for the question of isomerism between the chief alkaloid of one beverage plant and the chief alkaloid of another, such as the difference between atropine and hyoscyamine.

As to the isomerism of caffeines, its probability can be denied only by full study of all research hitherto done on the molecular constitution of this group of bodies. The possibilities of isomerism are coming in greater number into view, as science advances. When the chemist believed himself able to find the arrangement of atoms within the molecule as truly as the order of the fingers upon his hand he seemed to have reached a limit of isomerism. Then it appeared that nature had not stopped at this limit. Whereupon the chemist bethought himself that the order of five fingers as they face on the one hand is

¹ Caffeine occurs in small amount in cacao beans, according to Schmidt (1883), theobromine being, as is well known, the principal alkaloid. The U. S. Department of Agriculture, in Division of Botany, has lately published (Bulletin No. 14, 1891) descriptions of the *Ilex cassine*, growing from Virginia to Texas, and used by the aborigines as a beverage on festal occasions. Prof. E. P. Venable found it to contain caffeine 0.27 per cent.; tannins, 7.39 per cent.; total nitrogen, 0.73 per cent. This plant is another species of the maté, *Ilex paraguensis* (Am. Jour. Pharm., 57, 389). The South African "bush tea," used for a beverage, consists of species of *Cyclopodia*. Three of these species were examined by Greenish in 1881 (Phar. Jour. Trans., [3] 10, 217-221) for caffeine, and none was found. Another species was examined for caffeine by Church in 1870 (Chem. News, 22, 2), and none was found. A few months ago a small sample of a leaf stated to be a species of *Cyclopodia*, and a "bush tea" from South Africa, strayed to my laboratory. Analyzed by Mr. Gombert it was found to contain caffeine. A further sample has been sent for.

not the order of the five as they face on the other hand, and lo! these were just some of the additional possibilities that nature had filled out. Moreover, the most recent biological chemistry is full of suggestions of isomerism as yet not traced out at all. But caffeine is a body so well controlled in its structure, that the limits of variable order in its molecular parts are not out of the reach of chemical studies.

A difference of physiological effect, once well established for a pure body, a body that is one in all its laboratory reactions, chemical and physical, is a difference to be accepted as proof of isomerism. This might be termed physiological isomerism, but it must be a chemical fact none the less. It must be due to the manner of chemical union. Matter is made up of molecules, and a molecule is always a product of chemical action, whether such action can be traced out or not. If a function of life can serve as a qualitative reaction for any chemical body, a reaction to which chemical union is more sensitive than it is to light or heat or laboratory reagents, it belongs to the chemist to measure the results as well as he can.

But it were well first to avail ourselves of existing evidence as to the relative effects of tea as a whole and coffee as a whole. Such evidence, whether taken from certain functions of the body or from the sum of all the functions, is conclusive to many persons. If not conclusive to the pharmacologist, who would measure effects of each constituent upon each function taken separately, still the evidence drawn from the action of the whole of tea or coffee is not without bearing upon our estimate of the value of caffeine. We have a right to ask what there is in tea, and in coffee, beside alkaloids, to which the observer can ascribe the effects of these articles as beverages. Some answer to this question ought to be afforded by chemical analysis, as I have urged from time to time since 1876. The question, like others of the same sort, is not so simple as it is apt to be supposed; and much careful analytical work is wanted upon it.

What is wanted is a full analysis of the entire content of the ordinary beverage infusion of tea and of coffee. If we go to the common analyses of the books, we fail to find out what and how much, out of tea or coffee, goes into solution and into the stomach and into the blood, for dynamic registration by the brain, the heart, the vascular system, etc. Such account of the actual content of the beverage infusions as I have been able to collect, I have grouped together in the accompanying table. Some of the earlier data were obtained in my laboratory, a former student of mine has independently furnished the fullest data, other quite comprehensive results are from sources remote from my personal knowledge, and to fill up a few gaps I have resorted to factors of comparison. The citations specify the several sources of the figures presented.

The following conclusions are evident:

1. The alkaloid counted as caffeine is mostly dissolved by ordinary hot infusions and by decoctions of tea and coffee, even if brief in maceration. Of the two beverages, coffee is apt to be a little the richer in alkaloid, but this difference is not distinctive. Three grains per pint is a common proportion.

2. Tea beverage is very rich in tannins, which are nearly absent from coffee beverage. Tannins are very slowly drawn into infusion, so that the time and temperature of infusion govern its astringency. A cup

of tea may have from two to six times as much of tannin as it has of alkaloid.

	Alkaloid.		Tannins.		Soluble Ash.		Potassa.		Other Soluble Substances.	
	Tea.	Coffee.	Tea.	Coffee.	Tea.	Coffee.	Tea.	Coffee.	Tea.	Coffee.
I. Total Content, in percentages:										
1. GEISLER, 1884: in averages of 30 grades (Note A)	2.6	..	15.2	..	3.5	..	..	..	21.7	..
2. DRAGENDORFF, Univ. Dorpat, 1874: 23 grades (Note B). . .	2.0	1.1	12.4	..	..	..	2.3	2.4	17.0	..
3. The writer and Mr. Clark, 1876: 15 grades (Note C)	..	..	12.0	..	..	..	..	..	..	..
II. Dissolved in Infusions, as per cent. of dry article:										
1. GEISLER, 1884: by infusion at 100°C. (Note D)	2.4	..	9.2	..	3.8	..	1.4	..	12.5	..
2. FELLOWS, 1880: by 10 minutes (Note E)	..	..	0.6	0.0	..	..	..	..	..	..
3. FELLOWS, 1880: by 20 minutes	..	..	1.5	0.1	..	..	..	..	..	..
4. FELLOWS, 1880: by 30 minutes	..	..	2.5	0.8	..	..	..	..	..	..
5. KENRICK, 1891: (Note F) 13 black teas	2.8	..	5.4	..	3.5	..	..	..	12.0	..
6. KENRICK, 1891: 18 Japan teas	2.5	..	9.4	..	3.6	..	..	..	14.6	..
III. Content of Infusions, in Grains per Pint:										
1. Calculated from Geisler (II. 1) (Note G)	2.5	..	4-13	..	3.8	..	1.4	..	12.5	..
2. Calculated from Kenrick (II. 5, 6) (Note G)	2.65	..	5-9	..	3.5	..	..	..	13.3	..
3. By Fellows (Note E) direct	..	..	3.3	0.9	..	..	..	..	..	..
4. Calculated from I. 2 and other sources (Note H)	..	3.5	..	..	9.5	..	6.3	..	56.0	..
5. Frequent proportions, summarized	2.5	3.5	7.0	0.7	3.5	9.5	1.4	6.3	13.0	56.0

Note A.—J. F. Geisler, chemist to the New York Mercantile Exchange, American Grocer, October 23, 1884; Prescott's Organic Analysis, 1887. The thirty grades embrace six "Indian teas," with an average of 15.8 per cent. tannins; thirteen Oolong, 16.4 per cent. tannins; and eleven Congon, 12.6 per cent. tannins. The teas were obtained of importers, as selected representative grades. Percentages are given on the tea dried at 100° C.

Note B.—"Werthbestimmung," p. 60. Recalculated to give percentages on the tea dried at 100° C. From twenty-three grades and varieties of tea; the tannins from only four varieties. From twenty-five varieties of coffee; the potassa from only seven of these. The analyses of teas are credited to Prof. Dragendorff and Mr. Weyrich.

Note C.—Univ. Mich., 1876; Am. Chemist, 7, 44. In use of a method of volumetric analysis with cinchonine, titrating the excess with iodo-mercurate, as adapted for analysis of tea in the report upon.

Note D.—The contribution cited in Note A. Average of results from sixteen varieties. These results are separately given in the report, as are those of I. 1. The infusions were made by 100 parts of distilled water, poured on boiling, and standing ten minutes. The percentages are given on the air-dry tea. (The thirty teas of I. 1 average 6.6 per cent. of moisture.)

Note E.—Chem. Lab. Univ. Mich., 1880; Physician and Surgeon, 2, 342. From eleven varieties of tea and six of coffee. Infusions in 50 parts of distilled water at about 90° C.; the estimations by the same method designated in Note C. In some way, perhaps in not accounting for retained liquid (out of the 50 parts of solvent) the results are probably too low, but they are of value in comparison with each other, showing the effect of prolonging the period of infusion, and the difference between coffee and tea in parallel conditions.

Note F.—Laboratory of Internal Revenue Department, Ottawa, Canada, 1891, Bulletins No. 24 (tea) and 29 (coffee). The infusions were made under the conditions adopted by Geisler, Note D, namely: ten minutes action of 100 parts of water, taken boiling. The percentages are given upon air-dry tea; the moisture being 6.5 per cent. for the black, and 4.0 per cent. for the Japan varieties.

Note G.—In these calculations a certain "strength" of each beverage must be assumed. The standard of common strength which the writer arrived at, from various data, in 1880, is here adopted. The data are given by the present writer, in Physician and Surgeon, 2, 342, and the standards are as follows: For tea, 73 parts of water, 1 pint from 100 grs.; for coffee, 23 parts of water, 1 pint from 317 grs. This gives 224 five-ounce cups from one pound of tea, and forty-five eight-ounce cups from one pound of coffee. To this strength the results of Geisler and of Kenrick are reduced. Of course Geisler's infusions, more dilute, would dissolve somewhat more than an infusion of this domestic average. The greater concentration of coffee beverage should bring down these figures, and infusion for over ten minutes would raise them.

Note H.—Calculated to the assumed average strength of beverage stated in Note G.

3. Coffee beverage carries quite constant potassium salts amounting to four times the quantity in tea beverage. A cup of coffee contains potassium salts about twice the quantity of its alkaloid. Some of the potassium is in phosphate.

4. The nutrient and other remaining solids in coffee infusions amount to four times the quantity of the corresponding solids in the infusions of tea. A pint of coffee contains an average of 50 to 60 grains of solids beside alkaloid, ash, and tannin. The

pharmacology of some of these bodies ought to be studied.

5. There follows to be determined the homologues of caffeine (theophylline, theobromine, and xanthine), their presence, quantity, and effect. Then remains, if found at all, any evidence as to isomeric caffees. For these inquiries it is needful to discuss the known constitution of caffeine itself.

Caffeine stands apart from vegetable alkaloids as a class. It is not a derivative of pyridine. It does not give evidence of a closed chain of carbon atoms in the same state of saturation found in pyridine derivatives. It does not contain any part of the fruitful benzene molecule. When it is broken up in any way, aromatic compounds are not formed out of it. In all these related particulars caffeine is unlike the numerous alkaloids of cinchona, or opium, or hydrastis, or coca, or pepper, or conium, or henbane, or tobacco. It stands apart, also, in the great content of nitrogen it carries, namely 28.8 per cent. Proteids have 16 per cent.; quinine has 8.6 per cent.; strychnine, 9.0 per cent. of the same element.

Caffeine is a thrice methylated xanthine as clearly as chloroform is a thrice chlorinated methane. As trimethyl-xanthine its chemical possibilities in general are those of xanthine, itself. As a tri-derivative of xanthine, it is methyl-saturated, and does not have the obvious theoretical possibilities of isomerism that di-derivatives and mono-derivatives possess. These have been readily realized in synthesis.

Of the four atoms of hydrogen in xanthine, $C_5H_4N_4O_2$, only three are linked to nitrogen, and only these three are replaceable by methyl. The fourth atom of nitrogen in xanthine is linked to carbon only, in the manner of a tertiary base. Probably this is the point of unyielding difference between uric acid structure and xanthine structure, preventing the conversion of the one ($C_5H_4N_4O_3$) into the other ($C_5H_4N_4O_2$). The resistance to such conversion was shown by E. Fischer in 1884.²

Four methyl groups can be introduced into uric acid; only three into xanthine.³ In every case the introduction is a substitution for hydrogen, and a linking to nitrogen. In every case, when the methylated compound is broken up, the methyl groups remain linked to the nitrogen, either in methylated urea or in methylated ammonia.

Xanthine and uric acid agree in this, that they contain two molecules of urea united to an unsaturated chain of three carbon atoms. The carbon chain holds the fourth hydrogen atom of xanthine, and the third oxygen atom of uric acid. Each urea group contains two ammonia groups. When an ammonia group is broken off, it is capable of neutralizing one valence of an acid, forming a strong salt. Were the four nitrogen groups of xanthine, or caffeine, sufficiently positive in their polarity, then they would hold four valencies of an acid. Then caffeine would be a quadrivalent base. But it lacks the positive polarity to be a decided base at all. Urea is almost as near an acid as a base, such is the negative power of its carbonyl group. The three-carbon chain of

xanthine, and of uric acid, introduces such a negative preponderance that they are acidulous rather than basal. The mono-methyl, and di-methyl derivatives of xanthine are less basal than caffeine. When three methyl groups are introduced their polarity as positive groups appears to create a slight balance of electro-positive quality to the molecule. As a result caffeine is capable of serving as a base, but not to the extent of more than one valence. So urea can at most hardly neutralize more than one acid valence. When an acid valence is united either to caffeine or to urea, its negative polarity so far preponderates in the entire molecule that the remaining nitrogen groups are powerless to unite with acids. The case is like that of acetamide. That caffeine unites with strong acids, slowly but in final proportions quite true for monovalent base, was demonstrated last year in the admirable paper of Mr. H. W. Snow.⁴ The acetate, however, was found by Biedermann⁵ to be divalent.

In the halogen derivatives, however, such as bromo-caffeine, chloro-caffeine, etc., the halogens are received as they are by a hydrocarbon. One halogen atom can be united by substitution for the fourth atom of hydrogen. Also two halogen atoms can be united by a saturation of the unsaturated couple in the carbon chain. Union of hydroxyl, the amido group, an ethoxy group, etc., in this way, are unions independent of the nitrogen groups, or of any basal properties whatever.

The introduction of a methyl group in connection with the carbon chain of caffeine has not been accomplished. To do this would be to make an interesting homologue of caffeine. To make the same introduction in theobromine would give us a clearly distinct chemical isomer of caffeine. An attempt to make this isomer by different well-known methods for such substitution, has been faithfully made in my laboratory, this season, by Mr. M. Gomberg, as a part of investigations, not yet published, upon the question of isomerism of caffeine.* Various conditions of reaction were employed. This much is evident, the carbon chain does not readily attach either methyl or ethyl. On the other hand, the impossibility of such methyl introduction has not been established. Mr. Gomberg has introduced other groups, not heretofore brought into union with the carbon chain, and will proceed upon the line of work in which he is engaged.

As to the possibility of a plural of trimethyl-xanthine, some things are obvious. Assuredly its isomerism, in the more common ways, is not pointed out to us by the chemistry of the xanthine group. The fourth atom of nitrogen in this body does not receive methyl, except by bivalent addition, a sort of over-saturation. No asymmetric carbon atom appears in the body. And whether from coffee or from tea, the alkaloid is inactive to polarized light.⁶ But it would be rash to assert the impossibility of isomerism of any sort. For example it is open to ask whether the atom of hydrogen not methyl cannot link to the intermediate carbon of the mesoxalic chain, doing

² Ber. d. chem. Ges. 17, 328. The report of Strecker, from the work of Rheineck, in 1864. (Ann. Chem. Phar. 131, 121) that uric acid is deoxidized to xanthine by sodium amalgam, was a singular instance of error lingering long in literature. It was disproved by E. Fischer in 1884 (Ber. d. chem. Ges. 17, 1776.)

³ This is true of the substitution compounds. The addition of methyl iodide to caffeine, obtained by Tilden (1865: Jour. prakt. Chem., 94, 374) and examined by Schmitt (1883: Ann. Chem. Phar. 217, 270) (1885: Ibid 141) furnishes an apparent approach to a xanthine derivative. This addition compound is, however, a sort of supersaturated body.

⁴ 1891: Proc. Am. Phar. Assoc., 39; Further, Lloyd, 1881: New Rem., 10, 38.

⁵ 1888: Archiv. Phar. [3] 21, 175; Jour. Chem., Soc., 46, 185.

* Read in Am. Assoc. Advancement of Science in August, 1892, "Trimethyl Xanthine and some of its Derivatives," by Moses Gomberg, M.S.: Am. Chem. Jour., 14, 611. (Reprints.) Mr. Gomberg continues this investigation, working in the laboratory of the writer.

⁶ This was determined in the writer's laboratory in 1887. Other physical differences were sought for and not found. (Unpublished records.)

this in exchange with the valence of nitrogen of the third position.

With some outline of caffeine structure before us, it will be easier to see its relation to certain of its homologues, some of which, as already intimated, have been found in tea. There is a lack of thorough-going analysis to this end. The reports, so far as I have found them, are as follows:

Theobromine, or dimethyl xanthine, the alkaloid of chocolate, was found in Himalaya tea by Zöller in 1871.⁷ Its solubilities in water and in ether are not so large as those of caffeine, but in smaller quantities it will not be excluded in customary preparations of caffeine. Neither will it be detected by ordinary tests. Xanthine itself, and hypoxanthine, were found in several samples of tea by Baginski, in 1885.⁸ It has not been much searched for. Its very slight solubility in water would, apparently, reduce its proportion in infusions to very narrow limits, even if present in tea leaf, but as it is exceedingly soluble in alkalies it may be affected in solubility by the presence of the alkali salts of tea.

A dimethyl xanthine, isomeric with theobromine, was announced as a discovery in Himalaya tea, by Kossel, in 1888,⁹ who named this new vegetable body, theophylline. Like theobromine it unites with alkalies as well as with acids. Its methyl derivative was found identical with caffeine. Broken up, its alloxan is a dimethyl compound, its urea is not methylized; so its methyl groups are in positions 1 and 2. This explains its difference from theobromine, in which a methyl group occupies position 3.¹⁰ Theophylline was found much more soluble in water than theobromine. Therefore, if in tea leaf, it will be in the infusions. As described, its presence in caffeine would probably be overlooked.

The existence and occurrence of theophylline has not been verified or followed up. Kossel had been known in chemical literature for his frequent contributions analytic and synthetic upon xanthine and allied bodies, for eight or nine years prior to the announcement in question. The year after, Messrs. Paul and Cownley¹¹ examined the extract of 200 grams of tea of Himalaya, and found an alkaloid not fully determined. They have since¹² reported a series of estimations of "theine" in tea, without, so far as I have seen, any account of residual alkaloids. Coffee does not appear to have been carefully examined for alkaloids homologous to caffeine, that is, trimethyl xanthine, and the same is true of guarana, maté and kola.

It has been usually assumed that pure "theine" is the alkaloid of tea completely freed from matters not alkaloids. "Caffeine" and guaranin" have been defined in the same way. There is now a degree of uncertainty as to the chemical purity of the several articles under these names, an uncertainty which it belongs to the chemist to clear up. Let us see what stipulations of purity have been made for these articles when they have been taken for physiological trial.

Shortly after Emil Fischer's researches on the xanthine group, showing how little relation xanthine

has to uric acid, and how clear is the homology of caffeine and theobromine to xanthine, Wilhelm Filehne made a pharmacological investigation of these four bodies. This was in 1886.¹³ Happily, Fischer supplied Filehne with the articles, xanthine, caffeine, theobromine. No mention is published of any precautions against xanthine as an impurity in caffeine, nor any statement as to the source of the caffeine, whether from tea or coffee or synthetic work. The object was a physiological comparison of xanthine, dimethyl-xanthine, and trimethyl-xanthine. Filehne found the three bodies to differ in degree rather than in kind of action, and that the effect of xanthine was the most intense, that of trimethyl-xanthine the least intense of the three. He found, as others have, that uric acid does not possess the power of xanthine at all. Ethoxy-caffeine was found by Filehne, as also by Baumetz,¹⁴ to have a distinctly different, somewhat stronger action.

Dr. Thomas J. Mays, in 1886,¹⁵ made a full and careful comparative trial of caffeine and theine. He had the alkaloids prepared for him by designated makers, to ensure that the one came wholly from coffee and the other from tea, but no mention is made of other precautions as to purity. In his conclusions the two are not identical.

In 1887 Dr. T. Lauder Brunton put caffeine and theine upon pharmacological trial.¹⁶ His precautions as to true samples are mentioned as follows: He obtained the caffeine from Schuchardt. The theine was a pure specimen from Messrs. Hopkins and Williams. In referring to the "discrepancies" between Dr. Mays results and his own, Dr. Brunton says they may be "due to difference in the animals employed or to variations in the theine," "*for it is just possible that there can be differences in the active principles obtained from different kinds of tea, or even from the same kind by different methods of treatment.*" Dr. Brunton did not find his "theine" and his "caffeine" to have the same action, nor did he find the difference between the two to be the same recorded by Dr. Mays.

In the present state of evidence, then, we reach certain conclusions as follows:

1. The five beverage plants owe some of the differences in their effects to their different yields of bodies not classed as active principles.

2. The total active principle of a beverage plant, the "theine," "caffeine," etc., as obtained, is perhaps liable to contain small quantities of xanthine and other homologous bodies of physiological effect.

3. The main active principle in each of the five beverage plants is, unquestionably, a trimethyl-xanthine. Chemical studies indicate, as yet, only one trimethyl derivative of xanthine. If, however, strictly pure trimethyl-xanthine, known as caffeine, from one plant clearly differs in physiological effect from the same body taken in strict purity from another plant, then the chemist will recognize a proof of isomerism, and await its explanation by later chemical researches.

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Discussion.

Prof. Remington called attention to the scientific foundation for the custom of simply making an infusion of tea, by

⁷ This body may have been theophylline.

⁸ Zeitsch. physiol. Chem., 8, 395; Jour. Chem. Soc., 48, 286.

⁹ A. Kossel, 1888; Ber. d. chem. Ges., 21, 2164; Jour. Chem. Soc., 54, 114; Am. Jour. Phar., 60, 461.

¹⁰ From theobromine, a monomethyl alloxan is obtained with a monomethyl urea.

¹¹ 1889; Phar. Jour. Trans. [3] 19, 24; Jour. Chem. Soc., 56, 416.

¹² 1891; Phar. Jour. Trans. [3] 21, 61; Jour. Chem. Soc., 60, 358.

¹³ W. Filehne, 1886; Archiv. Anat. Physiol., p. 72; Therap. Gazette, 10, 628.

¹⁴ 1886; Therap. Gazette, 10, 765.

¹⁵ Therapeutic Gazette, 10, 586; Proc. Am. Phar. Assoc., 35, 335.

¹⁶ T. L. Brunton and J. T. Cash, 1887; Proc. Royal Soc., 42, 238; Jour. Chem. Soc., 52, 985; Jour. Physiology, 9, 112.

which the flavoring substances and caffeine are extracted, leaving the insoluble tannin behind.

The chairman stated that if the statement is to be accepted that theine is different from caffeine, it will be necessary to write "there" after caffeine, since much of the supply of caffeine is obtained from damaged tea. Dr. Edward R. Squibb, in a letter some years ago, declared that there was no difference between theine and commercial caffeine, and threw some doubt upon the existence of caffeine, as such in the living plant. A practical point, showing that tea is prized for something more than its alkaloidal content, lies in the fact that some cheaper grades of tea are richer in caffeine than the higher-priced teas. As regards the difference alleged to exist between the alkaloid derived from tea and that from coffee, it is possible that some of the volatile substances of the tea are not fully separated from the caffeine, and modify its physiologic action; just as piperine may owe much of its stimulating qualities to volatile substances usually associated with it.

In practical medicine, the insolubility of tannin should be remembered, and in making infusions for the astringent effects, as in antimonial poisoning, or for their action on mucous membranes, the tea or coffee should be boiled. On the other hand, when the stimulating effects alone are desired, a rapid infusion is all that is needed.

In closing the discussion, Dr. Prescott said that, During the discussion which followed the reading of this paper, the question had been asked, what extent of the effect of tea and of coffee is due to their essential oils; also to what extent caffeine or theine is changed by methods of extraction. To this he replied that, undoubtedly the essential oils in question are of decided influence. Many volatile oils are of active physiological effect. However, these oils have not been separated and examined. That of coffee is developed by roasting; that of tea, not improbably, is developed by the curing process, with its stage of fermentation, and of firing. As to the alteration due to modes of extraction, he believed they could hardly extend much beyond the liberation of the alkaloid from certain combinations of the same.

COLLABORATION IN MATERIA MEDICA AND PHARMACY.

Read in the Section of Materia Medica and Pharmacy, at the Forty third Annual Meeting of the American Medical Association, held in Detroit, Mich., June, 1892.

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The new movement of establishing closer and official relations between the two professions of medicine and pharmacy was inaugurated at a time when its desirability, or rather necessity, had become generally recognized. Both professions have many interests in common, and both have to supplement each other by their special knowledge and attainments. Many are the topics—ethical, legal, historical, hygienic, statistical, educational, social, and particularly scientific—which can and will be profitably discussed at joint meetings of representatives of the two professions; and some of these topics may even be said to form burning questions which have hitherto been treated by the medical and pharmaceutical press mostly in an *ex parte* manner. It is hoped that these may, hereafter, be brought to a solution satisfactory to all.

But the discussion of professional topics, or the reading of papers thereon, at the joint annual meetings, does not seem to be sufficient to infuse life into a copartnership such as it is proposed to establish and maintain between the two professions. Something else, of a more lasting and permanent interest, something of tangible utility, so to say, seems to be wanted to serve as a firmer bond. In the judgment of the writer, such a bond can be established—and indeed its want has long been felt—by the official interchange of, and decision on professional or scien-

tific problems between the two professions. The physician as well as the pharmacist, each possesses, if properly trained, a fund of special knowledge, often laboriously acquired and constantly augmented by daily practice and experience, which, in these days of rapid progress, can no longer be expected to be met with combined in one and the same person, but which has to be gathered and studied by specialists for the benefit of the other members of their own or a kindred profession. Yet it is an indisputable fact that many important facts which have long been known to or recognized by one profession, and which yet vitally concern the other, remain often entirely unknown, or only imperfectly known to the latter for a long time. If there were an official channel through which such useful information could be conveyed, at regular intervals, from one profession to the other, much would thereby be gained. It may be well to mention an example by way of illustration. Many physicians are in the habit of prescribing *aconitine* without specifying what kind they intend. They are not aware that there are *four* or *five* different kinds in the market, each of them in vogue or preferred in some particular country or locality—one being the pure, crystallized alkaloid of great power; another an amorphous substance of comparatively feeble strength; another one made by a different process, or perhaps from a different kind of aconite, being of an intermediate strength, etc.—and that they are liable to have the most powerful dispensed when they perhaps intended the weakest, or *vice versa*. Would it not be useful to present to the medical profession, once a year at least, a concise summary of important matters of this kind, which would suggest themselves from time to time? As a rule, physicians do not read pharmaceutical journals, or circulars issued by chemical houses, hence information regarding subjects like that above mentioned often reaches them only when some serious accident has happened. If there were a source of information on topics of this kind, prepared by pharmacists specially for the benefit of physicians, much good would result. On the other hand, physicians often observe objectionable features connected with the form or efficacy of pharmaceutical or galenic preparations—as for instance deficiency of therapeutic action due to improper vehicles, improper coating, etc. The same medium of communication could be used for drawing the attention of the pharmacists to these matters.

If it is conceded that such a mutual exchange of information or of problems is desirable, it will not be difficult to devise a plan by which it may be carried out. The writer suggests the following, at least as a basis upon which something better may perhaps be erected:

1. The American Medical Association, through its proper Section (or in any other way that may be determined on), may annually appoint *seven* (or any other number) members, who, together with a like number of pharmacists, who may be appointed by the American Pharmaceutical Association, shall constitute the "Committee on Therapeutics and Pharmacy" (or whatever other name may be given to this).

2. This committee shall elect a chairman and vice-chairman, only one of whom shall be chosen from the same profession. These two officers shall also be the chairmen of their respective sections (medical and pharmaceutical) in the committee.