

THE ASTHMA-SUPPRESSIVE ACTION OF POTASSIUM IODIDE

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OSLER, although reputed to be a therapeutic nihilist, held the view that "in preventing the recurrence of the attacks [of bronchial asthma] there is no remedy so useful as iodide of potassium, which sometimes acts like a specific."¹ Cooke² also remarked that this drug is "occasionally surprisingly effective in asthma." Sheldon, Lovell, and Mathews more recently stated that "in addition to their expectorant action iodides sometimes seem to bring about a prolonged remission . . . though the explanation for this phenomenon is obscure."³ This report presents ten cases which illustrate this exceptional and often striking asthma-suppressive action of potassium iodide, still not widely recognized, and little utilized (Table I). Five cases are described in more detail.

CASE REPORTS

Case 1.—E. R., a 34-year-old man, first had bronchial asthma and atopic dermatitis at the age of 2 years. Later he had pollinosis and nasal polyps. At 25, despite many years of multiple desensitization, his previously intermittent asthma became increasingly intractable, and he required cortisone for the first time.

Despite psychoanalysis, he needed continuous oral bronchodilators and epinephrine nebulizer day and night. His total vital capacity was 3,000 to 3,400 ml., 78 per cent of normal. One-second timed vital capacity was reduced to 1,000 to 1,200 ml.

In early 1954, when 27 years of age, he was dyspneic and wheezed audibly. The chest was hyperresonant and distended in inspiration, with typical sibilant rhonchi and diminished breath sounds. Fluoroscopically, there was evidence of emphysema. Results of intracutaneous tests given were: ragweed, timothy (10 protein nitrogen units per milliliter), 3 plus; Hormodendrum, 3 plus; Alternaria, 2 plus; house dust, 4 plus.

Potassium iodide was prescribed in the form of 0.3 Gm. enteric-coated tablets, two tablets four times a day, 2.4 Gm. a day. He reported his asthma improved "after the third dose" and at the end of one week he no longer needed Tedral or the nebulizer. Twenty-eight days later his total vital capacity had risen to 4,300 ml., or 100 per cent of normal, and his one-second vital capacity to 1,800 ml. He could play softball without the use of supplementary medication.

Iodide therapy was continued for five years, with persistent good effect. In addition to a sense of general well-being there was a weight gain of 12 pounds during the first year. Examination of the chest showed signs neither of asthma nor of emphysema.

Occasionally he noted a few pink papules on face or chest which disappeared without

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change in iodide dosage. When the dose was reduced to 1.2 Gm. per day there was prompt recurrence of wheezing, relieved by a return to previous dosage. He required higher doses, up to 3.6 Gm. per day, following colds or during the ragweed season. In the third year he went skiing in the bitterest winter cold without need of other medication. His total vital capacity rose to 4,800 ml. (above normal).

In the fourth year he first observed a small adenomatous nodule in the isthmus of the thyroid. He was started on thyroid extract, 60 mg. per day, with diminution in the size of the nodule.

In the fifth year of treatment, iodide was less effective, especially in the ragweed season. When the usual dosage of iodide was ineffective the drug was stopped. He again needed bronchodilators and the nebulizer. Iodide therapy, repeatedly reinstituted during the next three years, remained of no help. The thyroid nodule disappeared. Prednisone in short intermittent courses became necessary for control.

Case 2.—W. H., a 37-year-old woman, had had bronchial asthma since she was 18. Nasal polypectomy was performed at the age of 15. At 16 she had an acute febrile illness, thought to be polyarteritis nodosa, with purpura, renal damage, and hypertension. Following bilateral sphenoidectomy for infected polypoid sinusitis due to *Pneumococcus* type 7, the acute systemic illness subsided, but she developed mitral stenosis. Intracutaneous tests were negative except for a 4 plus reaction to house dust. There was a questionable asthma flare-up in the ragweed pollen season.

From 1949 to 1952 her attacks flared intermittently while she was on antiallergic management. On several occasions she was given the "Dr. Gay mixture," each teaspoonful containing 0.25 Gm. of potassium iodide. She experienced prompt relief for a prolonged period, but her asthma became increasingly severe and required hospitalization. A daily dose of 100 mg. of cortisone was needed until the seventh month of her first pregnancy.

In February, 1954, she was again seen because of a severe flare-up of asthma despite cortisone. She was thin and dyspneic, with diffuse sibilant rhonchi. The blood pressure was 170/110. A murmur and prominence of the pulmonary conus seen on fluoroscopic examination were typical of mitral stenosis.

Potassium iodide, two 0.3 Gm. enteric-coated tablets four times daily, was prescribed, while cortisone dosage was tapered off progressively. One week later she reported that she did not need the isoproterenol hydrochloride inhaler. After one month there was complete freedom from asthma and a gain of 5 pounds in weight. Although cortisone was stopped she remained asthma free while on iodide in her second pregnancy, in contrast to the very severe asthma in her first.

She remained well, never needing steroids. When iodide was stopped the asthma recurred in six weeks. She resumed her regular dosage with good effect until 1959, when she observed decreasing benefit from this medication, and again had to resort to steroids.

Case 3.—J. S., a boy of 12, had had rhinitis since infancy, usually worse in the summer. Asthma first appeared in July, 1952, with a one-month flare-up in September. He was clinically allergic to cats and house dust.

There were typical sibilant rhonchi and the nasal membrane was gray and edematous. Results of intracutaneous tests were: ragweed, timothy, house dust, 4 plus; feathers, dog hair, *Aspergillus*, 3 plus; English plantain, mixed trees, horse hair, wool, cottonseed, kapok, *Alternaria*, 2 plus.

On a strict antiallergic regimen with desensitization he was scarcely ever free of asthma and required bronchodilators and frequent use of a nebulizer.

While in status asthmaticus, only partially controlled by cortisone, he was first started on two 0.3 Gm. enteric-coated potassium iodide tablets four times daily, with clear-cut relief apparent in five days. If the dose of potassium iodide was less than three tablets a day, asthma recurred. He remained well for about seven months, needing no other antiasthmatic medication. Potassium iodide was stopped, with only occasional recurrence of asthma during the following two years.

Case 6.—G. T., a 55-year-old woman, first had asthma in 1957 at the age of 52, with repeated nasal polyps and vasomotor rhinitis for many years. The asthma was better in

TABLE

PATIENT'S NAME		AGE		CLINICAL TYPE OF ASTHMA	SEVERITY OF ASTHMA
CASE	SEX	(YEARS)	(YEARS)		
1. E. R.	Male	34	—	Paroxysmal; extrinsic	4+
2. W. H.	Female	37	48	Paroxysmal; intrinsic	4+
3. J. S.	Male	12	14	Paroxysmal; extrinsic	3+
4. L. O.	Female	12	7	Paroxysmal and bronchitic; extrinsic	2+
5. M. C.	Male	62	58	Bronchitic and paroxysmal; intrinsic	2+
6. G. T.	Female	55	52	Paroxysmal; intrinsic	4+
7. M. B.	Male	62	60	Paroxysmal; intrinsic	2+
8. A. S.	Female	59	48	Paroxysmal and bronchitic; intrinsic	2+
9. C. W.	Female	18	14	Paroxysmal; extrinsic	4+
10. F. S.	Female	14	5	Paroxysmal; extrinsic	4+

summer and there was no seasonal hay fever. Intracutaneous tests with inhalants, pollens, molds, and representative foods were negative. She responded well to Quadrimid, containing 0.3 Gm. of potassium iodide per tablet.

Asthma returned during the winter following an upper respiratory infection. Prednisone was needed over a three-month period and reduction in dosage to 5 mg. a day was attended by reappearance of asthma.

In September, 1960, she was first given potassium iodide, two 0.3 Gm. enteric-coated tablets four times daily. After two weeks she was first able to stop prednisone without recurrence of asthma. Despite a slight wheeze on exertion there was no dyspnea. Typical sibilant rhonchi prominent on the first examination were now few, but nasal blocking was more noticeable than when she was taking prednisone.

For over two years she has remained completely well on iodide without supplementary medication. On two occasions deliberate withdrawal of the drug resulted in recurrence of asthma. Each time she again responded to reinstitution of treatment.

Case 10.—F. S., a 14-year-old girl, was first seen at age 5 when she developed wheezing and a cough on Labor Day. The chest was full of sibilant rhonchi and showed diminished breath sounds. She required cortisone for a short period when she failed to respond to bronchodilator medication. She had little asthma until the following ragweed season, when she again needed prednisone.

At the age of 8 she reported continuous wheezing throughout the previous year, with intractable cough and dyspnea on slight exertion. Intracutaneous tests showed a 4 plus reaction to ragweed and house dust; 2 plus reactions to grass, mixed tree pollen, feathers, and milk. Systematic manipulation of the diet was of no help.

Prednisone and the nebulizer were used with increasing frequency. After three years,

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PREVIOUS STEROID THERAPY	SKIN TEST FINDINGS	POTASSIUM IODIDE EFFECT		
		TIME TO ONSET	DURATION	DEGREE OF CONTROL (%)
Brief	Pollens 3+ Alternaria 2+ House dust 4+	1 day	5 years	90
Repeated, pro- longed	House dust 4+ Otherwise negative	7 days	5 years	85
Brief	Pollens 4+ Aspergillus 3+ House dust 4+	5 days	7 months	85
None	Scratch tests: pollens, danders 2+	7 days	12 months	90
None	House dust 2+ Otherwise negative	7 days	12 months	90
Prolonged	Negative	14 days	2 years	95
Brief	House dust 2+ Otherwise negative	14 days	4 months	95
None	House dust 1+ Otherwise negative	7-10 days	10 months	85
Prolonged	Pollens 2+ House dust 4+	14 days	8 months	80
Repeated courses	Ragweed 4+ Other pollens 2+	14 days	10 months	95

desensitization with pollens and house dust was stopped because of distinct asthma flare-ups in the pollen seasons. For two years thereafter prednisone had to be used again and again for control.

In January, 1963, at the age of 14, she was again having asthma. Potassium iodide was prescribed as two 0.3 Gm. enteric-coated tablets four times a day. Within two weeks the asthma was much improved and in the following five months she needed no prednisone. The nebulizer was used occasionally. The patient's rhinitis was also improved on iodide.

On May 27 enteric-coated tablets of potassium chloride were substituted for the potassium iodide without the patient's knowledge. The parents understood this to be "another form of potassium iodide." Within four days there was a severe recurrence of asthma, requiring 40 mg. of prednisone for the first day with tapering dosage for one week. Reinstitution of potassium iodide again brought the asthma under good control during a total of ten months of observation.

DISCUSSION

The ten cases of this report (Table I) serve to confirm and document a significant, unusual effect of potassium iodide, that of suppressing attacks of bronchial asthma. These cases alone exhibited this marked effectiveness among those of approximately two hundred asthmatic patients who otherwise showed only slight benefit or for whom it was completely ineffective. There is some variation in the degree of iodide effect even among this favorable group. In Case 1 the response was little short of startling. Cases 1 and 2 illustrate that

the action of iodide in preventing asthma may be prolonged and persistent, lasting up to five years. The results in Cases 3 and 6 were scarcely less dramatic and unexpected, and in each case steroid therapy could be replaced by iodide. Case 9 illustrates a less striking degree of effectiveness.

That this potassium iodide action is more than a placebo effect seems likely for a number of reasons. The remarkably prolonged benefit seen in the first two cases appears unlike the usually more temporary character of placebo action. Moreover, in some cases the dose level appeared to be critical, too sharp a reduction in dosage permitting a relapse of asthma. Three patients responded repeatedly to this drug but to no others in a similar manner, except steroids.

In two cases there is more impressive evidence that the asthma-suppressive action of iodide is pharmacologic and not placebo in character. Case 2 responded not only to iodide in the enteric-coated tablet form but also to the formula of Dr. Gay of Biloxi which she could not know also contained iodide. Most striking is the reaction to sudden withdrawal of iodide in Case 10, although neither the patient, a girl of 14, nor her parents were aware that a change had been made to a noniodide placebo tablet. Within four days asthma had recurred so severely as to require prednisone in full dosage for one week. An extended double-blind study of this exceptional iodide effect might be difficult to interpret, the incidence of responsiveness to iodide being actually far less than to a placebo.

This asthma-suppressive effect of iodide probably cannot be anticipated in more than 5 to 10 per cent of cases. The unpredictability of this action is the drug's most serious limitation. It must nevertheless be emphasized that iodide will occasionally prevent attacks and suppress asthma as will no other therapy except corticosteroids. Its particular practical value is as an alternative to prolonged steroid therapy.

While this iodide effect usually becomes evident in from one to two weeks, in Case 1 it was noted on the first day and in Case 3 in five days. Two tablets of 0.3 Gm. of potassium iodide were prescribed (enteric-coated to minimize unpleasant taste) four times daily, before meals and at bedtime. This is approximately the equivalent in iodide of ten drops of saturated potassium iodide solution containing 1.0 Gm. of the drug per milliliter. Increased severity of asthma may be benefited by increasing iodide dosage to 3.6 Gm. per day (Case 1). The metallic taste of iodide, annoying to many despite the use of enteric-coated tablets, was scarcely noted by others. Iodide is excreted in the saliva as well as in the gastric secretions, and has been shown by Tuft and Levin¹ to appear also in the bronchial secretions.

This iodide action may be very persistent, lasting for years as in the first two cases, and for several to many months in others. It was a little less predictable in Cases 7 and 8, where some tendency to escape from its effect was noted. The asthma of childhood as well as that of later life may respond (Cases 3, 4, and 10). Male or female patients may be benefited. Whether the patient is skin-test positive or negative appears irrelevant. It may provide striking benefit not only in the cases with severe paroxysms but also where profuse expectoration is outstanding. In Case 5 reduction in sputum was striking, providing a contrast with the usual expectorant action of iodide.

Although generally well tolerated, potassium iodide treatment is not without side effects. Commonest are gastrointestinal upset, epigastric pain, and minor skin eruption. Mild papular erythema was frequent, and readily controlled by temporary reduction in dosage. There was no instance of severe iodide eruption. Three patients had mild "acute iodism" with edema of the lids or face and marked rhinorrhea which required discontinuation of the drug. In two cases pain in the parotid glands was controlled by careful manipulation of dosage.

The most serious side effect observed in this series was the development of a small thyroid adenoma after three years of continuous iodide therapy in Case 1. The nodule diminished somewhat in response to thyroid substance but disappeared completely only when iodide was withdrawn. Adenoma of the thyroid in response to iodide treatment has been reported frequently, and myxedema may also occur.^{5, 6} A more serious hazard of iodide therapy which has recently attracted attention is goiter of the newborn, with pressure effects which may result in fatal asphyxia. This has been observed even when the drug has been used in relatively modest dosage, as in Quadrinal tablets which contain 0.3 Gm. of potassium iodide.⁷ It is therefore safest to avoid iodide in the treatment of the pregnant asthmatic patient. As illustrated by the experience in Case 2, such an ill effect upon the newborn is not invariable. Severe sensitivity phenomena occasionally ascribed to iodide, such as hypersensitivity angitis, were not seen.

What explains the extraordinary asthma-suppressive effect which potassium iodide exhibits so strikingly but only in certain patients? It has been emphasized that the iodide-responsive asthmatic subject presents no other distinctive clinical features. The history of iodide in medical therapy includes a notoriously wide application in many disorders. Its chief use was formerly in late syphilis for the resolution of gummas, and in acute syphilitic meningitis for which it was administered in huge doses. In sporotrichosis iodide remains the drug of choice and may be used in doses as high as 40 drops of saturated solution three times daily.⁸ Such dosage, three times as much as that used in this series, might be tried in bronchial asthma.

The therapeutic effectiveness of iodide is described by Goodman and Gilman⁹ as its "histolytic action," the mechanism remaining uncertain. A related observation, to which they refer, was its tendency to cause a flare-up of tuberculous lesions. This warning to avoid iodide in tuberculosis recalls similar current practice as to steroids unless accompanied by specific antituberculosis chemotherapy.

Such observations suggest that the action of potassium iodide in asthma may be part of a more general anti-inflammatory or antiallergic effect. In this series, allergic rhinitis as well as asthma was occasionally observed to improve on iodide. More often, however, there was no effect on rhinitis; rarely, it was aggravated. Iodide was also used in a small series of patients with atopic dermatitis, urticaria, and angioedema, but in no instance was there improvement and in some the condition grew worse. Iodide could not be shown to diminish the immediate skin test response to allergen extracts. In a case of cold urticaria

the edema reaction to topical application of cold was unaffected. In three instances a positive intracutaneous tuberculin test with PPD remained unchanged when the test was repeated during iodide administration. It is possible that some effect might be detectable if a minimal tuberculin stimulus were used, aimed at eliciting a threshold reaction. The fundamental mechanism by which iodide exerts its asthma-suppressive action remains speculative. What insight this exceptional action may provide as to some fundamental difference between iodide-responsive and iodide-unresponsive asthma likewise constitutes a provocative question.

SUMMARY

The exceptional asthma-suppressive action of potassium iodide is described as observed in ten cases among approximately two hundred treated with this drug. A high degree of control of asthma may persist for prolonged periods, up to five years. The degree of effectiveness may be such that prolonged steroid therapy can be avoided. The data suggest that this is not a placebo effect.

Potassium iodide was in general well tolerated, but its side effects warrant consideration and their management is discussed. Thyroid adenoma was the most important complication of therapy. Iodide, long considered to possess some anti-inflammatory action, appears to exert little benefit on other common allergy syndromes. It did not diminish either immediate or delayed allergic skin test reactions. The mechanism of the asthma-suppressive action of iodide remains obscure. What accounts for the peculiar iodide-responsiveness of certain cases of bronchial asthma constitutes a related provocative problem.

The author wishes to acknowledge the stimulus of an early observation by Dr. Clifford Spingarn to his continuing interest in this subject.

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Comments on Dr. Siegal's manuscript

INTRODUCTION

The preceding paper was accepted for publication in *The Journal of Allergy* because it raised an important question concerning the evaluation of clinical data. The author suggested that only a small fraction of the asthmatic patients respond favorably to potassium iodide. If this is so, then this favorable response might not produce a statistically significant effect on a double-blind study performed on a large group of patients with this disease. Dr. Siegal's manuscript was presented to eight reviewers with the following questions:

1. Is the author's thesis of the heterogeneity of asthma reasonable?
2. If so, do you agree that this reduces the value of the double-blind study in determining the effectiveness of a given drug such as potassium iodide?
3. Has the author exhausted the possibilities other than a double-blind study for establishing the effectiveness of potassium iodide in individual patients?
4. If not, what else could he do?

The answers to these questions provide an instructive analysis of many of the problems of clinical investigation.

Editor

Dr. Francis C. Lowell.—This issue of the *JOURNAL* contains an article describing strikingly beneficial effects of iodides in relatively large daily doses (2.4 Gm. potassium iodide as an enteric-coated preparation) in 10 patients. These were the only ones among some 200 asthmatic patients in whom a trial with iodides had been successful. As I am sure the author will agree, retrospective selection of cases, without any systematic effort to maintain experimental control (a placebo was given in a single trial, in one case only) and with the single criterion for selection, the very response for which a claim is made, cannot be accepted at face value. The striking response described in these cases may or may not be correctly attributed to an effect of iodides, specific or otherwise—one would like to *know*.

Can one know? One probably can in spite of substantial obstacles. Admittedly, on the basis of the report presented, one can predict that a study of unselected asthmatic patients will fail to show any significant effect of iodides since the effect was seen in only 10 among 200, or 5 per cent. Therefore one must proceed on the assumption that, with respect to effectiveness of iodides, the asthmatic population is heterogeneous. Pre-selection of suitable, or what seem likely to be suitable, patients would be necessary. One might begin as the author did and try the effect of iodides in a large group. One could thereby identify those who seem to derive benefit. Having made a selection of "indicators" of a therapeutic effect of iodides, the next step would be to conduct a formal study of this group with suitable experimental control.

Another approach would be to survey the iodide-responsive group to determine whether they have one or more clinical features in common which might make preselection possible. For example, nasal polyposis was present in three (Nos. 1, 2, and 6) of the five patients who are described in sufficient detail to allow the reader to know whether polyps were present or not. This information is not given for the remaining five patients. It would be interesting to know, for example, how many among the 10 patients included in the report had nasal polyps and what the incidence of nasal polyps was among the 200 patients from whom the selection of 10 was made. One could perhaps make some estimate of the likelihood that nasal polyposis is related to "iodine responsiveness" and could therefore serve as a means of preselection.

An "informal" clinical observation can have great value, but only if it can be made to "stand on its own two feet." This one cannot, but nevertheless, it may point to a fruitful line of study. Most observations have to be put to a rigorous test and it is the report of this test that deserves priority in our journals, more often than the original observation.

Dr. Irving H. Itkin.—Dr. Siegal has made several astute observations of the effect of potassium iodide on the clinical course of ten patients with asthma. Some of the patients who responded favorably may have suffered also from other conditions aggravating bronchial obstruction. Before accepting the idea that the disease asthma should be divided into that sort which is iodide responsive and that which is iodide unresponsive, one must examine the evidence and find that no other explanation is more reasonable, for unnecessary classifications serve only to add confusion.

An interesting report appeared recently in the Italian literature. Rosa and associates¹ studied the effectiveness of potassium iodide when given to 664 patients who wheezed. Clinical observations as well as spirometric readings were obtained during alternating ten-day periods with and without the drug. The usual dose was 1.4 Gm. daily, but on occasion this was raised to 2.8 Gm. or 3.15 Gm. daily. Asthmatic bronchitis (bronchial infection with wheezing), had been diagnosed in 420 patients, 84 with allergic asthma (extrinsic or intrinsic), and 160 with mixed (both allergic asthma and bronchial infection present). Of the 420 bronchitic patients, 85 per cent responded "optimally" to potassium iodide, 14.28 per cent "moderately," and only 0.72 per cent had no response. Of the 84 patients with allergic asthma, no patients responded "optimally," and only 2 responded moderately well. Of the 160 mixed cases, "optimal" response was recorded in 43.75 per cent, "moderate" response in 50 per cent, and "no response" in only 6.25 per cent. Good results were attributed to the expectorant action of the drug, with the abolition of reflex wheezing when the mucus causing bronchial obstruction was reduced. Beneficial results appeared rapidly, in ten days or less, and were lost rapidly when the medication was discontinued.

Considering some of the difficulties involved in differentiating asthma alone from asthma complicated by bronchial infection, it would seem reasonable to suppose that at least some of Dr. Siegal's successfully treated patients were in the latter category. The patient with both conditions is more likely to suffer from cough early in the attack, to note fever during or just before attacks of asthma, to suffer a large number of attacks during the winter season, to find that the usual bronchodilator drugs are relatively ineffective, that the corticosteroids are less dramatic in their effect at some times than at other times, and that antimicrobial drugs are often surprisingly beneficial.

Cytologic examination of the sputum may reveal that polymorphonuclear cells frequently predominate, although eosinophils in great number may be present in a yellow sputum. Cultures of the sputum may reveal the growth of *Haemophilus influenzae*, staphylococci, or pneumococci, although the absence of pathogens on culture does not rule out bronchitis due to infection. Bronchoscopic examination may be helpful not only on the basis of differences in gross appearance, but also because of the opportunity afforded of obtaining mucus from the lower bronchial segments. N-acetylcysteine appears to be singularly ineffective in dissolving the mucus from uncomplicated asthma, while it may influence dissolution of the mucus obtained from infected patients.

Bronchography and cinefluorobronchography may be helpful.

When infection is a complicating factor, blood tests may show elevations of the total white blood count, the polymorphonuclear percentage, the sedimentation rate, the C-reactive protein, the mucoproteins, and the gamma globulin fraction.

Ventilatory studies done over a long period may show a lesser degree of variation in the chronically infected patient. Extreme sensitivity of the bronchial tree to the inhalation of mecholyl chloride is characteristic of the asthmatic patient; lower degrees of sensitivity are found in the bronchitic patient without asthma. The test is helpful in confirming the presence of asthma where infection may overshadow the latter.

After infection has been eliminated as a likely possibility to account for the effectiveness of iodide, more crucial studies of the action of iodides on asthma may be undertaken. These should, indeed, include double-blind studies, using, for example, other expectorants, as well as placebos, for control.

Another method has been in use at the National Jewish Hospital for the past year. After the lowest maintenance dose of steroids has been determined for steroid-dependent patients, airway functions are recorded for several weeks at that dose. Then iodides are

added to the regimen for several weeks, and attempts are made to lower the steroid dose again without producing a corresponding decrease in airway function. At the present writing, none of fifteen patients on whom this has been tried has benefited.

Dr. Siegal has reported convincingly in his paper that the iodide action is unlikely to be directed against the antigen-antibody reaction. Work in progress at National Jewish Hospital with dose-response curves of bronchial reactivity to allergenic extracts as compared with reactivity to solutions of mecholyl chloride using the quantitative inhalation challenge suggests that these may be separate responses. Can it be that iodides interfere with the reaction to mecholyl? We shall attempt to investigate this hypothesis. Other approaches than that by inhalation challenge are also applicable.

The possibility that iodides may have some action upon molds different from that which is recognized should also be entertained. Mold allergy may be more prevalent than has been suspected.

In conclusion, Dr. Siegal deserves great credit for bringing his clinical observations to the attention of a wide circle of readers. Discussion of them cannot but bring more valuable knowledge to light.

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Dr. Richard S. Farr.—It is a pleasure to have an opportunity to comment on Dr. Siegal's paper, because I would like to record an opinion in support of his thesis regarding the heterogeneity of the clinical state called asthma. The symptom-complex consisting of bouts of intermittent bronchospasm associated with mucus secretion and difficulty in exchanging air can be caused by a variety of immunologic and nonimmunologic insults to the lung. Generally speaking, these bouts are usually referred to as asthma. Specifically, we can sometimes differentiate between asthmatic attacks primarily caused by such things as (1) bronchial infection, (2) infection associated with structural changes in the lung, (3) antigen-reagin interaction, (4) local tumors, and (5) even tumors located in organs other than the lung but secreting biologically active amines. Unfortunately, however, it is often difficult or impossible to ascertain which of the many possible factors is playing the major role in a given case. Indeed, more often than not, several factors appear to be more or less equal contributors to the symptom complex. The evaluation of a given case of asthma is further complicated by the variation from person to person with respect to end-organ responsiveness when an individual is confronted with a stimulus capable of eliciting asthma. For these reasons, a group of asthmatic patients almost certainly must be heterogeneous with respect to both causal factors and end-organ threshold levels. Although it is possible to select a more homogeneous group of asthmatic patients than those included in Table I of Dr. Siegal's report, a considerable degree of heterogeneity must surely exist in even the most carefully selected cases of asthma due to any specific causal factor one attempts to isolate. Further, because of this heterogeneity and variation from case to case, it is not unexpected that measures designed either to minimize the impact of an asthmatic stimulus to the lungs or to reduce the responsiveness of the lungs to the various stimuli will prove beneficial in some cases and not in others.

In the present study no apparent attempt was made to reduce the heterogeneity of the group of asthmatic patients presented but, under the circumstances, it seems to me that Dr. Siegal has done about all he can do to control his heterogeneous population of patients. In the face of the obvious heterogeneity in his patient population, he used each case as its own control which is a perfectly valid experimental procedure. Perhaps it could be argued that Dr. Siegal should have done more with substitution therapy using placebo tablets and this would be my major criticism of this report. On the other hand, many of

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Editor

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Can one know? One probably can in spite of substantial obstacles. Admittedly, on the basis of the report presented, one can predict that a study of unselected asthmatic patients will fail to show any significant effect of iodides since the effect was seen in only 10 among 200, or 5 per cent. Therefore one must proceed on the assumption that, with respect to effectiveness of iodides, the asthmatic population is heterogeneous. Pre-selection of suitable, or what seem likely to be suitable, patients would be necessary. One might begin as the author did and try the effect of iodides in a large group. One could thereby identify those who seem to derive benefit. Having made a selection of "indicators" of a therapeutic effect of iodides, the next step would be to conduct a formal study of this group with suitable experimental control.

Another approach would be to survey the iodide-responsive group to determine whether they have one or more clinical features in common which might make preselection possible. For example, nasal polyposis was present in three (Nos. 1, 2, and 6) of the five patients who are described in sufficient detail to allow the reader to know whether polyps were present or not. This information is not given for the remaining five patients. It would be interesting to know, for example, how many among the 10 patients included in the report had nasal polyps and what the incidence of nasal polyps was among the 200 patients from whom the selection of 10 was made. One could perhaps make some estimate of the likelihood that nasal polyposis is related to "iodine responsiveness" and could therefore serve as a means of preselection.

An "informal" clinical observation can have great value, but only if it can be made to "stand on its own two feet." This one cannot, but nevertheless, it may point to a fruitful line of study. Most observations have to be put to a rigorous test and it is the report of this test that deserves priority in our journals, more often than the original observation.

Dr. Irving H. Itkin.—Dr. Siegal has made several astute observations of the effect of potassium iodide on the clinical course of ten patients with asthma. Some of the patients who responded favorably may have suffered also from other conditions aggravating bronchial obstruction. Before accepting the idea that the disease asthma should be divided into that sort which is iodide responsive and that which is iodide unresponsive, one must examine the evidence and find that no other explanation is more reasonable, for unnecessary classifications serve only to add confusion.

An interesting report appeared recently in the Italian literature. Rosa and associates¹ studied the effectiveness of potassium iodide when given to 664 patients who wheezed. Clinical observations as well as spirometric readings were obtained during alternating ten-day periods with and without the drug. The usual dose was 1.4 Gm. daily, but on occasion this was raised to 2.8 Gm. or 3.15 Gm. daily. Asthmatic bronchitis (bronchial infection with wheezing), had been diagnosed in 420 patients, 84 with allergic asthma (extrinsic or intrinsic), and 160 with mixed (both allergic asthma and bronchial infection present). Of the 420 bronchitic patients, 85 per cent responded "optimally" to potassium iodide, 14.28 per cent "moderately," and only 0.72 per cent had no response. Of the 84 patients with allergic asthma, no patients responded "optimally," and only 2 responded moderately well. Of the 160 mixed cases, "optimal" response was recorded in 43.75 per cent, "moderate" response in 50 per cent, and "no response" in only 6.25 per cent. Good results were attributed to the expectorant action of the drug, with the abolition of reflex wheezing when the mucus causing bronchial obstruction was reduced. Beneficial results appeared rapidly, in ten days or less, and were lost rapidly when the medication was discontinued.

Considering some of the difficulties involved in differentiating asthma alone from asthma complicated by bronchial infection, it would seem reasonable to suppose that at least some of Dr. Siegal's successfully treated patients were in the latter category. The patient with both conditions is more likely to suffer from cough early in the attack, to note fever during or just before attacks of asthma, to suffer a large number of attacks during the winter season, to find that the usual bronchodilator drugs are relatively ineffective, that the corticosteroids are less dramatic in their effect at some times than at other times, and that antimicrobial drugs are often surprisingly beneficial.

Cytologic examination of the sputum may reveal that polymorphonuclear cells frequently predominate, although eosinophils in great number may be present in a yellow sputum. Cultures of the sputum may reveal the growth of *Haemophilus influenzae*, staphylococci, or pneumococci, although the absence of pathogens on culture does not rule out bronchitis due to infection. Bronchoscopic examination may be helpful not only on the basis of differences in gross appearance, but also because of the opportunity afforded of obtaining mucus from the lower bronchial segments. N-acetylcysteine appears to be singularly ineffective in dissolving the mucus from uncomplicated asthma, while it may influence dissolution of the mucus obtained from infected patients.

Bronchography and cinefluorobronchography may be helpful.

When infection is a complicating factor, blood tests may show elevations of the total white blood count, the polymorphonuclear percentage, the sedimentation rate, the C-reactive protein, the mucoproteins, and the gamma globulin fraction.

Ventilatory studies done over a long period may show a lesser degree of variation in the chronically infected patient. Extreme sensitivity of the bronchial tree to the inhalation of mecholyl chloride is characteristic of the asthmatic patient; lower degrees of sensitivity are found in the bronchitic patient without asthma. The test is helpful in confirming the presence of asthma where infection may overshadow the latter.

After infection has been eliminated as a likely possibility to account for the effectiveness of iodide, more crucial studies of the action of iodides on asthma may be undertaken. These should, indeed, include double-blind studies, using, for example, other expectorants, as well as placebos, for control.

Another method has been in use at the National Jewish Hospital for the past year. After the lowest maintenance dose of steroids has been determined for steroid-dependent patients, airway functions are recorded for several weeks at that dose. Then iodides are

added to the regimen for several weeks, and attempts are made to lower the steroid dose again without producing a corresponding decrease in airway function. At the present writing, none of fifteen patients on whom this has been tried has benefited.

Dr. Siegal has reported convincingly in his paper that the iodide action is unlikely to be directed against the antigen-antibody reaction. Work in progress at National Jewish Hospital with dose-response curves of bronchial reactivity to allergenic extracts as compared with reactivity to solutions of mecholyl chloride using the quantitative inhalation challenge suggests that these may be separate responses. Can it be that iodides interfere with the reaction to mecholyl? We shall attempt to investigate this hypothesis. Other approaches than that by inhalation challenge are also applicable.

The possibility that iodides may have some action upon molds different from that which is recognized should also be entertained. Mold allergy may be more prevalent than has been suspected.

In conclusion, Dr. Siegal deserves great credit for bringing his clinical observations to the attention of a wide circle of readers. Discussion of them cannot but bring more valuable knowledge to light.

REFERENCE

1. Rosa, L., Bergami, G., and Zaccardi, G. F.: The Test With Potassium Iodide in the Differentiation of Some Forms of Bronchial Asthma, *Lotta Tuberc.* 31: 835, 1961 (Italian).

Dr. Richard S. Farr.—It is a pleasure to have an opportunity to comment on Dr. Siegal's paper, because I would like to record an opinion in support of his thesis regarding the heterogeneity of the clinical state called asthma. The symptom-complex consisting of bouts of intermittent bronchospasm associated with mucus secretion and difficulty in exchanging air can be caused by a variety of immunologic and nonimmunologic insults to the lung. Generally speaking, these bouts are usually referred to as asthma. Specifically, we can sometimes differentiate between asthmatic attacks primarily caused by such things as (1) bronchial infection, (2) infection associated with structural changes in the lung, (3) antigen-reagin interaction, (4) local tumors, and (5) even tumors located in organs other than the lung but secreting biologically active amines. Unfortunately, however, it is often difficult or impossible to ascertain which of the many possible factors is playing the major role in a given case. Indeed, more often than not, several factors appear to be more or less equal contributors to the symptom complex. The evaluation of a given case of asthma is further complicated by the variation from person to person with respect to end-organ responsiveness when an individual is confronted with a stimulus capable of eliciting asthma. For these reasons, a group of asthmatic patients almost certainly must be heterogeneous with respect to both causal factors and end-organ threshold levels. Although it is possible to select a more homogeneous group of asthmatic patients than those included in Table I of Dr. Siegal's report, a considerable degree of heterogeneity must surely exist in even the most carefully selected cases of asthma due to any specific causal factor one attempts to isolate. Further, because of this heterogeneity and variation from case to case, it is not unexpected that measures designed either to minimize the impact of an asthmatic stimulus to the lungs or to reduce the responsiveness of the lungs to the various stimuli will prove beneficial in some cases and not in others.

In the present study no apparent attempt was made to reduce the heterogeneity of the group of asthmatic patients presented but, under the circumstances, it seems to me that Dr. Siegal has done about all he can do to control his heterogeneous population of patients. In the face of the obvious heterogeneity in his patient population, he used each case as its own control which is a perfectly valid experimental procedure. Perhaps it could be argued that Dr. Siegal should have done more with substitution therapy using placebo tablets and this would be my major criticism of this report. On the other hand, many of

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his cases are convincing even without this refinement. It appears that Dr. Siegal has found a few patients with asthma in whom iodide therapy tipped the balance between the state of having asthma and the state of being symptom free when all other factors in these individual cases were held relatively constant. The rationale to justify the concept that the group of conditions which we now call allergies, including asthma, should rightly be looked upon as a medical state of being rather than entities in and of themselves has been partially set forth elsewhere.¹

Regarding the question about the usefulness of the double-blind technique to evaluate a drug or agent, granted that the given agent to be tested is in fact effective in doing the therapeutic job, then the double-blind study will be able to detect this effectiveness most easily under circumstances when (a) the drug in question is directed toward alleviating a situation which is a dominant causal factor in each of the cases selected for the study, and (b) each case selected for the study must not have a second or third etiologic factor which, if left untreated, is a strong enough stimulus to perpetuate the asthma by itself. If too many cases not in either category (a) or (b) described above are included in a double-blind study, it is not only likely but probable that even a very effective agent being tested as the primary objective of the study will yield only equivocal results.

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Dr. Paul P. VanArsdel, Jr.—If potassium iodide were a new drug, subjected to the critical assessment recommended for testing new drugs, it would probably be declared worthless for all conditions except thyroid disease. Unfortunately, or fortunately, depending on one's point of view, iodide therapy has a long clinical tradition. We are confronted then, with a dilemma which Ebert¹ pointed out two years ago in an editorial on evaluation of therapy in chronic illness: "While many of the traditional modes of treatment in medicine would not withstand careful scientific scrutiny, there seems to be no urgency in discarding them."

Yet many physicians with extensive experience in the treatment of asthma would agree with Dr. Siegal that the occasional patient improves dramatically with iodide therapy. This impression, or intuitive association, is reinforced by long-standing tradition. Indeed, the background of such therapy is nicely expressed by the couplet on page 827 of the text by Goodman and Gilman.²

"Wenn man nicht weiss Wieso und Warum,
Dann gibt man Jodkalium."

The usual claim for the value of iodide therapy is that it is effective in thinning or altering the volume of bronchial secretions. There is nothing to indicate that such an effect was important in Siegal's patients. This means that only the patients' subjective responses could be utilized; at least no quantitative basis for comparison was mentioned.

Asthma is characterized by wide variations in etiology, morbidity, and response to therapy, not only from patient to patient, but from time to time in the same patient. Except for the patients who react specifically to known extrinsic stimuli, and are free of asthma otherwise, most asthmatic subjects will have some remissions or relapses which are totally unexplained. It is possible that the patients reported upon by Dr. Siegal did respond specifically to some anti-inflammatory effect of iodide as he proposed. This hypothesis, however, cannot be subjected to experiment, and is less tenable than a proposal based on a simple grouping of asthmatic patients:

If group (A + B + C + D) = all asthmatics

and group (A + B) = all asthmatics who get better

and group (B + C) = asthmatics who receive iodide therapy,

then group B includes all patients who get better with iodide.

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group B. That only ten patients from a total of 200 (B + C) were in this group strengthens the possibility of coincidence.

Clinically, there is nothing unique about Siegal's patients except that they improved with iodide therapy. This means that they provide us with no common denominator which might allow preselecting of other asthmatic patients who would be appropriate candidates for a controlled study. To undertake a controlled double-blind evaluation of iodides in a large group of unselected asthmatic patients is a formidable task, and probably futile, particularly relative to Siegal's hypothesis. As pointed out by Modell and Houde,³ there are too many factors at work "immaterial to the specific problem at hand." Shure and St. John⁴ brought this out in one of the few controlled studies pertaining to iodide therapy in asthma. They were forced to reduce their series for analysis from 126 to 28 patients to get rid of "background noise"—that is, the reports from patients who were unable to discriminate between one agent and another.

Another approach might be to select patients for a controlled study on the basis of their earlier favorable response to iodide. Even if we disregard the fact that some of Siegal's patients became unresponsive to iodide, their responses, as well as those of other patients who have experienced iodide therapy, would be almost impossible to control. There is an unavoidable bias introduced by the distinctive iodide side effects which cannot be duplicated by placebos. One wonders about this bias also in the improvement reported by some patients in the above-mentioned controlled study.⁴

The problem is compounded when one attempts to evaluate the expectorant action of iodide, which is dose related and closely allied to the other physiologic reactions of iodism.² Changes in sputum should at least provide a more objective index of the pharmacodynamic action of iodide. Alas, in controlled studies, the observed effects on sputum viscosity or volume have been unimpressive, and the changes that were observed did not correlate with clinical improvement.^{5, 6}

The greatest contribution of this paper is the evidence that iodide therapy is worthless for a majority of asthmatic patients, and may be harmful. Considering the casual, and often routine, use of iodides by some physicians, this deserves repeated emphasis. Asthma is a capricious disease and iodide treatment has capricious effects. Only when the occasional patient shows distinct improvement with potassium iodide, can we justifiably resort to an old empirical rule of therapy, "if the patient is improving, keep using it." However, such a practice has not led to the discovery of any general truths about the nature of asthma or the specific action of iodide. Until dependable methods of evaluation become available, this practice should be subjected to continual critical scrutiny during the long-term management of each patient.

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vironmental agents. We do not expect complete *spontaneous* remission among patients with disease of the bronchi or the lungs. Any amelioration of their asthmatic symptoms ordinarily is associated with rational therapy and is to a certain extent predictable. However, in dealing with the latter category of asthmatic subjects, I am impressed by my inability to predict the course of the condition. At almost any time after its onset, and for reasons that are rarely clear, the symptoms may disappear entirely. The duration of remission is also unpredictable. It is unfortunate that we do not know the probability that spontaneous remission will occur, or the distribution of the durations of remissions. Nevertheless, the fact that remission occurs is a reality, and the presumption that it is spontaneous is supported by a number of considerations. Iodides are not the only drugs which have received credit for a "cure" of asthma. Arsenic, stramonium, bromides, Lobelia, tobacco, vaccines, and many other substances have been mentioned favorably in the literature. Change of occupation, moving to the city—or to the country, strenuous regimens of exercise (walking 20 miles a day), psychotherapy—the list is long—all have "cured" some asthmatic patients. In addition, it is common knowledge that an unspecified fraction of juvenile asthmatics cease to have symptoms after puberty.

Our inability to distinguish between a spontaneous remission and the effect of a drug—such as potassium iodide—makes it virtually impossible to evaluate Siegal's report. Most physicians recognize the pitfalls involved in attempting to attribute the "cure" of a chronic disorder, such as asthma, to a particular regimen. The fact that *post hoc ergo propter hoc* may be fallacious is accepted, and, in an effort to avoid faulty attribution, statistical methods to evaluate evidence have been employed.

It is not easy to design a satisfactory clinical trial to evaluate the effectiveness of individual drugs in bronchial asthma. There are so many variables in the individual case that most workers hesitate to commit themselves to conventional trials of the double-blind variety. Until a new format is devised we are forced to depend upon clinical judgment in respect to drugs, which means that we can only state that a particular regimen appears to be better, worse, or no different than the one it supplants. This, of course, is a *post hoc* judgment which is necessarily provisional.

Siegal carries the *post hoc ergo propter hoc* reasoning one step further than usual and suggests that there may be some fundamental difference between iodide-responsive and iodide-unresponsive asthma. This kind of reasoning is difficult to categorize. Another physician confronted with the same experience might well say: "Since all my asthmatics were treated with enteric-coated tablets of potassium iodide, and since an unexpectedly long remission failed to occur in 95 per cent, some factor *other* than iodide must have been responsible for the complete remissions that occurred in these 10 cases." It is possible that a scrupulous investigation of the lucky 10 might provide insights into factors—other than the conventional drugs—that were responsible for the remission. If, as I suspect, such remissions are spontaneous in the sense that the drugs used are not responsible, it would be most helpful if we knew something more about the process. I have the strong impression that a change, perhaps a subtle one, in the total life-situation of the patient is the single most important factor. Unfortunately, we seldom have sufficient information on which to base such a conclusion before a remission occurs. When the patient is free of symptoms he has no further need of the doctor, and it is virtually impossible to investigate the situation retrospectively.

Future studies of asthma would be benefited if reports such as Siegal's were more complete with respect to diagnosis and details. Some day we may have information on the incidence and distribution of symptom-free periods in patients with bronchial asthma. Until we have such data evaluation of therapy must remain subject to the impressions of the clinician.

Dr. Kenneth P. Mathews.—Especially since there are a limited number of ways in which bronchioles can react, it seems very possible that a variety of circumstances may eventuate in apparent asthma. If so, certain drugs could produce a beneficial effect in some instances but not others. If, as Dr. Siegal suggests, the percentage of cases where conditions are favorable for demonstrating the action of a drug is less than the usual percentage of

patients responding to a placebo, it would be difficult to demonstrate the efficacy of the drug by the usual type of double-blind study employing unselected asthmatic patients. Theoretically, however, a difference should be demonstrable if a large enough group of subjects were studied. For instance, if 30 per cent of patients improved on a placebo, if a drug actually helped 5 per cent of patients, and if the percentage of placebo responders is the same among those actually benefited as among those not benefited by the drug, 5 per cent of the 70 per cent not responding to placebos also should be improved on the drug; i.e., in an infinitely large series of patients, 30 per cent would respond to the placebo and 33.5 per cent would benefit from the drug. To demonstrate such a difference at the 5 per cent level of confidence would require between 7,000 and 8,000 patients.

It certainly would be more feasible to study patients selected as prospective responders to the drug under study. In the absence of any clinical or laboratory criteria for selecting this group, a preliminary impression that the patient responded to iodides would have to be the basis of selection. A double-blind cross-over type of study might then be carried out. For instance, randomizing the sequence in which the drugs are administered, each individual might be given two courses of placebos and two courses of iodides and the severity of asthma rated, by appropriate means, toward the end of each treatment period. Gross differences might then be evaluated by the sign test, or an analysis could be carried out by such means as comparing patient days, weeks, or months of mild or severe asthma on the drug or placebo treatment. A difficulty in carrying out this type of study would be the probable impossibility of evaluating all patients simultaneously. The results, of course, would be applicable only to the selected group and not to the universe of asthmatic individuals.

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continuous variation) which is given graphic expression in Gauss's distribution curve. What Siegal points out is what Kalow further states, that methods attempting to deal with the discontinuous variation (such as the iodide response he noted) by the means developed to assess continuous variations (determinations of dose producing a given effect in 50 per cent of individuals) may lead to misjudgments and failures. I think he may be right, but I do not think his own series alone establishes the point, and it lacks what I am sure he would also be eager to have, some other measure than clinical of what the iodide *is* doing to the respondent as well as *not* doing to the nonrespondent. One disturbing note in assigning a genetic basis to the described differences of effect of iodides is the temporary nature of the iodide effect in a number of Dr. Siegal's patients. Furthermore, it appeared to me that some of his patients had first failed to respond to iodide, subsequently did so to extraordinary degrees, and finally lost the responsive capacity.

The following comments were made by Dr. John E. Silson, Medical and Pharmaceutical Research Consultant, who is very knowledgeable in the design and analysis of controlled clinical trials with drugs. Although I have gone over the details of Dr. Silson's commentary with him, what follows is essentially his. My own concluding remarks would emphasize what Dr. Silson suggests, that it would be exceedingly useful to compare the historical, physical, and laboratory characteristics of the patients who respond to iodide and those who do not, in an effort to elucidate the nature of the difference. Dr. John Silson's remarks follow:

Dr. John E. Silson.—First, the concept of heterogeneity cannot be applied to the evaluation of a primary therapeutic response, since the very basis of the statistical evaluation of a response is its heterogeneity: namely, that some patients respond to the treatment, while others do not. Homogeneity (absence of heterogeneity) tests should be used only to insure that the test and control groups are similar with respect to secondary characteristics, such as severity and duration of illness, age, and sex, which might influence response. This type of testing is intended to insure that the sampling procedure, whether random, stratified, cluster, or card-matched, does not introduce any bias factors between the groups being compared (for which correction factors might be necessary, or which in an extreme case might even completely invalidate the results). Tests for homogeneity are necessary only in cross-over studies, in which the same population is used for all groups, when a large order effect is present, in which case the starting groups should be compared.

Second, the factor with which Dr. Siegal is concerned is not heterogeneity, but rather the effect of dilution. If a true therapeutic effect exists, but only in a small percentage of patients, then both test and control groups, assuming proper sampling, become diluted with an approximately equal number of nonrespondents; and the sample size necessary to pick up statistical significance becomes so great as to be impractical. Under these circumstances, it would be inexpedient to run a controlled study in an unselected population to demonstrate effectiveness.

Third, it is unfortunate that "double-blind" has become the *sine qua non* of a controlled study. Actually, blinding is only one of the many tools available to the biostatistician, to be used with discretion to minimize bias factors. In asthma, where evaluation of response is largely subjective, a double-blind check of a medication is normally advisable. It is fully permissible and often preferable, however, first to eliminate the nonresponders by means of an uncontrolled, nonblind clinical trial. A double-blind controlled study only on those showing a favorable response (which will include both drug and placebo respondents) can then be instituted, preferably using a cross-over design. A single-blind check, such as Dr. Siegal used in Case 10, still leaves room for doubt, since the physician may have unconsciously influenced the patient by his knowledge of the change in medication even though patient bias is eliminated and the difference in response observed by the physician appeared too great to be questionable.

Besides its use in validating clinical effectiveness, statistical methodology can play an important role in helping to elucidate the characteristics of the patient likely to respond to the medication, or even the mechanism of its action. Dr. Siegal mentions that "it has been emphasized that the iodine-responsive asthmatic subject presents no other distinctive clinical features," but we wonder how exhaustively all the characteristics of both the positive

and negative reactors have been tabulated and then compared statistically to seek some clue as to their differences. Similarly, how carefully have extensive laboratory studies of the two groups been compared, with particular attention to tests related to iodine metabolism.

Dr. Siegal.—It was only after considerable hesitation that I permitted myself to submit for publication these observations on the asthma-suppressive effect of potassium iodide. This experience has been collected over a period of ten years but it was difficult to subject to adequate controlled experiment. I was well aware that any claims for such an unusual degree of effectiveness for so notorious an agent as potassium iodide would automatically meet with disbelief and rejection.

These cases, culled from private practice, made it difficult to resolve the ethical question of upsetting the patient's favorable clinical course by the administration of falsely labeled tablets. Moreover, it is not the custom in this community for a physician to dispense medication to a patient directly. Thus, the control medication would itself raise some doubt in the patient's mind. Furthermore, as indicated by one of the discussants, such an experiment is only an imperfect control.

Fully realizing that clinical observations of this type are in some disrepute, I did not think it right to allow possibly significant observations to remain unreported, permitting a treatment perhaps of real value to remain unrecognized.

I wish to indicate my sincere appreciation both to the Editor of the JOURNAL and to the discussants. I am happy to observe with what seriousness this subject has been considered. My hopes have been fulfilled that the publication of data on this exceptional action of potassium iodide, even though inconclusive, might stimulate the kind of interest that would ultimately lead to a final answer to the problem.

Dr. VanArsdel made the very important point that my observations certainly indicate that iodides are worthless for the majority of asthmatic patients. It is also true that they ought not to be used casually. It is the point of this paper that iodides should be prescribed with the purpose of determining whether they will induce an asthma-suppressive action. If not, they should be discontinued. Increased awareness of the thyroid complications of iodide treatment as well as the management of other more minor side effects are also practical considerations of value. However, I would wish to express some disagreement with the statement that "only the patient's subjective responses could be utilized; at least no quantitative basis for comparison was mentioned." In Case 1, timed and total vital capacity measurements changed favorably during therapy. More important, judgment as to improvement was based upon the disappearance of bronchopulmonary physical signs; upon diminution in the requirement for other antiasthmatic medication, even with discontinuance of steroids; upon the observed increased well-being of the patient, as to general appearance, complexion, color of membranes, weight gain; and above all on the patient's increased capacity to perform both normal and even strenuous exertion which had formerly seriously handicapped him. Such observations may be as objective, if not as quantitative, as those that appear on a pulmonary function testing record.

Dr. VanArsdel and others have raised the question of spontaneous remissions in asthma as explaining the apparent response to the drug. While well aware of this difficulty, I would suggest that it is precisely our incapacity to provide such patients with prolonged remissions that impels them to shop from doctor to doctor and even from climate to climate to seek relief. This is especially true of well-established asthma. In Case 1, asthma had lasted thirty-two years; in Case 2, nineteen years; in Case 8, eleven years; in Case 10, nine years; in Case 4, five years. Such patients only rarely have spontaneous remissions for an extended period. In more than twenty years of special experience with asthma, I have never been able to induce such remissions with aminophylline. Why did it follow potassium iodide? Can this be coincidence only?

Perhaps too much emphasis in the discussion has been placed upon the ancillary question of a fundamental differentiation between iodide-responsive and iodide-unresponsive asthma. This concept was after all limited to a provocative one-sentence question. Dr. LeRoy was quite correct in implying that such a question is premature, but the reasoning involved

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in raising this question is not too difficult to categorize, for it is simply one of curiosity. At this juncture, the fundamental problem is to determine whether iodide does exert the pharmacologic effect claimed for it, and if so, what the mechanism is that underlies this action. For this reason I would agree with Drs. Bukantz and Silson that one cannot now cast light on the fundamental difference which may exist between the iodide-responsive and unresponsive asthmatics. First let it be well established whether there is in fact such a select group who respond so uniquely to this simple compound. Our problem now is not so much one of genetics as of pathogenetics.

Dr. Lowell asks particularly about nasal polyps. Since I was asked to present these cases as compactly as possible, negative observations were omitted. Where nasal polyps were present they were reported; when not reported they were absent.

As to Dr. Itkin's question concerning the role of bronchial infection in relation to the iodide effect, there did not seem to be any relationship. In some patients iodide control appeared to prevent an asthmatic flare-up despite acute respiratory infection. Iodides were helpful when bronchial infection seemed absent. I have no way of knowing whether this action is related to a fungicidal effect of iodide, but I doubt it. Dr. Mathews indicated the difficulties which would be involved in attempting to establish the asthma-suppressive action of the iodides by means of a double-blind study.

I am delighted to learn of the systematic observations of Dr. Falliers and his group in Denver under the favorable controlled conditions available in an asthma institute. While conclusions must await the result of the full three-year program, perhaps it is significant that on preliminary analysis the children on iodide fared more favorably. However, the iodide dosage employed in this study appears to me a little too small for maximum effectiveness. I have previously had the pleasure of discussing this iodide effect with Dr. Falliers and am happy indeed that he has set such a study in motion.

The possible mode of action of the drug as suggested by the various discussants certainly is not elucidated by my observations. I have no data on either potassium or iodide metabolism in these patients. In response to one question, it should be stated that in Case 1 asthma was benefited even though the patient was taking desiccated thyroid for his thyroid adenoma.

Perhaps as a scientist I ought to have presented this problem quite differently: "These are the data; what do they signify?" But as a practicing physician and allergist one inevitably feels the impact of the enthusiasm and gratitude which these patients express in reaction to their unexpected and persistent relief from suffering. As a result of this, I have come to hold the conviction, perhaps wrongly, that there is in fact such an effect as the asthma-suppressive action of potassium iodide.