and left kidney were removed, dissected free of fat, and weighed on a torsion balance. Total adrenal cholesterol was determined on paired adrenals from single animals by the Schoenheimer-Sperry method as modified by Sperry (*8*). Appropriate nonirradiated controls were sacrificed along with the irradiated rats. The completeness of hypophysectomy was checked at sacrifice.

The per cent changes in organ weights and in adrenal cholesterol after total-body X radiation of intact and hypophysectomized rats are indicated in Fig. 1. In calculating the per cent change for both groups of rats, comparison was made with the appropriate nonirradiated controls sacrificed at the same time. A summary of the data is presented in Table 1.

It will be noted that the adrenal response to X irradiation was prevented by hypophysectomy. The small changes seen in adrenal cholesterol and adrenal weight at 3 hrs and 4 days were not statistically significant. Furthermore, the terminal adrenal changes which are observed in intact animals were not seen in two hypophysectomized irradiated rats sacrificed in a moribund condition. Statistically significant changes identical with those reported previously were observed in the unoperated irradiated animals.[1]

Pituitary ablation did not alter the degree or time course of the splenic and thymic involution resulting from X irradiation. Kidney, which was weighed as a control, did not change appreciably in either group after irradiation. The small increase noted in kidney weight calculated on the basis of body weight may be accounted for by the observed decrease in body weight.

Hypophysectomy appeared to potentiate X-ray toxicity. Forty-five per cent of 20 hypophysectomized irradiated rats died 3–4 days after the exposure, whereas none of the intact irradiated animals succumbed at this time. Deaths in the latter group began at 6 days, and there was only a 30% mortality by 16 days after the irradiation. There were no deaths in the nonirradiated hypophysectomized group.

Atrophy of the adrenals was evident in the hypophysectomized group at the time of irradiation, 7 days after the operation (22% decrease in adrenal weight calculated on the basis of body weight). At this time the concentration of cholesterol in the gland was increased above that observed in the intact rat. However, the total cholesterol content of the adrenals was almost equivalent in both groups. Adrenal weight was decreased still further and the cholesterol concentration was reduced in the animals sacrificed 11 and 15 days after the operation. Rather similar changes in adrenal cholesterol in hypophysectomized rats have been described by Sayers, *et al.* (*6*), and Tyslowitz has reported a gradual fall in adrenal ascorbic acid after removal of the pituitary (*11*).

[1] It should be pointed out that the concentration of cholesterol in the adrenals of the intact nonirradiated rats was low in comparison with the many determinations made by us previously on other shipments of rats. We cannot account for this. The control rats were sacrificed at different intervals during the course of the experiment, and no gross evidence of disease was found.

There is evidence which suggests that the response of the adrenal cortex to the pituitary tropic hormone is dependent upon a certain level of activity of the cortical cells and diminishes with time after hypophysectomy (*6*). It remains to be determined, therefore, whether the adrenal cortex in the 7-day hypophysectomized rat does not respond to X radiation because it is generally less sensitive, owing to the removal of pituitary influence, or because its stimulation after irradiation is mediated solely by the adrenotropic hormone. In order to evaluate this point we plan to study the adrenal response in animals irradiated 2–3 days after hypophysectomy, before appreciable glandular atrophy and decreased sensitivity are evident. Nevertheless, we may conclude from the present experiments that hypophysectomy performed one week prior to irradiation prevents the intermediate and terminal as well as the initial adrenal changes resulting from exposure to X-rays. Under these conditions, the extent of the splenic and thymic involution is not altered, although toxicity appears to be enhanced.

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The Inhalation of Norisodrine Sulfate Dust

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There have been many favorable reports on the use of Norisodrine Sulfate as a bronchodilator. This drug has been known in the European literature as Aleudrin and has been chemically identified as 1-(3′,4′-dihydroxyphenyl)-2-isopropylaminoethanol. Its chief clinical use has been in the symptomatic treatment of asthmatic conditions. A considerable number of animal and human experiments have been carried out in relation to the properties of this drug. There is general agreement in the literature that (1) it is more effective than epinephrine in overcoming bronchiospasm induced experimentally; (2) it may cause vasodilation with a consequent fall in blood pressure; (3) it may cause an increase in the

coronary output; (4) it may cause tachycardia, dizziness, and nausea if given in large doses subcutaneously; (5) there is very little evidence of addiction; (6) it has proven effective in asthmatic patients who could not obtain relief with epinephrine, theophylline, or ephedrine; (7) there is no evidence of "fastness" for this drug; (8) administration by inhalation appears to be the route of choice; (9) it is effective when given orally, sublingually, subcutaneously, and by inhalation.

Previous reports (*5–7*) have indicated that the inhalation of penicillin in the form of a dust is a very practical and efficient means of introducing a drug into the respiratory tract. The inhalation of penicillin as a dust, it is

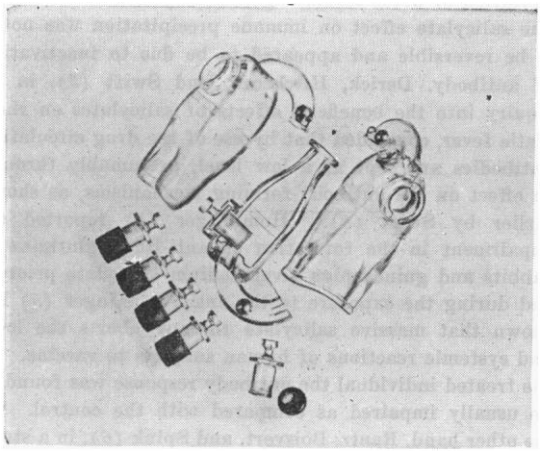

FIG. 1

pointed out, has a number of mechanical and therapeutic advantages, including simplicity of equipment and administration, maximum concentration of drug per unit area within the respiratory tract, slow absorption of the drug into the systemic circulation, lack of necessity for dilution of the drug, and use of a pocket-size apparatus which may be kept on one's person for instantaneous use at all times; in addition, no oxygen or nebulizer is required to aerosolize medicament. It was believed that these advantages could apply to Norisodrine if used in dust form and at the same time widen the application of a drug with such useful clinical properties.

The apparatus consists of a molded plastic discharge chamber with a detachable mouthpiece (Fig. 1). The Norisodrine dust is contained in a small plastic cartridge, the bottom of which is fitted with a fine-mesh wire screen through which the Norisodrine dust is released. The upper rim of the cartridge exhibits two small flanges which fit into a groove and allow locking the cartridge in position in the discharge chamber. The distal end of this chamber is formed into a curved tube runway containing an aluminum ball. On inhalation, the aluminum ball is rapidly drawn up the runway until it strikes the cartridge containing the Norisodrine dust; the impact causes the release of a small amount of the dust into the discharge chamber. The upper end of the runway is grooved so that the air to be inspired can bypass the aluminum ball after it strikes the cartridge. The inspired air, as it bypasses the ball, carries the released dust into the respiratory passages. Thus, with each respiration a small but uniform amount of dust enters the respiratory passages until the total dose has been consumed; this is usually accomplished within 3–5 min.

In view of some mild, but definite, untoward reactions observed with the use of Norisodrine Sulfate in aqueous solution, the response of 6 normal subjects to the inhalation of this drug in dust form was studied. Each subject inhaled the amount of dust (3–5 mg) released during one normal inspiration. Pulse rate, blood pressure, and subjective reports were recorded following inhalation. Pulse and blood pressure readings were taken immediately and at 2-min intervals.

A group of 24 asthmatic patients with histories ranging from 3 to 28 years were studied. These patients were apparently not satisfactorily controlled with the usual drugs such as epinephrine, either by injection or by inhalation, aminophylline, iodides, ephedrine, pyribenzamine, or Benadryl. Seven patients were classified as having bronchial asthma with bronchitis, and 17 as having bronchial asthma of the allergic type. All patients were taken off their previous medication and given a test dose of Norisodrine dust[1] to determine the presence of any unusual sensitivity or untoward reactions. The test dose consisted of the amount of drug released by one inspiration. The patients were then instructed to take one whiff of the Norisodrine dust during an impending attack of asthma. This was to be repeated within ½–1 hr as necessary.

It soon became apparent that, on the basis of the clinical response to the inhalation of Norisodrine dust, the patients fell into two basic groups. One group could be completely and satisfactorily controlled by the exclusive use of the Norisodrine dust. The second group could be controlled by Norisodrine only when either aminophylline and iodides and/or an antihistaminic were being used daily. In the latter group it would appear as if the "threshold" of bronchospasm was lowered by the use of this additional medication, thus making Norisodrine more effective in controlling the asthmatic paroxysm. It should be pointed out, however, that these same drugs did not prevent the occurrence of asthmatic attacks but rather made it possible for these paroxysms to yield to the Norisodrine. Response to inhalation of Norisodrine dust was evaluated in terms of how completely impending asthmatic attacks were aborted or the extent to which the actual attack was dissolved. Sixteen patients were controlled by the inhalation of the Norisodrine dust alone. Seven of these had an associated bronchitis and were given penicillin dust inhalation subsequently, although the asthmatic paroxysms were previously controlled with Norisodrine alone. The penicillin dust therapy in this type of case greatly reduced the need for the Norisodrine. Eight patients required aminophylline and iodides and/or an antihistaminic in addition to the Norisodrine. These patients received the

[1] The Norisodrine dust was processed and furnished through the courtesy of the Abbott Laboratories, North Chicago, Illinois.

aminophylline by mouth daily. In one instance the patient could not be controlled with Norisodrine plus additional medication, but she did not respond to epinephrine either.[2] Of the 8 patients requiring medication in addition to Norisodrine, 1 patient did not respond to Norisodrine at all, 4 patients gave a good response, and 3 responded satisfactorily. The results in these patients requiring additional medication might have been anticipated, since they did not respond to Norisodrine alone. In those instances where no additional therapy was required the response to Norisodrine was satisfactory in all instances. In normal subjects the inhalation of a single dose of Norisodrine dust did not appear to influence the pulse rate or the blood pressure. No discomforting symptoms were reported by this group. Four asthmatic patients reported symptoms of dizziness and/or palpitation after the inhalation of the Norisodrine dust. These reactions were not alarming and disappeared in all instances within 10 min. The blood pressure changes in these 4 patients showed a drop in systolic pressure ranging from 3 to 20 mm of mercury. In this group of 4 patients the pulse rate showed an increase ranging from 4 to 12 beats/min. There were no reactions in the remaining 20 patients. One patient, treated while in status asthmaticus, required a considerable amount of Norisodrine to maintain comfort. Since she tolerated the drug exceptionally well, she was permitted to inhale the Norisodrine dust freely. This patient consumed as much as 100 mg of the drug daily without any untoward reactions whatsoever. None of the patients, including the latter, has so far shown any tendency of fastness toward this drug. This group of patients has been using Norisodrine dust for 10 months.

On the basis of the clinical results obtained with the inhalation of Norisodrine dust, either alone or in addition to other medication, it would appear that this drug has a definite place in the symptomatic treatment of asthmatic diseases. It should be useful in many instances of bronchospasms of a nonasthmatic origin. It can apparently be inhaled in dust form with a wide margin of safety.

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[2] This patient appeared to be resistant to all forms of therapy. Her attacks would persist for 3–5 days and then stop spontaneously.

Inhibition of Anaphylactic Shock by Acetylsalicylic Acid

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Data have recently accumulated which indicate an effect on antigen-antibody reactions of members of the salicylate group. Coburn and Kapp (*2*) reported that salicylates modify the precipitation of normal rabbit serum protein by tungsten and partly inhibit the precipitation of horse serum euglobulin by rabbit antiserum. The salicylate effect on immune precipitation was noted to be reversible and appeared to be due to inactivation of antibody. Derick, Hitchcock, and Swift (*3*), in an inquiry into the beneficial effects of salicylates on rheumatic fever, concluded that by use of the drug circulating antibodies are kept at a low level, presumably through an effect on the antibody-forming mechanisms, as shown earlier by Swift (*8*). Homburger (*4*) reported the impairment in the formation of anti-Rh agglutinins in rabbits and guinea pigs given sodium salicylate prior to and during the exposure to the antigen. Jager (*5*) has shown that massive salicylate therapy aborts the local and systemic reactions of human subjects to vaccine. In the treated individual the antibody response was found to be usually impaired as compared with the control. On the other hand, Rantz, Boisvert, and Spink (*6*), in a study on the effects of salicylates, sulfa compounds, and penicillin on antibody response to streptococcal (sore throat) infection, found no significant alteration of antibody response in those individuals treated, rather conservatively, with sodium salicylate. In a more recent paper, Sullivan, Parker, and Hibbert (*7*) report protection of rabbits against arteritis, apparently through interference with antigen-antibody reaction.

The experiments reported below were designed to clarify the protection offered by these drugs to anaphylactic shock and were related to a study of their effects on neurotropic virus disease.

Young adult (ca. 2-kg) rabbits were sensitized to egg albumin by injection of egg white on alternate days in the following doses: 1 cc, i.v.; 0.5 cc, i.v.; 1 cc, i.m. Acetylsalicylic acid was used as the drug and was administered orally as 5-grain (0.324-gm) tablets. The animals were restrained in a stock-like box and the tablets inserted, with long forceps, well back in the mouth. A squirt of water from a syringe followed the tablet and speeded its dissolution. Care was taken to replace any drug which was spit out.

Twenty-one rabbits were sensitized on March 24, 1947. At 2:00 P.M. on April 9, 11 were given 5 grains of acetylsalicylic acid orally. This was repeated at 10:00 P.M. the same day and at 10:00 A.M. on April 10. One hour later, these animals, together with the remaining 10 for controls, were injected intravenously with 0.6 cc of egg white. Nine of the 11 experimentals (Table 1) showed no shock, the remaining 2 showing moderate and