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SPIRIT OF NITROUS ETHER.*

BY WILLIAM A. HALL.

The burden of work in this paper is what the writer accomplished as a member of the Sub-Committee on "Spirits" of the Revision Committee U. S. P. X and so that the results may be known to you all, to the end of marking progress and assisting in solving a troublesome problem, the subject matter is brought before you, with the facts obtained.

After a long period of physiological investigation, study and extended experiments with spirit of nitrous ether, this is addressed to you and you are asked to give a careful consideration of the facts deduced.

Throughout all these trials the utmost care was taken to avoid disturbing errors of observation and to keep our minds clear and open for the true scientific data and deductions. Dr. James Cleland, Jr., a fellow of the American College of Physicians, graciously worked with me in making the physical tests and joined

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with me in the preliminary report in February 1922, to Chairman, E. Fullerton Cook, of the Committee of Revision of the U. S. P.

Reading papers on these investigations and results, by invitation, before the Detroit Medical Club and The Detroit Academy of Medicine—two bodies of most excellent medical standing—I include resolutions each organization passed, expressing the favorable opinion of its members on this preparation, by the Squibb process.

I will give a brief history of this 600-year old preparation especially during the last 100 years as recorded in the successive decennial revisions of the U. S. P. since and including 1820.

The *U. S. P. 1820* process called for nitric acid and alcohol and gave a product containing 4.5% to 5% of its peculiar ether. The *U. S. P. 1830–1840–1850* processes called for potassium nitrate and sulphuric acid in such proportions as would yield the same amount of nitric acid as the preceding called for and also the final yield of nitrous ether 4.5 to 5%.

Dr. E. R. Squibb brought out his process for the manufacture of Spirit of Nitrous Ether in 1856 and this was adopted and accepted by the Revision Committee of the *U. S. P. 1860.* This process folowed the *U. S. P. of 1820* in using nitric acid (in proportional quantity to the KNO_3) obtaining a yield of 5% ethyl nitrite out of 8.33% total ethereal liquid and this process has been followed by his house ever since as yielding, in their judgment, a better product.

I may say in passing, this work has not been pressed by the House of Squibb although at my request they have supplied material for the investigations and have given me what data they could supply from time to time.

The *U. S. P. 1870* followed closely the British Pharmacopœia changing the process by using copper and sulphuric acid on theoretical grounds, but increased the amount of alcohol, thereby lowering the per cent of ether to less than one-third of the *U. S. P. 1860.* In doing this the *B. P.* was followed partly and the *1860 U. S. P.* partly.

The *U. S. P. 1880* left out the copper but retained the sulphuric acid of the 1870 process; washed the crude ether; reduced the 1870 amount of alcohol, yet retained the tests of 1860 and claimed it to yield 4 per cent of ethyl nitrite but really about 2 per cent. So we see the process of different revisions yielded the following percentages of ethyl nitrite:

1820, 4.5–5%; 1830, 4.5–5%; 1840, 4.5–5%; 1850, 4.5–5%; 1860, 5%; 1870, 1.75%; 1880, 2.00%; (*Ephemeris*, Vol. 3, p. 1192).

We now come to 1890, when Dr. Squibb offered the Revision Committee his improved process with 40 years of experience to back it, but which for some reason they did not accept, probably because it wished to have a product containing only ethyl nitrite and not the other crude ethers, and on the supposition that all therapeutic efficiency was due to the ethyl nitrite.

The author claimed valuable properties for his process not possessed by pure ethyl nitrite—which was the only therapeutic agent produced by the accepted 1890 process.

The proposed process gave a product containing 5 per cent of ethyl nitrite and 3.33 per cent other ether *not nitrites.*

Spir Aetheris Nitrosi U S P IX Process

Concentrated Ether diluted with alcohol (4% Ethyl Nitrite)

	120 min. dose undiluted		120 min. + 120 min. water taken 15 minutes later		same dose and dilution taken 48 hours later	
Temp. F	Before taking	3 hours after	Before	3 hours after	Before	3 hours after
	98 7°	98 3°	98 6°	98 6°	98 5°	98 5°
Pulse Rate	84	90	84	88	84	90
Arterial Tension	Systole 138 Diastole 82 mean 110	Systole 130 Diastole 84 mean 107	Systole 140 Diastole 80 mean 110	Systole 135 Diastole 83 mean 109	Systole 140 Diastole 90 mean 115	Systole 140 Diastole 80 mean 110
Pulse Pressure	56	46	60	52	50	60
Diuresis	58 ozs	67 ozs	58 ozs	60 ozs	63 ozs	59 ozs
Diaphoresis	Good for 3½ hours, not strong after. moderate prickling sensation		Not marked but noticeable for 2 hours Tingling of skin noticed for 3 hours		Slight diaphoresis	
Pain &c	15 minutes after taking, slight pain left occipital region, 25 minutes after taking, decidedly strong, but not disagreeably so, base of cerebellum, Sticking down left pillar persisting 3 hours Equilibrium slightly affected		No pain occipital region, noticed at base of cerebellum but good deal less than when undiluted dose was taken		No pain	

Spir. Aetheris Nitrosi, Squibb Process M'f'd, 11-13-20. 5539 Recd 12-19-21. 4479

	120 min., dose no previous dilution		120 min. + 120 min. water, taken 15 mints later		same dose & dilution, taken 48 hours later	
Temp. F	Before taking	3 hours after	Before taking	3 hours after	Before taking	3 hours after
	98.5°	98 °	98 6°	98 3°	98.6°	98.5°
Pulse Rate	84	96	80	86	84	86
Arterial Tension	Systole 150 Diastole 90 mean 120	Systole 135 Diastole 70 mean 1025	Systole 150 Diastole 90 mean 120	Systole 130 Diastole 80 mean 105	Systole 140 Diastole 85 mean 112.5	Systole 136 Diastole 85 mean 1105
Pulse Pressure	60	65	60	50	55	51
Diuresis	56 ozs	68 ozs	60 ozs	71 ozs	61 ozs	71 ozs
Diaphoresis	Very marked, 6 hours with full bounding pulse marked 4 hours more No pain or headache but sense of fullness in cerebral region		marked for 4 hours and noticeable 4 hours more		5 hours but not so marked as in two previous trials	
Pain &c	Decided prickling sensation all over the body					

15 minutes after mixing Spr Nitrous Ether with water Ethyl Nitrite loss is 33%
48 hours after, loss is 75%
Other ethers than the nitrite, little affected

The washed complex ethereal liquid of the Squibb Process is about 8% before dilution with alcohol, of which 5/8 is Ethyl Nitrite

Approximate Results:

Deductions of Diaphoretic action of the whole series with Ethyl Nitrite content as determined and deduced U.S.P IX meaning: concentrated Nitrous Ether diluted with alcohol to contain 4% Ethyl Nitrite Results are approximately proportional

Observations on all the Series

Reduction in Arterial Tension much more from complex ethereal liquid

Diuretic action more from " " "

Diaphoretic " much " " " " "

Pulse accelerated more by Ethyl Nitrite

Antipyretic action more by " "
than by complex ethereal liquid, but much more from Ethyl Nitrite content in the Squibb process than from pure Ethyl Nitrite in U.S. IX process, showing apparently that the complex ethereal liquid affects the result

William A. Hall, Ph. B.
62 Adams West Detroit, Mich.

	Dose	Ethyl Nitrite Content	Complex Ethereal Liquid minus nitrites	Action
U.S.P IX	120 minims	4%		45%
U.S.P. IX	120 minims + 120 minims H_2O	2.66%	(15 minutes)	22%
U.S.P. IX	120 - + 120 - H_2O	1 %	(48 hours)	10%
Squibb Process	120 minims	1.59%		75%
" "	120 minims + 120 minims H_2O	1.03 %	(15 minutes)	42.%
" "	120 " + 120 " H_2O	.40%	(48 hours)	34%
" "	120 minims	4.79%	2.89%	100%
" "	120 minims + 120 minims H_2O	3.19%	(15 minutes)	50.%
" "	120 " + 120 " H_2O	1.20%	(48 hours)	25%

The *1890 U. S. P.* product was made by sodium nitrite and sulphuric acid and, as stated before, consisted of an alcoholic solution of ethyl nitrite (4%).

The *1900 U. S. P.* product was the same and

The *1910 U. S. P.* product was also the same.

Now after this brief statement, descriptive of the U. S. P. products from 1820 down, we come to the crux of the matter: Is the present U. S. P. process which produces *only Ethyl Nitrite* 4%, inferior or superior to the product made by the 1860 U. S. P. process as judged by therapeutic standards and results? Is it desirable to continue this process into the U. S. P. X, or take up the process *proposed* for the U. S. P. 1890, used with very favorable results for 72 years and practically the same as that of the U. S. P. 1860?

To answer these questions, the extensive series of tests and observations were undertaken, the results of which are shown on the chart included with this paper. The present U. S. P. product is practically a 4% alcoholic solution of *Ethyl Nitrite;* the proposed process product contains about 8.33% of a complex ethereal spirit $^5/_8$ of which is *Ethyl Nitrite* and $^3/_8$ *not nitrites at all* but other ethers and nitrous compounds which are physiologically strong in their action and add greatly to the effect of ethyl nitrite alone. In addition there is ethyl nitrate and traces of acetaldehyde, di-ethyl-ether and acetic acid.

Our *first* series was tried with a Squibb product, two years old and assaying 1.59% of ethyl nitrite, the *second* series with Squibb's product one year old and assaying 4.79% ethyl nitrite; the *third* series with a U. S. P. product assaying 4% ethyl nitrite. All the tests were repeated two to five times so as to narrow any possible errors.

Having done considerable work on this preparation, at intervals, during the past 25 years, I have been confirmed in my opinion of the marked superiority of the Squibb process product as compared with the pure ethyl nitrite, and the especial value of the preparation in reduction of arterial pressure. Recent study during the past five years has confirmed and enlarged my opinion of the value of the earlier results along with the development of more exact data.

Dr. Squibb said (*Ephemeris*, Vol. 3, p. 1235–6):

"The writer has never been able to assent to the proposition that *Ethyl Nitrite* is the only element of therapeutic value in Spirit of Nitrous Ether, and therefore that a solution of this ether in alcohol should take the place of the solution of the *complex ethereal liquid* in medicine." (Then he comments on several papers taking that view.) Continuing, he says: "*First* the favorable experience of 600 years (from Raymond Lilly in the 13th century) with preparations which, for a long time were crudely made and badly kept, should not be so easily set aside. These have often contained a considerable proportion of other ethereal products, and the sensible properties have been fairly uniform. *Second*, because, under the most favorable conditions, ethyl nitrite does not constitute over $^3/_5$ of the complex ethereal product which is the basis of spirit of nitrous ether, while the other $^2/_5$ belongs to an ethereal series known to have definite physiological effects."

I ask a careful study of results as shown on the chart and especially call the attention of the committee to the *Diaphoretic* table showing the *Squibb product* to have over twice the effect of the *U. S. P. IX* product; similar comment on "*Arterial Tension*" and "*Temperature*" and on *Antipyretic* effect. The diuretic effect also shows a marked difference. Please note also the loss in ethyl nitrite content in *15 minutes* and *48 hours* by dilution with equal volume of water and

the logical inference that the 3.33% complex ethereal liquid—not nitrites—is responsible for the marked therapeutic results.

The nitrites' content goes off first in the decomposition of the preparation while the *complex ethereal* spirit, not nitrites, persists for a much longer time and gives valuable physiological results. (Shown by data with the two-year old specimen containing only 1.59% ethyl nitrite and especially in comparison of results between the U. S. P. IX spirit and the *one*-year old Squibb process product.)

When Spirit of Nitrous Ether (U. S. P. 1860) is taken, the effects are very even with *scarcely any pain;* apparently the *ethyl nitrite* content is tempered and controlled by the *complex ethereal liquid*, so that one obtains the results with very little disturbing influence in the way of pain.

I am endeavoring to obtain the coöperation of an expert investigator of Yale University as to the composition and physiological effects of the 3 1/3% complex ethereal liquid not ethyl nitrite, but for the present he is unable to tackle this problem owing to the pressure of other work.

Included is a process proposed for the manufacture of this spirit.

PROCESS PROPOSED FOR SPIRIT OF NITROUS ETHER.

An alcoholic solution of a complex ethereal liquid composed of ethyl nitrite and other ethers. This complex ethereal liquid comprises about 8 1/3% of the finished spirit and yields on assay 5% on an average, of ethyl nitrite and 3 1/3 of other ethers, mainly ethyl nitrate with smaller amounts of ethyl acetate, acetaldehyde and acetic acid.

Alcohol: specific gravity 0.817 at 15° C., specific gravity 0.808 at 23° C., sufficient quantity or 1065 cc.

Nitric acid (67.6%) 163 Gm.

Sodium bicarbonate 20 Gm.

Aq. Ammon. fort. 2 cc.

Into a one-liter flask put alcohol 475 cc. and slowly add, while stirring constantly, the nitric acid. Mix and pour into a one-liter distilling flask into which a few pieces of broken glass have been placed. Stopper with a cork containing a thermometer and connect side arm with a Liebig condenser. To the other end of the condenser is attached an adapter, the end of which goes into the neck of a one-liter flask which is stoppered with a cotton plug. The latter flask, acting as a receiver, is marked where it will contain 475 cc. and is immersed in ice. A strong stream of cold water is run through the condenser. Heat the distilling flask by means of a water- or steam-bath, seeing the temperature does not rise above 85° C. and regulate distillation so that the liquid comes only by drops from the condenser. It may be necessary at times to remove the source of heat. Control too vigorous action by means of an ice-water bath. Continue distillation until distillate measures 475 cc.

Rinse apparatus with water followed by alcohol. Add to distillate sodium bicarbonate, 20 Gm. Mix intimately and transfer into the one-liter distilling flask. Make connections as before with receiver packed in ice and marked at 415 cc. Use very little heat for distillation which should be carried on very slowly. To the distillate (415 cc.) add alcohol, 590 cc. Mix and add stronger ammonia water, 2 cc. Mix and transfer to 8-oz. amber bottles and store in a cool place.

GIGANTIC MERCHANDISE MART FOR CHICAGO.

Chicago is to have a gigantic merchandise mart in its own building which will be twice the size of the largest business structure in the world. This mammoth structure is to be two city blocks in length, and is planned for the service and convenience of merchandise buyers; in it will be housed foremost manufacturers, wholesalers and importers. There will be incoming and outgoing freight stations on the ground floor of the building. The approximate cost is $30,000,000.