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Inhalation therapy in influenza

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INHALATION THERAPY IN INFLUENZA.

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BY

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INHALATION THERAPY IN INFLUENZA.

Physicians from the remotest periods of time have been attracted by the logic of the utilization of the normal act of inspiration for the conveying of air impregnated with medicine into the respiratory tract to combat diseases of this region. Hippocrates wrote and described an excellent apparatus for the purpose of administering drug inhalations. From this time on down through the ages, methods of inhalation have been extensively used, only to fall into disrepute, probably later to be revived. New discoveries have brought renewed efforts at various times. In the middle of the 18th century the discovery of oxygen, and later the finding of iodine, chlorine, bromine, etc. brought waves of use and experimentation. History shows us that in each instance this method of treating upper respiratory infections has been discarded only to again be revived.

For the fifty years preceeding the World War little use was made of this method of medication; however with massed concentration of troops and the severe epidemic of influenza during this same time presented some rather definite facts relative to some of the war gases, and brought again to the front, inhalation as a treatment for respiratory diseases. Such blazing statements from literature as: "..... ..The sharp contrast in the number of cases of influenza during the severe epidemic of 1918,

INHALATION THERAPY IN INFLUENZA.

observed at Edgewood arsenal among the soldiers on duty in the chlorine plants, to others in the Chemical Warfare Service on the reservation. (1)."; or " The general impression which has been created, that work people employed in the various processes connected with the production of poison gases enjoy a large degree of immunity from influenza." (2), has led the medical profession to again consider the possibility of treating the respiratory diseases by inhalation methods.

It then will be the purpose of this paper to attempt to show by a review of the literature, by cases, and by personal experiences of the author, that in the treatment of influenza, inhalation methods either do or do not have a definite place. In so doing, because there is no agreement among the profession as to the exact specific cause of influenza and also because of the inevitable secondary infection, to assume certain facts to be true. We must define and get as clear cut a picture of the disease as possible, noting its course, its location, its toxicity, and its causative agent. Also to a certain degree we must limit the scope of inhalation.

To do these, let us first analyse the description of the disease as given by our foremost authorities. From Osler we quote " An acute infectious disease..... clinically the disease has the protean aspects, but a tendency to attack the respiratory mucous membranes. A

INHALATION THERAPY IN INFLUENZA.

special organism, Bacillus influenza is found. There is no agreement that it is the specific cause of the disease, and in any case secondary infection with the organism and other organisms is common." (3). Osler further states that there are four forms of influenza, respiratory, nervous, gastro-intestinal, and febril. As we are dealing with inhalations only, the first form is the only one that we will consider. As to this form Osler states " The mucous membranes of the respiratory tract from the nose to the air cells of the lungs may be regarded as the seat of the infection. In the simple form the disease sets in with coryza and presents the features of an acute catarrhal fever, with perhaps prostration and debility. In other cases after the catarrhal symptoms tracheitis and bronchitis occur. The cough is usually severe. Edema of the larynx is not uncommon". From this we can definitely locate the infection as being on or in the mucous membranes of the respiratory tract, causing irritation, coryza, and evidences of an exotoxin absorbed by the blood stream, resulting in fever, prostration, and debility. From Dorlands Medical Dictionary we quote, "Influenza- An acute, infectious disease, epidemic, marked by depression, distressing fever, acute catarrhal inflammation, of the nose, larynx, and bronchi.." He goes on to say that the disease is probably caused by the Bacillus influenza. Influenza in horses is also common.

INHALATION THERAPY IN INFLUENZA.

From these authorities we learn that the present idea is that influenza is caused by an organism, which is probably B. influenza and that the infection is located in the mucosa of the upper respiratory passages. If this is true, then logically since in order to treat any infection, one must get at the seat of the trouble, here we must treat the mucosa of the upper air passages. Due to the fact that all gases diffuse rather rapidly, all surfaces of the tract can easily be bathed in impregnated air, one would believe that treatment by inhalation should be logically sound. Likewise if the disease is caused or is complicated by organisms which enter by way of, or are common to the upper respiratory tract, any means of lessening the virulence or tending to make the mucosa steril would act as a prophylactic in the disease.

With these facts in mind, and for the sake of argument assuming them to be true, then our next problem is to find agents that may be used. The requirements of such a substance would be that if in compound it can readily be passed into a gas if normally a solid, or if a gas could be easily controlled and handled. It must also be an anti-septic, while at the same time must not be injurious to the mucosa to any great extent. Of all the agents that have been tried, the most outstanding ones at the present time are chlorine, iodine, nitrous oxide, sulphur dioxide, benzoin, and eucalyptus oil. Steam, although when inhaled is probably

INHALATION THERAPY IN INFLUENZA.

not in the form of a gas it must be considered along with other inhalants.

A thorough comprehensible study of this subject must include not alone the morphology and histology of the respiratory tract, but must also take into consideration the ability of the mucous membrane to absorb the various substances. The location of the causative organism and the extent of toxicity are very important, for if the medication does not reach the source of the disease treatment would be futile.

Since as previously cited, our authorities today consider that the organism enters by way of the mucous membranes of the nose and pharynx and probably probably remains there except in severe cases, we will first consider the histology of the mucosa of the upper respiratory tract. Bailey (5) in his text on histology, points out that the respiratory region of the nares has epithelium made up of stratified columnar variety and rests on a distinct basement membrane. The cells of the surface layer of the epithelium are ciliated and are interspersed with goblet cells. In a portion of the mucosa, the stroma contains large veins in tissue that resembles erectile tissue. There is considerable lymphoid tissue in the area, composed of small lymph nodes and interspersed simple tubular glands. Since the organism that causes influenza is thought to lodge and proliferate here, it is easy to conceive that such a place is excellent for

INHALATION THERAPY IN INFLUENZA.

its growth. It is very probable that the exotoxin gains entrance to the blood stream by way of the veinous drainage, or through the lymph nodes. Likewise if the organism enters the blood stream this is the logical place to consider as a portal of entry. It is very possible also that such tissue that has been invaded may prove a foci of infection. Whatever the process it is evident that this is the one place in the body where the organism can be reached during the early stages of the disease. However one must consider the fact that the germ could easily embed in the globlet cells or in the simple glands and remain out of danger from any antiseptic placed on the surface of the mucosa. For this reason it is necessary that the agent used ^s must be absorbed so that its antiseptic value will be received deep in the mucosa.

Such a mucosa as the one just described in the nose, one can readily see that with irritation an increased blood flow to the region would result. This is exactly what we find in rhinitis with influenza. The mucous membrane becomes swollen, there is an increased activity of the glands, and the lymph drainage is interfered with. All of this acts favorable for the organism, giving it a better place to live and more food. This also tends to show that treatment should be directed not only to the killing of the organisms, but also to increasing the lymph flow and drainage. As will be shown later, perhaps chlorine gas comes nearer to meeting these requirements than anything else.

INHALATION THERAPY IN INFLUENZA.

Further down the respiratory tract we find that the epithelium covering the pharynx and larynx is stratified squamous variety, except that in the upper part of the larynx we find stratified columnar ciliated, similar to that of the nares. In this region we find the palatine tonsils which are lymphatic organs, covered on the under surface only by a fibrous capsule. The free surface of the tonsils is covered by a reflection of the stratified squamous epithelium of the pharynx. At several places in the surface of the tonsil, deep indentations or crypts occur. These are from ten to twenty in number and from these, secondary crypts arise. Here then is an excellent place for bacteria to lodge and multiply. The pharyngeal likewise are lymphoid tissue and lie in the naso-pharynx. Hypertrophy of these is common. The lymphatic structures undoubtedly play a very important part in harboring the germ that causes influenza. Medication either in a prophylactic way or to directly combat the disease must reach the very depths of these crypts.

The mucosa of the trachea is continuous with that of the larynx and closely resembles it in structure. Here again we find the goblet cells and some lymphoid tissue. This structure carries into the primary bronchi and their larger branches. So here again we have an excellent growing bed for any organism.

INHALATION THERAPY IN INFLUENZA.

With this anatomy in mind we now turn to the habitat of the causative agent of influenza. Obviously, since this is not definitely proven to be the B. influenza, we cannot definitely place the habitat. However in this discussion we are accepting the idea that influenza is a separate distinct disease which usually becomes readily complicated by invasion of other organisms. We will assume that the toxicity and prostration is due to an exotoxin and that the organism is probably B. influenza and for the most part ~~are~~ localized in the mucosa of the upper respiratory tract. To further bear this contention out, let us quote from M.C. Winternitz of Yale University: (6)

" Early in the disease of influenza there is marked congestion and hemorrhage of the mucous membrane of the naso-pharynx. This also is conspicuous in the lining of the trachea and bronchi. The membrane is swollen, turgid, red, and covered by a copious mucous exudate. The exudate peels off readily and leaves a velvety red surface, dotted here and there with darker and more intensely red foci. Small ulcerations of the mucosa occur." Winternitz further states that it is remarkable how long this picture may persist without showing variation. It is encountered not only in the most acute and fulminating types of the disease, but may be found in cases that end fatally after several weeks. This article and many others simply go to show that the habitat of the organism is in the mucosa of the tract. Also that the B. influenza is usually present. Certainly with all

INHALATION THERAPY IN INFLUENZA.

this evidence of hyperemia, necrosis, exudation, one can at ¹⁸⁹⁹ venture the opinion that the source of the infection of influenza is located in the mucosa of the upper respiratory tract, and as many of the authorities agree that B. influenza can be cultured from the throat, that it is the causative organism. Opie (7) to further this idea introduced the organism into monkeys, and produced a similiar disease. The bacillus was placed in the mucosa of the respiratory tract and ^f after a time was again recovered and again transmitted the disease. Many experiments have been carried on with practically the same results. (26), (27)

Before we start our discussion on the various inhalants let us summarize the points that we are going to accept as axiomatic:

- (1) Epidemic Influenza is caused by B. influenza in all probab^bilities.
- (2) The mucous membranes of the upper respiratory tract is the first point of invasion of the organism, and in the majority of cases localizes here. Prostration being due to exotoxin.
- (3) Tonsilar tissue, goblet cells, and between epithelia cells, is the location of the organisms.

With these points in mind let us now turn to the treatment of this disease by means of inhalation.

INHALATION THERAPY IN INFLUENZA.

The first inhalant to be considered will be chlorine gas. The reason that this has been chosen is that it comes nearer to meeting the requirements set down earlier in this paper than any other agent. Since it is one of the best most of the emphasis in this paper will be placed on this gas.

Chlorine is a gas at ordinary temperatures, heavier than air, and readily soluble in water (one volume of water will absorb readily two and one half volumes of chlorine). Its antiseptic power has been known for many years and now is universally used in the purification of water. Water systems use a one to five million solution to free the water of cholera and typhoid bacillus. This is a very dilute solution but is very effective and is mentioned here to show the high antiseptic value of the gas. The gas will easily liquefy under pressure and is easily produced from hydrochloric acid and common salt. It is cheap, easy to obtain, has a very definite odor and the minimum lethal dose is high and far above the point of concentration with air at which its odor is detected. Only in high concentrations will it do serious damage to the respiratory tract mucosa. Before this concentration is reached a person becomes nauseated. Since it is readily absorbed by water; and since in a watery solution it is highly antiseptic in very dilute solutions; and due to its chemical and physical properties listed above,

INHALATION THERAPY IN INFLUENZA.

it is almost an ideal substance to meet our requirements. However we must have proof of its toxicity for pathogenic organisms met with in the respiratory tract.

In our contention that chlorine has a toxicity for respiratory tract organisms and still can be controlled with little damage to the mucosa we quote from the article "Chlorin as a Therapeutic Agent in Certain Respiratory Diseases" by E.B. Veeder and H.P. Sawyer of the U.S. Army Medical Corps. These men have been very active in this field and have done extensive research along this line. For this reason we quote the article in detail: (8)

"Chlorin has been used on several occasions to prevent certain infections. Kuster states that in 1915 chlorin gas was used successfully to clear up meningitis (meningococcus) and diphtheria carriers. Hale used chlorin in an unknown concentration at the University of Arkansas during the influenza epidemic and believed that the students that took the treatment suffered less than others. Employees in plants producing, or using chlorin have always believed themselves relatively free from respiratory diseases. This was brought to our attention during the war when the chlorin plant at Edgewood arsenal was producing to full capacity, the great influenza epidemic struck the post and the hospitals were full to overflowing. It is stated that no cases were reported among the operators of the chlorin

INHALATION THERAPY IN INFLUENZA.

plants, although every other organization on the arsenal had its full quota of cases. We therefore determined to investigate the value of chlorin as a therapeutic agent.

"Our first investigations were directed to determining the concentration of chlorine in air required to kill certain bacteria. After a number of preliminary experiments the following method was adopted. Agar plates were inoculated in duplicate with organisms to be plated. One of the plates was exposed to a known concentration of chlorin in one of our continuous chambers. The other plate served as a control. As soon as both plates were incubated they were observed for several days.

The results are: (Note All of records of the article are ^{not} given but these are typical.)

	Incubated hrs.	Steril after exposure.
1. Typhosus	24	45 min.
	72	60 min.
2. Strept. Viridens	24	90 min.
	72	90 min.
3. Diphtheria	24	75 min.
	72	75 min.
4. Staph. A.	24	75 min.
	72	90 min.
5. Pneumococcus II	24	60 min.
	72	90 min.
6. Meningococcus	24	45 min
	72	60 min.

INHALATION THERAPY IN INFLUENZA.

"These experiments showed that the different bacteria were killed by a concentration of .021 mg. of chlorin per liter, if the time of exposure was sufficient. Also that the more delicate organisms such as meningococcus was steril after a short time. There is good reason to believe that the organisms producing the common colds and influenza belong to this group of so called filterable virus and may even be more susceptible to the action of chlorin than the ordinary bacteria.

" The following table determined experimentally shows the limit within which chlorin may be safely inhaled:

Odor plainly perceived.....	.01 mg. per L.
Irritation of throat in 3 min....	.048 " " "
Tolerance for a few sec.....	.300 " " "
Lethal Concentration, 30 min....	3.00 " " "

" The effect of inhaling chlorin on the bacteria of the naso-pharynx was then tested. Swabs from the naso-pharynx were taken in the usual way and smeared over a surface of 3 sq. cm. on agar plates. The patient then inhaled chlorin of a concentration of approximately .02 mg. per L. for one hour. At the end of the time swabs were again passed over the same area and cultivated in a similar manner. About fifty cases were tested in this manner with practically uniform results. ABUNDANT GROWTHS WERE SECURED IN THE FIRST PLATES, WHILE THE SECOND CULTURE REMAINED STERIL OR AT MOST

INHALATION THERAPY IN INFLUENZA.

ONLY A FEW COLONIES. Further experiments showed that a treatment of one half hour did not diminish the growth materially; forty five minutes of exposure reduced the colony to about one half, while one hour exposures appeared sufficiently long to sterilize the tonsillar, post nasal and pharyngeal surfaces.

* The fact that bacteriocidal action of inhaled chlorin is so much greater than chlorin exposed on agar plates is undoubtedly to be explained by the film of moisture present on the mucous surfaces. Chlorin is an active germicide in aqueous solutions in concentrations of one to one million. As a concentration of .02 mg. per L. of air is approximately equivalent to ten parts per million, and as chlorin is readily soluble in water, it is evident that concentrations of one per million or higher may be reached in fluids bathing the respiratory tract over which chlorin is passing continuously for one hour. On the other hand chlorin would have little or no penetrating power and could hardly be expected to sterilize tonsillar tissue or other deep seated infections.

"Actual tests on patients in an air tight chamber 13' X 13' X 10', passing 42000 L. of a gas air mixture per minute with even distribution and concentration of .015 mg. per L.

INHALATION THERAPY IN INFLUENZA.

	Results from above experiment.			
	cases	cured	improved	no change
Coryza	388	288-74%	91 24%	9 2%
Acute Laryngitis	127	99- 78%	24- 19%	4 3%
Acute Bronchitis	241	192- 80%	47- 19%	2 .5%
Chronic Rhinitis	106	33- 31%	41- 38%	32-30%
Chronic Bronchitis	47	34- 72%	12- 25%	1- 2%
Whooping cough	9	8- 88%	1- 11%	0 0
Influenza	11	9- 81%	2- 19 %	0 0

"Conclusions:

Inhalations of chlorin of a concentration of .015 mg. per L. for one or mor hours have a distinctly curative value in common colds, influenza, whooping cough and other respiratory diseases in which the infecting organisms are located on the surface of the mucous membranes of the respiratory passages."

From such extensive experiments carried on in the U.S.Army by very competent men as no other could have been, except with military rule, one is apt to become overly enthused at the results, but let us not be too hasty to judge. However from these results one fact can be taken almost without question and that is that chlorine gas will

INHALATION THERAPY IN INFLUENZA.

kill bacteria within a relatively short time and in doses that are far below the minimum lethal dose. Likewise we see that chlorine gas is absorbed by the film of fluid covering the mucosa and thus becomes a better germicide than when just as a gas.

These same authors, after further research along this same line and again conducted under exacting conditions in the U.S. Army, write: (9)

" Estimating the tidal air at 500 cc per respiration, and the number of respirations per min. at 18, 540,000 C.C. of air is inhaled and exhaled during one hour. Since a concentration of .015 mg. per L. is approximately equal to 5 parts per million by volume and since practically no chlorine inhaled is exhaled, about 25 cc. of pure gaseous chlorine is absorbed in the respiratory tract during one hour of treatment. . The thin film of fluid bathing the respiratory tract if gathered together would hardly be in excess of 50cc. and hence during the course of the hour this film of fluid received gaseous chlorine which may be estimated at 5%. To be sure this amount of chlorine is not present at any one time, but it requires more imagination to suppose that this amount of chlorine has no antiseptic action.

" The action of any irritant, including chlorine on the capillaries is to cause a primary brief constriction followed by a much larger dilatation. Thus a

INHALATION THERAPY IN INFLUENZA.

hyperemia of the effected mucosa is produced, which as Bier showed many years ago is conducive to recovery. Not only is an increased blood supply unfavorable per se to the infecting organisms, but such dilatation of the capillaries is invariably followed by increase in the number of polymorphonuclear leukocytes, supplied to the parts that cling to the vessel walls and escape by diapedesis. Thus an increased number of phagocytes are brought to the infected mucous membranes."

In this same article (9) the authors describe an apparatus that will deliver the proper concentration of chlorine and is controlled automatically. It consists of a small electric motor in a box with a fan, the chlorine being generated by electrolysis from hydrochloric acid. The patient breaths this impregnated air by adjusting a funnel shaped bag to his face through which this air is passing. Its construction allows free passage of air at all time. They further discuss the contra indications for the use of chlorine, and list them as; hay fever, pneumonia, and tuberculosis of the lungs.

These men are very much enthused by their results, but "one swallow does not make a spring", so let us see what other men have found to be true with this so called ideal gas for inhalation.

On the chlorine death points for bacteria let us quote from Dr. Tooney, Geer, and Danford, (10) who added

INHALATION THERAPY IN INFLUENZA.

gaseous chlorine to distilled water. The cultures were washed, centrifuged and suspended in steril distilled water and then diluted to a suitable number of organisms. The exposure to chlorine was made in steril distilled water with 100 to 300 organisms to each of two flasks, one of which was to be used as a controll. From one flask one cc was plated and definate amount of the chlorine added. The amount of chlorine was tested in both flaska while one was used to make platings from at 8, 15, 30, 45, 60, seconds. These plates were incubated 48 hours.

Results

Typhoid group..... killed by .1 P.P.M. in 15 seconds.
 DiphtheriaKilled by .1 P.P.M. in 30 to 45 Sec.
 Strept. Sore Throat.Killed by .1 P.P.M. in 45 seconds.
 Pneumococcus..... .Killed by .2 P.P.M. in less than 1 min.

" From these results it will be seen that.... bacteria of the respiratory organs are killed in a few seconds with rather small doses of free chlorine. When exposed in a suspenstion containing no organic matter or other substances that react or obsorb chlorine, the chlorine death points are lower."

These experiments, although they do not include the organism of influenza, they do show that chlorine gas does have a definite action on the pathogenic bacteria of the respiratory tract, so why should it not also be effective against B.influenza. If this antiseptic action is true, just what clinical evidence do we have to bear this

INHALATION THERAPY IN INFLUENZA.

out? In reference to this we might again site the evidence of the gas workers during the War and the great epidemic at that time. However some men were rather sceptical about these results and so we find that Dr. Chas Baskerville, Head of the Chemistry Department, College of the city of New York, collected data from all the plants that he possibly could that were using or manufacturing chlorine. Please allow us to quote his article, (11): " Conclusions: Evidence has been collected from all the chlorine producing plants and many works and arsenals where chlorine was used. Predominating evidence favors conclusion that chlorine exerts a preventative influence against influenza. The evidence is not conclusive however as contrary data was obtained from some plants. The contra indication may possibly be harmonized on the basis of concentration, the more dilute, up to limits, the more effective. Small amounts of bromine in the air appear to prevent influenza completely. "

All these examples tend to point in one direction and that is that the causative agent of influenza does not thrive in the presence of chlorine gas. Although there is no record to back up the assertions, perhaps the experiences of the author of this paper during the World war may add to the list of experiences already listed. During the summer of 1918 the influenza epidemic reached the city of Washington D.C. At this time the war was at its height.

INHALATION THERAPY IN INFLUENZA.

Thousands of extra office workers and others were crowded into the city. Street railway cars were packed at all hours; as were theaters, churches, and other places. Several new army camps were located close by. Here indeed was one of the points of greatest concentration of human beings in the entire United States. Here indeed the epidemic was at its worst. At this time the author was a private in the Chemical Warfare Service, working at the American University for nine hours daily, riding the cars to and from the place, and living in the Northwest part of Washington. With the family of five that the author was staying was another soldier working in the same laboratory as the author.

During the day we were engaged in experimental work on the so called war gasses, testing masks, and in short being in close contact with chlorine several times during the day. The entire family with which we were staying was stricken within one week with the influenza. These people could not get nursing aid as all people were either afraid of the disease or already so engaged. This other soldier and myself cared for this family during their illness. Neither myself or the other man contracted the disease nor did a man in our laboratory or as far as can be recalled in the entire reservation of some 2000 men. Now the natural question cannot be answered as to whether or not the chlorine was responsible or was it due to the physical conditions. Certainly it is well worthy of thought.

INHALATION THERAPY IN INFLUENZA.

Since the World War, several extensive experiments have been carried on with the view that chlorine gas can be used as a preventative in epidemics of influenza. Perhaps the experiments of Harrison Hale, Head of Chemistry, University of Arkansas is a good example. (12) On Feb. 1, 1920 due to the extensive epidemic of influenza the the schools and churches of the town of Fayetteville, where the University of Arkansas is located, were ordered closed by the health authorities. The University remained open. Dr. Hale decided that this was an excellent time to give chlorine a try. Daily tests were started on Feb. second with volunteers from the university. They used a room 22 ft. by 15 ft. by 12ft. Chlorine was generated by action of sulphuric acid on sodium chloride. The concentration varied from .011 to .068 percent. Those receiving the treatment came for a period of five minutes. Eight hundred treatments were given to one hundred and eighty four individuals. None of these developed influenza except one that began to feel sick very soon after the treatment, so was considered as having the disease before his inhalation. At this same time 150 cases developed in the town, which was 40 per thousand. In conclusion he states in his paper that " Our results tend to show chlorine does act as a preventative of influenza".

Nor is it necessary that we confine our - selves to the action on humans. List. C.S. Williams and Lieu t.

INHALATION THERAPY IN INFLUENZA.

C.S. Woodruff, of the U.S. Army, working with an epidemic of influenza that broke out among the horses at the remount station at Ft. Hoyle Md. (14) in the Veterinary Bulletin of April 9, 1924 writes "... The following report covers the use of chlorine gas in the treatment of an outbreak of influenza among the animals at this station, and directed by a group of experts in the Medical Research of the Chemical Warfare Service.

" The initial cases were discovered on Feb. 8, and on Feb. 14, 41 cases were registered. This we believe included every animal in the command which disclosed any symptom of the disease..... At this time the first attempt at treatment was made.

" The entire 41 animals were placed in one of the organizations stables, crosstied with heads toward the alleway, all windows and doors were closed and the roof ventilators closed by means of wadded blankets. Chlorine from 75# cylinders was used, the gas escaping beneath the surface of water and being distributed by means of electric fans. No attempt to measure the concentration exactly was made during this treatment, but judging from the irritation produced, the concentration was approximately .019 mg. per L. The period of treatment was continued for one hour as planned in spite of the high humidity which caused the formation of hydrochloric acid.

" Immediately following the treatment

INHALATION THERAPY IN INFLUENZA.

the animals were returned to the stables of the various organizations with other horses. On Feb. 15, next day, the examination of all animals was as usual, and only three new cases were discovered. Of the forty-one exposed to the gas on the preceeding day, every one showed improvement. In some very marked, while in others only slight."

Acurate records were kept and from these which included five series of treatment, they conclude, " A study of the above will show that within four days a very wide epidemic of influenza was under way. Within three days after starting treatment no new cases were found, and improvement shown in those treated, and after eight days completely clear of the disease, This is remarkable when we consider that there were several thousand mounts at this post and all closely associated."

Harrison Hale again writes (16) on further tests carried on at the University of Arkansas in Feb. and March of 1923, 400 cases were treated. Average cases in the college dormitories was 133 per thousand students. Among those taking the preventative treatment, some of whom came only once to take the treatment, the rate was 44 cases per thousand, and for those that took the complete course only 13 per thousand. The course of treatment was similar to that already quoted. (12).

And again, P. David Shutz, M.D., New York, writing on General Inhalation (17) says, " In

INHALATION THERAPY IN INFLUENZA.

the inhalation treatment we have one more aid in overcoming disease. It does not prevent the ^{use of} well known methods of medication as it may be used by itself or with other methods. It is helpful, it is always under control. The stomach is spared, it is ideal for sanitarium and hospital. "

In reviewing the literature, in only one instant do we find a single statement where chlorine has been used that it has not proved a distinct value, and this was in the report of Dr. Basherville(10), who collected from all the factories of the U.S. data and one factory reported that on the first epidemic of 1918 their workers in chlorine were relatively free from the disease, but on the second epidemic later in the year these workers had a high rate.

During December and January of the past year(1932-33), there developed an epidemic of influenza in the state of Nebraska. It was typical of the disease and became wide spread. The author, with only simple measures, attempted to treat some of these cases, while on outcall and briefly gives the following case reports:

Case No. 1.

Mr. L.E.J. student, male, white, age 35, was well and in good health until December 15, 1932, when on arising in the morning he noted weakness, fullness of the head severe prostration, fever aching and a cough. These symptoms continued to develop and on the following day he had a fever of 102 degrees, a severe bronchitis and

INHALATION THERAPY IN INFLUENZA.

more prostration. At this time chlorine inhalation was started using three table spoonfuls of the commercial preparation known as Chlorox to a pint of water, obtaining the fumes of chlorine by heat and inhaling by means of a paper funnel to the mouth. Immediate relief was obtained from the bronchitis, and after several hours the patient felt better. On the following morning the fever was down to normal and the patient was up and about the following day. The inhalation treatment was given over a period of an hour. The fumes could be readily noticed, but there was no irritation, showing that the concentration was about .02 mg. per L.

In this same house lived the wife and two children of this man, as well as five other students. No attempt was made to prevent contact, but chloride of lime was placed in water and heated. About one fourth pound of this was used during two days. No further cases developed in the house at this time.

Case 11.

Leo G. age 6, schoolboy suddenly became ill one morning, complaining of aching, headach, and vomiting. Fever 103 degrees, discharge from nose, tonsils enlarged and inflamed. Mucous membranes of nose inflamed. Given inhalation of chlorine from Chlorox as above for three twenty minuite periods. Also aspirin grains five every four hours. Patient seen following morning fever 99, very little discharge and feeling improved. Chlorinated lime was heated every hour during time boy was ill. Mother, father, one

INHALATION THERAPY IN INFLUENZA.

brother, one sister and an uncle living in the same house, none of whom contracted the disease.

Case III and IV.

Leonard D. and L. J. both men in their late twenties, white, and living in the same home. Both had the influenza in the middle of November 1932. On Jan. 9, 1933 both patients developed "colds in the head", with obstructed nostrils, discharging, and fullness of the head feeling. Neither ran a fever, there was no aching, there was no throat involvement. Both patients were up and felt fairly good. Inhalations of chlorine was given each from Chlorox in heated water and inhaled with tubes to the mouth. Treatments were given for twenty minutes three times during the first day. There was no change, except possibly an increase of the discharge from the nose. The condition continued in each case for several days with slight decreasing until both were well. Chlorine in these cases had no effect. The diagnosis here was an upper respiratory infection, and not influenza.

These cases point out two facts. First that improvement is shown in the true form of influenza when treated with chlorine, and second, that with the common head cold there probably is not enough of the gas absorbed by the membranes to do any good. Also the fact that other members of the household in the first two cases were protected from the disease, shows that chlorine has a

INHALATION THERAPY IN INFLUENZA.

protective action against the infection.

With the foregoing experiments, findings, theories, and cases, let us see where the use of chlorine now stands as given by our standard texts. As far as can be determined by a review of a number of the best texts on medicine written by such men as Tice, Tiddy, Osler, etc., they have nothing to say relative to the use of Chlorine in any disease. However in the "Technic of Medication", written by Dr. Fantus of Chicago, and published by the American Medical Association in the 1930 edition in discussion of gas inhalation says; "Therapeutic chlorine has of late acquired such notoriety that it may deserve special consideration. Although sterilization of the mucous surfaces is not achieved, there can be no doubt that many bacteria are killed. There are, however, other actions that may be of even more importance in securing therapeutic results. One of the first actions is to secure an increase in nasal and bronchial secretions, causing productive coughing and blowing of the nose, and this cleans the membranes. The action of any irritant, like chlorine, on the capillaries, is to cause a brief constriction, followed by a much longer dilatation. Thus a hyperemia of the affected mucous membranes is produced which may be conducive to recovery." From this we see that very few are accepting chlorine as a means of medication, but that the American Medical Association recognizes that there is a possibility of it having a value.

INHALATION THERAPY IN INFLUENZA.

Before we proceed with the consideration of some of the other agents used in inhalation therapy for influenza let us summarize the standing of chlorine.

1. During the World War and since, workers in contact with chlorine gas have been repeatedly shown to be relatively immune to influenza, especially brought out on a large scale during the war.
2. Chlorine gas has been shown by experimentation of several men to have a definite inhibiting factor on the bacteria of the mucosa of the respiratory tract(12), and to be a germicidal at low dilution, .015 mg. per liter, which tends to sterilize the respiratory tract on exposures of one hour or more, and without injurious effects.
3. Dr. Hale, at the University of Arkansas was able to show on two occasions that chlorine used as a prophylaxis was of very definite value.
4. Animal experimentation has shown excellent results in animal influenza(14).
5. Outcall patients treated wfor influenza with chlorine were definitely Benefited and families were protected from contracting the disease.
6. That in the common head cold, little or no value is received from the use of chlorine.

INHALATION THERAPY IN INFLUENZA.

Let us now briefly consider some of the other gases used to combat influenza. Iodine and bromine are very similiar to chlorine in all their properties and their actions are equally good on bacteria, but due to the expense and the fact that, ~~that~~ has been very little commercial use made of either on a large scale, conclusive evidence is not at hand. Iodine crystalizes at a lower temperature than does either of the other halogens, and for this reason can be used where a thin deposit over the mucous membranes is desired. Very little experimentation has been done with Iodine but all that has been reported has been favorable. The most recent and outstanding work reported was that done by Dr. Chas. Sajous and reported in the New York Medical Journal in 1920. (18).

Dr. Sajous contends that sterilization of the respiratory tract is produced most effciently by stimulating the lymphoid tissue of the nasopharyngeal area and the mucosa of the entire tract to the bronchioles, with iodine fumes deeply inhaled, which beside promote phagocytosis and sentisitize the B. influenza to the action of the defensive cells. He believes that by placing 3 grains between two layers of cotton pads and inhaling the fumes that one will receive enough to stimulate the lymphatic tissue and to tend to sterilize the tract. He also has used effectively a small inhaler. Later he writes (22) concerning the effect of iodine on the endocrines and indirectly on the phagocytosis.

INHALATION THERAPY IN INFLUENZA.

Cohen, in his book on inhalation (19) published in the early part of the last half of last century cites numerous cases where iodine fumes have been used to cure coryza and phthisis. Of course at this time he knew nothing of B. influenza. His case follows.

Case. V.

M. Luc, an army surgeon, seized with bad coryza, attenuated by fever, cephalgia, and excessive secretion, determined upon trying the effect of inhalation of iodine vapor. The coryza first appeared at 9A.M. and inhalations were commenced at 3P.M. They were repeated every 3 minutes for one minute during one hour. The headache was first relieved, secretion stopped and by six o'clock all traces had disappeared. The inhalation was by means of a bottle of Tinct. of iodine warmed by the hand and placed to the nostril.

Although little work has been done with Iodine in the treatment of influenza, that that has been reported is favorable, and it further seems logical that since chlorine has been tested extensively and proved valuable, that all the halogens would likewise prove a benefit in this disease.

Many other substances have in the past been used for inhalation, including sulphur dioxide, nitrous oxide, volatile oils, etc. but none have stood the test of time. At the present Tincture of Benzoin Compound, inhaled from heated water, is being used rather extensively.

INHALATION THERAPY IN INFLUENZA.

With this substance the question naturally arises, is this substance when used with steam the cause of the relief, or would the steam alone do the same thing. In discussing benzoin in his text on Therapeutics (20), ^{Bastide} states that it is employed for inhalation in whooping cough, laryngitis, nasopharyngitis, bronchitis, and pneumonia, one teaspoonful being added to boiling water and the fumes inhaled. It is doubtful if there is any antiseptic action.

Bernard Fanlus, writing for the American Medical Association, (21) says, " Steam inhalations are grateful in acute inflammatory conditions of the respiratory passages, they soften the mucosa, favor expectoration, diminish irritation, and lessen cough" and later " Inhalation of steam acts mainly on mucosa by warmth and moisture, which is relaxing and soothing..... A popular addition to steam inhalation for acute laryngitis is tincture of benzoin, a teaspoonful to one half pitcherful of warm water, which essentially flavors the steam. We can hardly speak of this as medication from so small an amount used".

From these we can readily see that although Tincture of Benzoin, steam, etc are used for their immediate effect on the mucosa of the respiratory passages, they have little or no effect on the bacteria of the tract, nor do they in any way counteract the toxins of the disease of influenza. For this reason we can state that as far as influenza is concerned, the treatment by steam inhalation, with tincture of benzoin, etc., is only temporary and palliative and does

INHALATION THERAPY IN INFLUENZA.

not warrant a lengthy discussion in this paper. However for the sake of completion two cases will be cited.

Case VI.

Mrs. M., age 38, white, married, housewife, in October and first part of November, 1932 had severe diphtheria. Anti-toxin was given, patient recovered without complications. On Dec. 15. Outcall student called and found patient in bed, complaining of aching of joints, headach, cough, and general prostration. Case diagnosed as influenza after finding fever of 101, pulse of 90 and respirations of 20. She was given aspirin grains V every two hours. Patient was seen the following day and she showed no improvement. At this time she also complained of sore throat and severe coughing. A culture was taken, which proved to be streptococcus and Elixer of terpine hydrate with codein~~s~~, teaspoonful was given every two hours. The patient was seen again the following day and no improvement was noted. The fever now was 103, pulse 1200, and respirations 20. The lungs were clear, but the throat inflam ed, and cough more severe. Patient was then given given Tinct. of Benzoin Comp. teaspoonful to pint of hot water and fumes inhaled. Immediate relief of throat irritation was noted, but cough continued. For the following several days the inhalations gave relief, but Camphorated Tinct. of Opii, teaspoonful every two hours, was required to relieve the cough. Complications of Otitis Media and Rheumatic fever developed later, but the point

INHALATION THERAPY IN INFLUENZA.

here is that the inhalations of steam with Tinct. of Benzoin Compound gave relief, but did not stop or in any way change the course of the disease.

Case VII.

Mr. Aberhanson, male, age 45, white, married, came to the University Hospital for the second time Dec. 15th. 1932, complaining of deformity and tenderness over the lower lumbar region. Three months previous he had injured his spine, which had been deformed for the past twenty years. Three months ago he was placed in a cast, and now desired a cast change. The day after entrance he began to have nasal irritation, discharge, cough and fever of 100 degrees, with aching of the muscles of the extremities and joints all over the body. This was diagnosed as influenza and he was given Tincture of Benzoin Compound inhalations every two hours for thirty-six hours, -lasting each time for fifteen minutes. A teaspoon of the compound was used to a pint of water and it heated and the fumes inhaled. At the completion of the course the patient had completely recovered.

In the above case we cannot say just what caused his immediate recovery. It is very possible that he had a good resistance, or it may be that the steam alone would have been just as good. However the general opinion of the medical men that use this method of treatment of influenza is that in addition to the relief that the inhalations give them, they also receive a benefit.

INHALATION THERAPY IN INFLUENZA.

Since we do consider that at least two of the gases used are of value in the treatment of influenza, then it becomes necessary to consider a mechanism by which we can administer scientifically. As previously noted the dosage of chlorine is between .015 and .02 mg per l. (8), it can be detected at .02 mg per l., and becomes irritating at .04 mg per l. However the lethal dose is much higher, being 3.mg per l. for one half hour. The figures then show a wide range of concentration, in fact few powerful drugs with such a wide margin can be found.

The first experiments described by Veeder(8) were in closed rooms, and perhaps this has been the method of choice, but for a practicing physician such an arrangement would not prove practical. However it is conceivable that small containers of liquid chlorine could be prepared and so used in the homes of patients, and by detection of odor protect the patient from an overdose. Another means to get chlorine is the heating of chloride of lime, driving off the fumes. The only means of gauging dosage here would be by odor. Still another method is to moisten a handkerchief with a water solution of chlorine. For example since water absorbs $2\frac{1}{2}$ times its volume 10 cc would absorb 25cc of the gas. This would be .08gm or 80mg which would give 4000 l. of air .02 mg of chlorine. Since the average breathe is less than $\frac{1}{2}$ liter this amount would be sufficient for 8000 inhalations, certainly enough

INHALATION THERAPY IN INFLUENZA.

to last one half an hour even with the great loss by diffusion.

On the other hand when there are epidemics and people are congregated in schools, churches, and theaters, by means of ventilation of concentrations of unnoticable amounts could be easily given. Does it not seem logical that by such means large epidemics could be brought under control. At least it seems worthy of a try since nothing has given satisfaction as yet.

Summary.

In this paper an attempt has been made to show the value of the treatment of influenza by inhalation of various substances and brings out the following points;

1. Earliest records of medication for upper respiratory tract infections, show that inhalation was one method.
2. The workers in chlorine gas during the world War and since have been shown to have been relatively free from influenza.
3. Experiments at the University of Arkansas on students, and in the U.S. Army on horses, show that epidemics can be controlled by use of chlorine gas.
4. Cases show improvement on use of chlorine gas and also on use of Tincture of Benzoin Compound inhaled.
5. Iodine fumes have been shown to have a value in the treatment of influenza.

INHALATION THERAPY IN INFLUENZA.

6. It is possible to control dosage of chlorine by simple methods and tests, that it is easy to obtain, and to administer.
7. Chlorine gas is at least worthy of a trial in the treatment of individual cases of influenza, and the control of large epidemics.

INHALATION THERAPY IN INFLUENZA.

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