Inhalation of Penicillin Dust

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In view of the favorable reports in recent literature on the inhalation of therapeutic agents, especially penicillin, and because of the many possibilities of the method, we have attempted to produce even greater and more protracted topical effectiveness by a method which involves the inhalation of the fine dust aerosol particles. This method has simplified the mechanics of aerosol therapy, thus expanding its scope more readily for office and home treatment.

Apparatus used for inhalation therapy in the past has been based on the delivery of the aerosol vapor under positive pressure of oxygen or air by means of a hand bulb or oxygen tank and gauge. The principle utilized in the new method is based on the negative pressure created by normal breathing during the inspiratory phase. Inhaling penicillin dust in this manner is more physiological and permits a more even and perhaps a wider distribution of medicament throughout the respiratory tract. The patient is not required to manipulate an exhaling valve during the expiration phase, and the cumbersome equipment of oxygen tank and gauge is unnecessary. The inhalation of the dust particles yields a greater effect than the vapor, because there is greater concentration of penicillin per unit area and because the penicillin must go into solution while in contact with mucous membrane before it can be absorbed.

The penicillin dust used in this study was crystalline sodium penicillin[1] processed to # 50–100-mesh particles. This was found to be less hydroscopic than the sodium penicillin salt and could be stored at room temperature, without losing its potency, more readily than the penicillin liquid which was used as the nebulin for the vapor method.

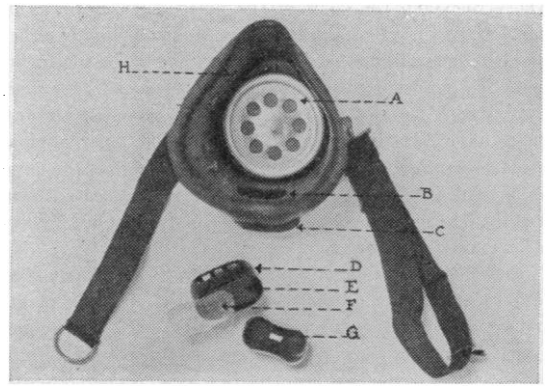

FIG. 1

The apparatus[2] represents numerous modifications of the original device, since penicillin dust possesses certain qualities which do not lend themselves to ordinary techniques. Penicillin is highly electrostatic, easily adhering to surface areas. In addition, it is hydroscopic and goes into solution readily. The technique finally developed allows the penicillin to be easily released as a dust and at the same time precludes the moisture of exhalation from dissolving the dust.

[1] The penicillin for this study was processed by, and furnished through the courtesy of, the Abbott Laboratories, North Chicago, Illinois.

[2] The present mask was kindly fabricated by the Chicago Eye Shield Company, according to specifications of one of the authors (Krasno).

The device (Fig. 1) consists of an oronasal facepiece which is held on by an elastic headband. The front of the mask contains a large exhalation valve (A) in direct line with the stream of exhaled air. The portion of the mask about the chin contains a rubber sleeve (C) fitted with an inhalation valve (B), which directs the inhaled air in a plane at right angles to the stream of exhaled air. This valve contains a special detachable metal chamber (D) containing the penicillin dust. The penicillin chamber is fixed with a fine wire-mesh platform (E), which is covered with a finely perforated cellophane paper (F). It has been found that penicillin dust is essentially nonadherent to cellophane. The dust is placed on top of this platform. During the inhalation, air drawn through the perforations of the penicillin chamber releases the dust, which passes through the inhalation valve and into the respiratory passages. The dust is protected from the moisture of exhalation by the one-way inhalation valve and by the fact that the exhaled air is conducted through a plane at right angles to the inhaled air. A small hole (H) about 6 mm. in diameter, on top of the mask just above the end of the nose, allows a substantial amount of air to be drawn in easily and avoids any feeling of "resistance" on inspiration. This supplementary inlet for air is also necessary to keep the amount of penicillin dust inhaled in optimum quantities.

This preliminary work, begun in October 1946 and extended through February 1947, comprises studies of 68 subjects (38 males and 30 females). Four experimental subjects (including the authors) inhaled the penicillin dust in varying proportions in order to detect any untoward effects or irritating properties. Fifty-five patients had upper respiratory infections: 46, symptoms of the "common cold"; 4, chronic nasopharyngitis; 3, chronic sinusitis; and 2, laryngotracheal bronchitis. Nine patients had lower respiratory tract infections: 6, bronchiectasia; 2, chronic bronchitis; and 1, bronchial asthma.

All patients received 100,000 units of penicillin dust by inhalation for 20 minutes three times a day. Throat and nose cultures prior to first treatment and daily cultures thereafter were taken on all hospitalized patients. Sputum cultures were taken in cases of bronchiectasia. Single blood-level determinations were made on various patients in this group. The duration of therapy was determined clinically and bacteriologically for each case.

The inhalation of dry penicillin quickly causes the reduction or disappearance of gram-positive bacteria and, in the massive doses used, seems to effect some of the gram-negative bacteria. This is accomplished readily, often in one treatment. Penicillinase has been added to the laboratory specimens without changing the bacteriologic results.

The clinical results were based on the patient's subjective improvement, the opinion of attending doctor, and the impressions of the authors. A study of the data of the 6 bronchiectatic patients revealed less cough and secretion on dismissal. The patient with bronchial asthma showed marked improvement, the infectious condition almost completely disappearing, although the allergy persisted to a decreased degree. The 2 patients with chronic bronchitis showed a moderate improvement. The symptoms of over 70 per cent of those patients with acute conditions of the upper respiratory tract cleared up markedly, in many instances after only one or two treatments. Seventy-five per cent of the patients with upper respiratory tract infections had only one treatment. Six had two inhala-

tions, and three had four treatments. The remainder had 4–18 inhalations, the highest number being reserved for the chronic bronchitis and chronic sinusitis. The range of duration of treatments for the patients with diseases of the lower respiratory tract was 10–18 treatments, administered in from 4 to 6 days.

It is singular that up to the present time no sensitivity reaction to the penicillin has been noted. With the vapor aerosol method, transient fever, dyspnea, or dermatitis has occurred in 4–20 per cent of the cases, depending upon the concentration of the drug used.

Penicillin assays of urine and blood were determined by the Flemming modification of the Wright slide cell technique. Values ranged from .03 to 1.92 units/cc. Blood-level curves would indicate a slow absorption, the maximum level being obtained 3-3½ hours after the inhalation.

This new method of administering penicillin appears to offer more effectiveness than other aerosol methods in ridding the upper respiratory tract of gram-positive bacteria. Appreciable blood levels would indicate the protracted effective absorption offered by this method, and the possible use of inhalation treatment for systemic conditions other than those of the respiratory tract. Although the method would appear to have a definite value in initiating the process of ridding the respiratory tract of pathogens, it may be necessary to supplement the process with other medicaments. In other instances its value may be adjunctive rather than primary.

Formaldehyde in Plant Collecting

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Recently Schultes has published an intelligent and much-needed discussion of the use of formaldehyde in the preparation of herbarium specimens, recommending its use to prevent disarticulation, molding, and decay when immediate drying is impractical (*Rev. Fac. Agron.* (Medellín, Colombia), 1946, **6,** 46-52; *Rhodora*, 1947, **49,** 54-60). His development of this method resulted from a conversation with Paul H. Allen, who has for some years employed alcohol and formaldehyde in the preparation of his excellent specimens of Panamanian plants.

Since I was present at the conversation referred to and have independently developed a somewhat different formaldehyde technique, it seems worth while to supplement Schultes' papers with an account of some of the possible variations and certain minor drawbacks, as well as to publish the method where it will reach a wider audience.

Allen's original method was to spray the freshly pressed specimens, using a common Flit gun, with a mixture of 70 per cent alcohol and enough formaldehyde to give it a strong odor. I tried this, but found that the specimens still molded and deteriorated to a certain extent, especially when final drying was delayed for a considerable time. Spraying with a Flit gun had the additional disadvantage of practically pickling the collector as well as his plants.

Much experimenting finally resulted in a mixture that seems to work under most conditions and has one big advantage over the straight formaldehyde-water solution advocated by Schultes. This mixture consists of approximately 1 part each of concentrated (40 per cent) formaldehyde, 95 per cent alcohol and water. If 70 per cent alcohol only is available, as in many small towns, I commonly use 1 part formaldehyde and 2 parts alcohol. The alcohol gives the mixture much better wetting properties than those of a straight water solution. Not only does it readily wet even waxy leaves and those with a prominent coating of hair or scales, but it also penetrates much more quickly and thoroughly.

After I had suffered an atmosphere of formaldehyde spray from a Flit gun for several trips, Norman C. Fassett suggested applying it with a small paint brush. This method was much more effective and lacked the unpleasant features. I had already discarded the dipping method as rather ineffective and clumsy at best, and completely unsuited to plants that tended to be limp. Of the three methods, use of a soft, 2-inch paint brush is by far the most satisfactory. H. H. Bartlett (in a letter) has suggested a rather different method which consists essentially of tying a fair-sized bundle of specimens together in folded newspapers, standing them on end, and pouring a sufficient amount of the solution described above into the bundle to wet it.

It is usually suggested that after the application of formaldehyde the bundles of specimens be wrapped in oilcloth, waxed paper, pliofilm, double canvas, or other material to retard evaporation. If specimens are to be mailed, this is doubtless necessary, since otherwise they would probably not be accepted by postal authorities. However, I have found that there are no evident bad effects if they are left simply wrapped in either wrapping paper or several thicknesses of newsprint. The solution largely evaporates off after killing the tissues of the plants as well as the spores of such fungi as are likely to cause trouble. The dead tissues lose their water much more readily than do living ones, and drying goes on to a certain extent even in the bundles. Subsequent drying over heat also takes place much more rapidly for this same reason.

Those to whom the color of the finished specimens is of importance will not find any of the methods employing either formaldehyde or alcohol very satisfactory, since the specimens are practically always either discolored or bleached. However, few collections from wet tropical regions, prepared by any method, have been preserved in anything like their original colors; furthermore, a few years in the atmosphere of the large cities in which our herbaria are unfortunately located soon makes the original color unimportant. Colors, if of any importance, should always be recorded on the labels.

I regard the formaldehyde method, not as something that should supersede the ordinary method of drying the plants over heat after a few hours in a tight press, but as a supplementary method for use in places where ordinary drying is difficult and with material that is not satisfactorily prepared by the ordinary methods. Leaving the material in a wet condition for any considerable length of time cannot have a good effect and probably results in a certain amount of brittleness. However as Schultes very effectively points out, many groups of plants that make traditionally bad specimens give very gratifying results with this technique. One has only to look into the covers of almost any genus of tropical mimosoid legumes to be convinced that improved methods are in order. Certain of these which were not dried for three weeks after gathering show no tendency whatever to lose their leaves. The formaldehyde apparently completely and instantaneously stops the formation of abscission layers. It might be well to try this technique on such conifers as *Tsuga* and *Picea* and on the almost mature cones of