

THE TREATMENT OF SYPHILIS BY MERCURY INHALATIONS

HISTORY, METHOD AND RESULTS *

H. N. COLE, M.D.; A. J. GERICKE, M.D.,

AND

TORALD SOLLMANN, M.D.

CLEVELAND

HISTORY

Fumigations in the treatment of disease have been used since the time of Hippocrates. They were highly recommended by Celsus, Galen and others. Probably one of their first uses was in the treatment of scabies; therefore, it was only natural, when the skin manifestations of the new disease syphilis appeared in Europe that fumigations should have been mentioned as being employed to treat it. According to Astruc, to whose admirable book ¹ we are indebted for much of our information regarding syphilis in early times, fumigations were first used in the treatment of syphilis by Angelo Bolognino, professor of surgery at the University of Bologna, in 1506. Jacques Catanee ² also used them about the same time. Massa ² speaks of them in his book on the treatment of the "Malady of Naples." Later, Matthioli, ² in 1535, recommends them; likewise Fracastor, in 1546; Gabriel Fallopius, in 1560, in his book on "Mal Francois," and many others. William Rondelet, ² in his book on the "Malady of Naples," reports "having cured by means of the fumigation of mercury a syphilitic ulcer on the nose which neither the Italian doctors nor those of Montpellier had been able to cure."

Fumigations as employed at first really combined fumigation and inhalation, but some of the later methods excluded inhalation; so that the methods may be discussed under two heads, the old type of treatment and the new type of treatment. With the old treatment, the patient, quite naked, was placed in a closed, heated chamber, in which were volatilized mercury compounds such as cinnabar, calomel, red

*From the Department of Dermatology and Syphilology, Cleveland City Hospital and Western Reserve University, and from the Department of Pharmacology and Therapeutics, Western Reserve University.

*Read at the Forty-Fourth Annual Session of the American Dermatological Association, Swampscott, Mass., June 2-4, 1921.

1. Astruc, Jean: *Traité des Maladies Venériennes*, Paris, Cavelier and Sons 2:177, 1754.

2. Quoted by Astruc (Footnote 1).

precipitate or turpeth mineral, often mixed with fats, resins, fragrant volatile oils, etc., to give off a dense smoke. The patient was exposed for from one-half to one hour, the treatment being given every day or so, depending on the patient's strength. Schiro³ describes the typical inhalation rooms, such as those at Campailla and Modica in Sicily, as made of wood, thickly plastered, with a capacity of about 700 cubic meters, and having a small door. They were heated to 150 C. with a charcoal brasier, the patient was placed on a chair, and on the brasier was put 2 gm. of the heated sulphid of mercury and 1 gm. of incense. The door was then shut and treatment given for fifteen minutes, ten treatments making a course. He claims that the results were rapid; that the treatment was favorable to the patient in that he took no mercury by mouth; that it was harmless—a statement which we will take up later; that it did not interfere with the occupation; that there was a favorable diaphoresis, and that the treatment continued its effects for many months. He quotes Dr. Marendino, who found mercury seven months afterwards in the urine of a patient who had taken twenty inhalations and fumigations.

The so-called new treatment with fumigation was devised in 1776 by Lalouette⁴ by the use of his "fumigation box." With this type the head was excluded entirely, and only pure calomel employed, which he claimed was not so irritating. As it is the scope of this paper to discuss rather the subject of inhalations, we shall not dwell further on Lalouette's method, except to mention Fournier's objections: 1. That it caused stomatitis and general debility if used too frequently. 2. That the dosage was uncertain. 3. That it was impracticable except in hospitals.

As concerns the old method of mercury inhalations, in which the head also was exposed to the vapors, there is no question that mercurial effects may be produced; but there can also be no question that the indefinite dosage makes the method either inefficient, or more often dangerous. This doubtless led to the abandonment of these inhalations. However, the lesson seems to have been forgotten, for these treatments are again advertised, as if they were new discoveries. A few citations from the literature should be useful for placing this matter in proper perspective.

LITERATURE

Astruc¹ reports the celebrated test of mercury inhalations as compared with mercury inunctions which was given before the city fathers and the faculty of medicine in the city of Paris, in 1733. His con-

3. Schiro, S.: *New Orleans M. & S. J.*, November, 1909, pp. 62-65, 349-357.

4. Quoted by Fournier, A.: *Treatment and Prophylaxis of Syphilis*, English Translation, New York, Marshall Rebman & Co., 1906.

clusions were that, for the thirty-seven cases of syphilis—all of them of a more or less mild type—which were treated with the mercury inhalations, the treatment took as much time as would be recognized for the mercury inunctions. Moreover, four of the patients died during the course of the treatment—one of them as early as the ninth inhalation. Twelve of the patients, about one third, seemed to be benefited at the time by the fumigations, but later some of them showed signs of recurrence of the disease. He concluded that mercury inhalations should never be used on old people, on weak or debilitated individuals, on asthmatics or on people affected with any lung trouble. Fallopius² states that the therapy is advisable only for vigorous individuals, as he had had some bad results even with such picked cases.

Since mercury volatilizes somewhat even at ordinary temperature, and of course more rapidly when heated, accidental and industrial poisoning by mercury vapor is not uncommon, and sometimes occurs on a wholesale scale. These incidents illustrate toxic effects that may also follow therapeutic inhalation, since it is as impossible to control the dosage in the one case as in the other.

In 1810, the British ship "Triumph" had some mercury containers broken in its hold.⁵ As a result, 200 sailors showed mercury poisoning and three of them died. All the birds and cattle on board the boat died. In 1804, as the result of a fire in a mine in India, a considerable amount of mercury was volatilized. Hermann⁶ says "Nearly all the townspeople showed effects of mercury, though in slighter degrees than the miners, by contact with these, whose clothing was impregnated with mercury and giving off mercury vapor in the air. Even the animals, for instance, cows that pastured near the furnaces or in their lea, were affected. The cows became salivated, cachectic, and aborted, or the calves born at term died early." Nine hundred persons in the neighborhood had mercury tremors. Wherry⁷ quotes Christison, who mentions two barometer makers who slept with their pot of quicksilver on the stove. One of them was slightly salivated and the other made tremulous for life. Seydel is quoted by Brouardel⁸ as reporting the case of a woman who inhaled the vapor of mercury thrown on glowing charcoal. After one or two minutes, she fell unconscious and, although no more mercury was inhaled, died in ten days with typical acute mercury poisoning. Merget is quoted by the same author as finding all the air from the floor to the ceiling in a mirror factory to contain mercury. A. Gautier is quoted by the same author as reporting the circumstance of

5. Binz: *Pharmakologie*, Ed. 2, 1891.

6. Hermann, L.: *Wien med. Wchnschr.*, 1850, No. 40.

7. Wherry, G.: *The Practitioner* **51**:168, 1893.

8. Brouardel, P.: *Les Intoxications*, 1904, p. 247.

some men who, having vaporized 200 gm. of mercury in a room, not entirely closed, become ill, one dying after a few days. Binz mentions two cases of poisoning from the presence of poorly silvered mirrors in the room. It is not necessary to adduce further examples of the tragic accidents following inhalations of mercury vapor in human subjects; but it is interesting to remark in passing that A. Krogh ("The Respiratory Exchange of Animals and Man") warns specifically against the use of any mercury in closed-space respiration apparatus.

Systematic investigations of the effects of mercury vapor have been made on animals, with important results. It is easy to produce mercury poisoning in this manner. In this country, for example, Schamberg, Kolmer and Raiziss⁹ showed that a rabbit may show effects of mercury by being exposed to the vapor of mercury arising from a second rabbit inuncted with mercurial ointment. Similar experiments were reported by Wile and Elliott.¹⁰ A series of excellent experiments was made by von Baerensprung¹¹ in 1850. Rabbits exposed for from one quarter to one hour to the vapor of boiling mercury died within a few days. Another rabbit kept in a cage with an open dish of mercury, at room temperature, became ill in two weeks, and died in the third week. All rabbits showed considerable irritation of the air passages and lungs; small hyperemic areas, and some areas of consolidation. In one of the rabbits that had been exposed to boiling mercury, droplets of mercury were found in these consolidated areas. Eulenberg¹² also found marked congestion of the mucosa, from the trachea to the smallest bronchi, in rabbits that died as the result of exposure to mercury vapor.

Binz cites the statements of Kirchgaesser, 1865, Samelsohn, 1872, and Fr. Mueller, 1806, that rabbits, when exposed to the vapor of mercury ointment in a closed, warm space, die after stomatitis and considerable swelling of the salivary glands. Merget¹³ exposed animals to amalgamated copper plates. Death occurred sooner in warm weather than in cold. Small animals were more susceptible than large, young more than old. He found no changes in the lungs. Solles¹³ found birds much more susceptible than rats. The symptoms were mainly nervous. Skudro¹² exposed mice to the vapor from gray ointment. Death occurred after one or several days. The principal lesions consisted of acute hemorrhagic inflammation of the lungs; the kidneys also showed

9. Schamberg, J. F., Kolmer, J. A., and Raiziss, G. W.: Absorption of Mercury, *J. A. M. A.* **70**:142 (Jan. 19) 1918.

10. Wile, U. J., and Elliott, J. A.: Absorption of Mercury, *J. A. M. A.* **68**:1024 (April 7) 1917.

11. Von Baerensprung: *J. f. prakt. Chem.* **50**:21.

12. Quoted by Ricker and Hesse: *Arch. f. path. Anat.* **217**:267-307, 1914.

13. Solles: *Bull. Soc. d'anat. et physiol. de Bordeaux* **2**:20-32, 1881.

degeneration. Pulmonary lesions occurred when mice were killed by inunction, in which inhalation also played a part, but not when inhalation was avoided by oral or hypodermic administration.

Important experimental comparisons of inhalation and other methods of administration were made by Ricker and Hesse.¹⁴ For inhalation, the animals were placed in cages with the opening half closed by linen cloth coated with gray ointment, arranged so that it could not be touched by the animals. The principal lesions were found in the lungs: hyperemia, with or without hemorrhage, and sometimes inflammation (pus cells). The lesions started as small, isolated areas, which fused as they extended. Inflammatory changes were often present also in the kidneys and colon.

With other methods of administration, the pulmonary changes were smaller, those of the kidneys and intestine greater. The pulmonary congestion is, therefore, mainly a local reaction to the inhalation.

SUMMARY OF THE LITERATURE

In summarizing the experimental literature, it is seen that the inhalation of mercury vapor, either by exposure for short periods to heated mercury or by longer periods to ointment, etc., at room temperature, produced all the ordinary phenomena of all grades of mercury poisoning, and, in addition, inflammatory changes in the air passages and lungs. A similar condition doubtless exists in human cases. For instance, Binz¹⁵ points out that, of the crew of the "Triumph," four men, who had been well previously, died from phthisis soon after the accident. A fifth, who had recovered from the mercury, died of pneumonia.

It may be remarked, in passing, that the possibility of producing mercurial effects from the vapors arising from the ointment has led to some curious methods of administration, such as Merget's "mercurial flannels" and Blaschko's "mercolint." These were made by soaking the fabric first in a bichlorid solution and then in a solution of ammonia. The mercury was thus precipitated in the form of a fine gray powder on the cloth. This cloth was then enveloped in lint and placed in a pillow or around the neck. It was claimed that this would give off sufficient vapor of the metal to produce the desired therapeutic effect.¹⁶ Merget,¹⁷ and Blaschko even go as far as to assert that in mercury inunctions the entire effect is due to inhalation of mercurial vapor that is volatilized from the skin. In like manner, Thalmann has suggested

14. Ricker and Hesse: *Arch. f. path. Anat.* **217**:267-307, 1914.

15. Footnote 5, p. 491.

16. Footnote 4, p. 94.

17. Quoted by Fournier, A. (Footnote 4, p. 80).

the use of unguentum hydrargyri placed inside the nose and Cromquist¹⁸ the use of snuffing gray powder. The same principle is used in "mercuriel," an amalgam of mercury, aluminium and magnesium. It is a dry powder, suspended in a bag on back or chest, and intended to give off mercurial vapor, which is supposed to be inhaled. Poulsson¹⁹ states that the clinical results are much feebler than with inunction. The fundamental error in all this type of attempted continuous inhalation is that they do not sufficiently confine the air that the patient breathes. They could be successful only if the patient sojourned continuously in a small cabinet.

THE THEORETICAL FOUNDATION OF INHALATION THERAPY

The advocates of inhalation methods must concede the very serious disadvantages of indefinite dosage, which they have made no serious effort to correct. To offset this, they must assume that the lung is a good absorbing surface for mercury; that inhalation prevents local contact with the digestive tract; and that irritation of the pulmonary system is less objectionable than irritation of the intestines. None of these assumptions is well founded; indeed, each is contrary to fact.

The assumption as to prompt pulmonary absorption was based on analogy with the absorption of gases. The analogy, however, does not hold, since only soluble gases could pass through the endothelium. The fallacy was pointed out by Hermann,²⁰ in 1874: "In the case of the inhalation of mercury vapors, there is no doubt that the metal is deposited as such, in fine droplets, on the mucosae of the respiratory and digestive tracts. Even though it were demonstrated experimentally that these may penetrate into the blood and lymph vessels . . . they would probably be oxidized before they could act . . . It is much more probable that the deposits of very finely divided metal on the mucosae are oxidized before absorption . . . It is a false physical conception that mercury vapors could be absorbed as such into the blood, through the lungs; when vapors pass a moist surface, they must be condensed there; and it is this condensed condition which comes in question for absorption." Fürbringer²¹ believes that mercury vapors, on coming into contact with the moist mucous membranes, are deposited as metallic mercury. It could not be taken up as metallic mercury until after it had been dissolved in the surface. In other words, absorption would occur, but would not be faster nor essentially different from that in any other mucous membrane.

18. Cromquist, C.: Arch. f. Dermat. u. Syph. **86**:180-196, 1907.

19. Poulsson: Lehrbuch der Pharmakologie. Horvel, Leipzig, 1912.

20. Hermann, L.: Lehrbuch der experimenteller Toxicologie, 1874, p. 212.

21. Fürbringer, P.: Arch. f. path. Anat. **82**:491, 1880.

The second assumption, that inhalation would avoid the local effects on the digestive tract, is incorrect because a considerable part of the mercurial vapor is condensed on the mucous membranes of the mouth and pharynx and is gradually swallowed with the saliva. The proportion that thus goes into the digestive tract doubtless varies with conditions; but it must be considerable, and may well be the major part. Certainly in the patients treated by Thalman and Cromquist, with their so-called "Schnupfungkur," much of the drug would be swallowed and absorbed through the digestive tract.

Finally, the seriousness of pulmonary injury is sufficiently illustrated by the experimental data. Nor is there any question of choice between pulmonary and intestinal effects, since inhalations are liable to produce both.

THERAPEUTIC METHODS AND OPINIONS

From the foregoing considerations, it would be expected that the inhalation or fumigation methods would be undesirable; it is difficult to conceive any real advantage over even the oral method of administration; while the uncertain dosage would be liable to make the treatment either inefficient or dangerous, the dangers being enhanced by the possibility of pulmonary irritation. By arranging the treatments so that only a small amount is actually inhaled, and most of the mercury goes innocuously into the air, the danger may be greatly reduced; and, by repeating such small treatments sufficiently often, an adequate dosage might finally be obtained; or by more audacious procedures, a more prompt action might be attainable, with corresponding and uncontrollable risk. In one or the other of these ways, inhalations could be used if they were the only available methods of administering mercury; but the uncertainty and risk would appear to compare unfavorably with the oral methods of administration.

It should not be forgotten that fumigations received a quite thorough clinical trial at one time, but were found unable to compete, in the long run, with other methods. Since the experience of one generation is so easily lost to the next, it may be worth while to quote the details of the methods formerly in vogue. Wood²² says, "The vapor when inhaled operates more rapidly than any other form in which mercury is used and has, therefore, been recommended in cases in which a very speedy effect is required, the impression being afterward sustained by the internal use of the medicine." However, he is then careful to go on to say that he has personally never met with a case in which it seemed to be desirable! and also to say that violent effects are said sometimes

22. Wood: *Therapeutics*, Ed. 1, 1856 2:277.

to have resulted from the inhalation of the vapor. Different forms of the drug were employed and recommended. Mr. Abernethy²³ employed the black oxid but this was especially for the true mercury fumigations: "The patient, being protected by a complete suit of underclothing, was placed at night in a vapor bath with the head projecting and the neck guarded by a cloth, and exposed for fifteen to twenty minutes to the vapor of two grams of the oxid put on a heated iron within the bath." He was then transferred to bed and passed the night in the same garments. Wood said salivation was possible by this method in forty-eight hours. Cinnabar,²⁴ has likewise been used, and to give the best effects the vapor must be inhaled. In using cinnabar, sulphurous acid would be inhaled at the same time, rendering the compound very unpleasant and even hazardous. From 10 grains to 1 dram was employed. In the past, calomel has likewise been used and is supposed to have caused less inflammation.

Calomel vapor was also applied directly to local lesions. Kans²⁵ devised an apparatus consisting of a bulb glass tube ending in a fine point. The bulb was heated in order that the calomel would vaporize, and a current of air was passed through the tube and the point was then directed against the skin lesion which he desired to treat.

CLINICAL EXPERIMENTS ON MERCURY INHALATION

Although neither the theoretical consideration nor the published experimental or clinical data appeared promising, it seemed worth while to investigate as to whether the method could be sufficiently improved to make it available for the occasional cases in which other methods might be undesirable. The obvious improvements could be made in two directions; to minimize the inaccuracies of dosage; and to select the least irritant preparation. The greatest inaccuracy in the existing methods lies in the fact that the mercurial vapor goes into the air without any control as to how much or little enters the mouth. This source of inaccuracy was avoided by placing a weighed quantity of the mercury compound in the center of a strong glass tube, about 10 inches long, bent to an angle of about 130 degrees, and open at both ends. The mercury was then volatilized by heating lightly in a Bunsen flame, the patient inhaling the vapor as it was formed, by deep inhalations from the end of the tube. Calomel could be volatilized directly in this manner. Metallic mercury, however, presented some practical difficulties. These were overcome by using a 10 per cent. trituration with chalk, and by heating this in the corked tube, depositing the

23. Quoted by Wood (Footnote 22, p. 287).

24. Footnote 22, p. 304.

25. Quoted by White, Hale: Textbook of Pharmacology and Therapeutics, 1901, p. 435.

mercury as a mirror on the walls. The chalk could then be emptied, and the mirror easily volatilized by heat at the time of the treatment.

This method insures the actual inhalation of a perfectly definite dosage, a point that has not been met by any previous method. Nor was any significant amount of mercury reexhaled, since the vapor condenses very rapidly in the mouth. How much of the vapor was deposited in the mouth, how much entered the trachea, and how little entered the bronchioles, we have no means of knowing.

The second object of selecting the least irritant preparation was also fairly accomplished. Metallic mercury was much less irritant than calomel; and it seems very improbable that any of its compounds could be less irritant than the metal itself.

DOSAGE

In selecting the dosage, we could not be guided by the doses employed in the older methods in which only a fraction enters the mouth. On the contrary, if the absorption of the mercury were really efficient, the dosage should rather be that used in intramuscular injections. Should this dosage be inefficient, then inhalation would evidently have no advantage, so far as absorption is concerned. On the other hand, increasing the dosage beyond this point would present two dangers: on the one hand, the fact that variable absorption might produce toxic systemic effects; on the other hand, the susceptibility of the lungs to local injury.

Calomel inhalations were begun according to the following schema:

COURSE I

The patient was given the first course consisting of:

First day, 5 mg. of calomel
 Second day, 10 mg. of calomel
 Third day, 20 mg. of calomel
 Fourth day, 20 mg. of calomel
 Total, 75 mg. of calomel
 Fifth, sixth and seventh days, no medication.

COURSE II

The patient was then given the second course consisting of:

First day, 10 mg. of calomel
 Second day, 20 mg. of calomel
 Third day, 40 mg. of calomel
 Fourth day, 80 mg. of calomel
 Total, 150 mg. of calomel.

We were careful not to use this treatment on any patient who was having symptoms of bronchial irritation or who was under treatment

with iodids or bromids. We also watched carefully for symptoms of bronchial and pulmonary irritability, albumin in the urine and salivation. Especial symptoms will be noted on each patient as observed.

This dosage was devised to lead up to the usual intramuscular dosage of calomel; i. e., about 200 mg. per week. However, the occurrence of local irritation made it inadvisable to increase the dosage further, so we turned to metallic mercury.

Brief abstracts of the clinical observations follow.

CASE 1.—C., a man, white, aged 31, with a diagnosis of secondary syphilis and having a maculopapular eruption, with patches in mouth, gave a + + + + blood Wassermann reaction. The spinal fluid was negative. The teeth in good condition.

COURSE I

First day, 5 mg.; observation negative.

Second day, 10 mg.; slight bronchial irritation during and fifteen minutes after inhalation.

Third day, 20 mg.; observation same as on second day.

Fourth day, 40 mg.; slight amount of salivation during inhalation, and bronchial irritation during, and twenty minutes after, inhalation.

Three days vacation intervened.

COURSE II

First day, 20 mg.; observations negative.

Second day, 40 mg.; patient coughed a few times during inhalation.

Third day, 60 mg.; slight bronchial irritation during, and ten minutes after, inhalation.

Fourth day, 80 mg.; observations same as third day.

Final Examination.—The urine was normal throughout the experiment. The gums and teeth were negative, there was no salivation, and the lungs were negative. At no time was there an improvement in the syphilitic condition. However, these symptoms cleared up nicely under arsphenamin and mercury inunctions.

CASE 2.—K., aged 26, presented a condition which was diagnosed as maculopapular syphilid. The blood Wassermann reaction was + + + +; the spinal fluid negative.

COURSE I

First day, 5 mg., observations negative.

Second day, 10 mg., slight bronchial irritation during inhalation.

Third day, 20 mg., bronchial irritation during, and fifteen minutes after, inhalation.

Fourth day, 40 mg., slight salivation and bronchial irritation during, and twenty-five minutes after, inhalation.

Fifth, sixth and seventh days, no medication.

COURSE II

Eighth day, 10 mg., slight bronchial irritation during inhalation.

Ninth day, 20 mg., slight salivation and bronchial irritation during, and bronchial irritation for twenty minutes after, inhalation.

Tenth day, 40 mg., increased salivation and bronchial irritation during, and bronchial irritation for thirty minutes after, inhalation.

Eleventh day, 80 mg., profuse salivation during, and bronchial irritation for thirty minutes after, inhalation.

After the inhalation on the tenth day, the patient complained that his gums were getting sore and bleeding easily when brushed.

Final Examination.—The gums were edematous and there was an increased amount of saliva at end of course. The syphilis showed no evidence of improvement. The urine was negative as to albumin throughout the experiment. The syphilitic lesions disappeared rapidly on use of arsphenamin and inunctions.

CASE 3.—M., a man, aged 23, presented a condition which was diagnosed as secondary syphilis, with a maculopapular syphilid. The blood Wassermann reaction was ++++; the spinal fluid negative.

COURSE I

First day, 5 mg., observations negative.

Second day, 10 mg., slight bronchial irritation during inhalation.

Third day, 20 mg., bronchial irritation during, and fifteen minutes after, inhalation.

Fourth day, 40 mg., slight salivation and bronchial irritation during, and twenty-five minutes after, inhalation.

Fifth, sixth and seventh days, no medication.

COURSE II

Eighth day, 10 mg., slight bronchial irritation during inhalation.

Ninth day, 20 mg., slight salivation and bronchial irritation during, and bronchial irritation for twenty minutes after, inhalation.

Tenth day, 40 mg., increased salivation and bronchial irritation during, and bronchial irritation for thirty minutes after, inhalation.

Eleventh day, 80 mg., profuse salivation during, and bronchial irritation for thirty minutes after, inhalation.

After the inhalation on the tenth day the patient complained that his gums were getting sore and bleeding easily when brushed.

Final Examination.—The gums were edematous and there was an increased amount of saliva at the end of the course. The syphilis showed no evidence of improvement. The urine was negative as to albumin throughout the experiment. Syphilitic lesions disappeared rapidly on use of arsphenamin and inunctions.

CASE 4.—M., a man, aged 23, whose condition was diagnosed as secondary syphilis, with maculopapular eruption, patches in mouth and primary lesion on glands, gave a blood Wassermann reaction which was ++++. The spinal fluid was negative.

COURSE I

First day, 5 mg., observations negative.

Second day, 10 mg., tickling sensation in throat and coughing a few times during inhalation.

Third day, 20 mg., observations same as on second day.

Fourth day, 40 mg., patient complained of sore throat, coughing a few times, and slight salivation during the latter part of inhalation.

COURSE II

Eighth day, 10 mg., observations negative.

Ninth day, 20 mg., slight bronchial irritation during, and ten minutes after, inhalation.

Tenth day, 40 mg., patient complained of tender teeth and gums, increased bronchial irritation during, slight salivation and coughing for thirty minutes after, inhalation; gums edematous.

Eleventh day, 80 mg., patient noticed the dosage was increasing because he was coughing more than after other inhalations. Increased salivation during, and for ten minutes after inhalation, together with coughing for thirty minutes thereafter.

Final Examination.—After the last inhalation, an examination revealed edematous gums and an increased amount of saliva. There was no improvement in the syphilitic symptoms; the urine showed no albumin. The eruption and mucous patches healed rapidly after the use of arsphenamin.

CASE 5.—C., a man, aged 32, with a diagnosis of maculopapular syphilid of a generalized type, gave a blood Wassermann reaction of + + + +. The spinal fluid was negative.

COURSE I

First day, 5 mg., observations negative.

Second day, 10 mg., patient noticed tickling sensation in throat, coughing twice during inhalation.

Third day, 20 mg., patient noticed increased amount of saliva, bronchial irritation during, and twenty minutes after, inhalation. No salivation after inhalation.

Fourth day, 40 mg., profuse salivation and bronchial irritation during and fifteen minutes after inhalation. Examination after inhalation revealed edematous gums and an increased amount of saliva.

Fifth, sixth and seventh days, no medication.

Eighth day, 20 mg., slight bronchial irritation during, and for fifteen minutes after inhalation.

Ninth day, 40 mg., profuse salivation and bronchial irritation during, and fifteen minutes after, inhalation.

Tenth day, 60 mg., observations same as day previous, gums and teeth not sore.

Eleventh day, 80 mg., profuse salivation and bronchial irritation during, and for twenty-four hours after, inhalation.

Final Examination.—This revealed edematous gums and an increased amount of saliva. The lungs eight hours after inhalation showed signs of a bronchitis. The temperature varied from 99 F. after the fourth inhalation to 103 F. after the eighth. Two days after the last inhalation, the temperature returned to normal. The syphilitic condition showed no improvement; the urine remained normal as to albumin throughout the experiment. The syphilitic lesions reacted at once when arsphenamin and mercury rubs were used.

SUMMARY OF OBSERVATIONS ON CALOMEL INHALATIONS

Inhalations of from 5 to 80 mg., totaling 225 mg. in two weeks, were taken by each of five patients, with active syphilitic lesions. None of these showed any therapeutic response, nor any renal changes. All but one exhibited definite bronchial irritation, salivation, and tenderness or edema of the gums. The bronchial irritation and salivation occurred at

the time of each inhalation, and were evidently due to direct local contact with the calomel, and not to systemic action. This probably holds true also of the irritation of the gums. In brief, then, calomel inhalation produced no systemic effects, therapeutic or toxic; but it caused local irritation, increasing with the dosage, that made further increase of dosage inadvisable, especially in view of the case, reported by Henry Lee,²⁶ of a young woman who, after breathing calomel vapor, became unconscious, livid and cyanosed, death ensuing. Necropsy showed the lungs to be congested, but the other organs healthy. This brings to mind also the four patients, reported by Astruc, who died while undergoing inhalation experiments.

INHALATION OF METALLIC MERCURY

The mercury was deposited as a mirror in the tubes, so that it could be readily volatilized. The following courses were administered, with the same precautions that were described under calomel.

First day, 5 mg. mercury
 Second day, 10 mg. mercury
 Third day, 20 mg. mercury.
 Fourth day, 40 mg. mercury (two inhalations of 20 mg. each)
 Total in week, 75 mg. mercury
 Fifth, sixth and seventh days. no medication.

COURSE II

First day, 10 mg. mercury
 Second day, 20 mg. mercury
 Third day, 40 mg. mercury (two inhalations of 20 mg. each)
 Fourth day, 80 mg. mercury (four inhalations of 20 mg. each)
 Total in week, 150 mg. mercury
 Fifth, sixth and seventh days, no medication.

Course III was added after experience had shown that Courses I and II did not produce either local or systemic effects.

Accepting the weekly dose for mercury by intramuscular injection as about 140 mg., this is equaled by the second course, and doubled by the third course of inhalation.

Abstracts of the clinical histories follow.

CASE 6.—R., colored, aged 25, single, with a diagnosis of secondary syphilis, presenting a generalized papular and annular syphilid. Laboratory findings were: Blood Wassermann reaction, + + + +; spinal fluid negative.

The patient received inhalations as specified in the first two courses without noticing any objective or subjective bronchial symptoms or symptoms of mercurialism. The patient received arsphenamin injections (six) while receiving the inhalations.

26. Quoted by Fournier, Footnote 4, p. 93.

CASE 7.—C., white, single, aged 25, presented a condition which was diagnosed as secondary syphilis, with lesion on the glans penis, a generalized papular syphilid and condylomata lata. The laboratory findings were: Blood Wassermann reaction, + + + +; spinal fluid negative.

The patient received the first two courses of inhalations as specified without noticing any subjective or objective bronchial symptoms or symptoms of mercurialism. The patient received arsphenamin injections (six) while receiving inhalations.

CASE 8.—W., white, single, aged 38, gave a diagnosis of secondary syphilis, with maculopapular eruption, mucous patches in the mouth, and condylomata lata around the anus. The blood Wassermann was + + + +; the spinal fluid negative.

This patient was started with the second course of inhalation and without a vacation given the third course. As far as the eruption was concerned there was very little change; the lesions were not as bright in color, but they increased in number. In addition, between the second and third inhalations of the second course the patient developed mucous patches in his mouth. The inhalations did not especially irritate him. The urine showed no albumin during the course of the treatment. The lesions cleared rapidly on use of arsphenamin and mercury inunctions thereafter.

CASE 9.—B., colored aged 29, gave a diagnosis of rupoid syphilid, generalized in type. The blood Wassermann was + + + +; the spinal fluid negative.

This patient received the second course of inhalations as specified in outline, three days vacation, and two inhalations of the third course. During the inhalations there was no change in the lesions, the teeth and gums were negative, the temperature was generally normal in the morning, rising to around 38.6 in the afternoon. There was no bronchial irritation. The patient complained of a sore throat which continued until arsphenamin was given. Examination showed no mucous patches. The inhalations were not continued because the patient was getting worse and running a temperature. After 0.5 gm. arsphenamin was given, the temperature became normal and the patient improved almost at once. The urine remained normal throughout the treatment.

CASE 10.—Q., white, aged 26, gave a diagnosis of secondary syphilis, generalized maculopapular in type. The blood Wassermann was + + + +; the spinal fluid negative.

The patient received the course of inhalation as specified in the outline. After three inhalations (Course I) the patient developed two mucous patches on the hard palate, the eruption remaining about the same. The observations were negative during the second course. During the third course the eruption faded a little, and after the fourth inhalation of Course III the patient noted a transitory salivation. No bronchial irritation was noted. Patient received no other therapy except the routine mouth washes. The lesions all cleared up rapidly thereafter with arsphenamin. The urine was normal throughout the treatment.

CASE 11.—C., white, aged 38, with a condition diagnosed as generalized macular eruption, primary on the glans, gave a blood Wassermann reaction + + + +. The spinal fluid was negative.

The patient received the courses, 1, 2 and 3 of inhalations, as specified above, without noticing any especial objective or subjective symptoms. There was no change in the character of the lesions, the patient developed no mucous patches, and experienced no bronchial irritation, or salivation. He complained of a frontal headache on admittance which continued until arsphenamin was

administered at the end of Course III. During the three courses of inhalations the patient received no other therapy except the routine mouth washes. The syphilitic lesions then reacted at once to arsphenamin.

SUMMARY OF METALLIC MERCURY INHALATIONS

Inhalations of from 5 to 160 mg. of mercury, to a total of from 225 mg. in two weeks to 750 mg. in three weeks, were administered to each of six patients. No systemic or local effects resulted; no salivation (except in one doubtful case) and no sore gums. The weekly dosage amounted to from two to five times the customary intramuscular dosage. It is evident that the absorption must be materially smaller than with intramuscular injections.

CONCLUSIONS

Inhalations and fumigations of mercury have been tried at various times, since the earliest days of the appearance of syphilis in Europe. They have always been abandoned as of uncertain efficiency, and occasional high toxicity. None of the methods so far proposed contain essential improvements over these antiquated methods.

The unsatisfactory results are due mainly to the uncertain dosage. Local injury to the lungs is an additional factor.

The assumption that mercury would be more promptly absorbed by the lungs was based on physical misconceptions. In fact, the mercury is condensed on the mucous membranes of the mouth, pharynx, and respiratory tract. That in the mouth and pharynx is, for the most part, swallowed. The absorption then takes place by the gradual conversion of the mercury into soluble compounds, just as it does with the ordinary administration of "gray powder."

An improved technic was devised to insure the complete inhalation of definite doses of mercury or calomel, equivalent to these used in intramuscular injection. This was applied by a series of patients with active syphilis, but without any therapeutic or other systemic response. Larger doses appeared unjustifiable. Calomel produced objectional local irritation.

The results indicate that the administration of mercury compounds by inhalation has no advantage over oral administration; but, on the contrary, it has the serious disadvantage of indefinite dosage, and the consequent difficulty of steering between inefficiency and danger, and of special danger of respiratory irritation.

ABSTRACT OF DISCUSSION

DR. AUGUST RAVOGLI, Cincinnati: When I had the service in the hospital, I used inhalations of calomel. I had a cabinet made with a chair and under the chair was placed an alcohol lamp with some water and, in the middle, 15 grains of calomel. The water began to boil and carried with the vapor

the particles of calomel. I can say I have found just what Dr. Cole says: the method is unreliable for we do not know the absorbed quantity of calomel, and the patients get weak and begin to suffer right away with stomatitis, gingivitis and so on. The fumigation with mercury I have not tried, but I do not think it is to be recommended.

DR. WILLIAM ALLEN PUSEY, Chicago: Dr. Cole has the disagreeable habit of asking in connection with popular practice, "What happens when you do this thing?" Then he goes ahead and shows us. Last year he read a very enlightening paper on the absorption of mercury injections and this year he gives us an excellent paper on this inadequate method. It is very important to have this information. The paper is also timely, because a preparation of this sort is being put out at present. The manufacturers have added frankincense and myrrh or something of that sort to the mercury and are giving us fumigation again.