# INDUCED HYPOADRENALISM IN PATIENTS REQUIRING ORTHOPEDIC SURGERY

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• *Prolonged administration of steroids often, but not always, results in adrenocortical insufficiency. It has been difficult to determine whether a patient so treated is actually devoid of adrenocortical function. Elective surgery on bones and joints in such a patient should be postponed until his adrenal status is ascertained and he has been weaned away, if necessary, from the steroid. The test used for this purpose consists in administering corticotropin and determining daily salt excretion during a period of constant salt intake; hypoadrenalism is likely to exist if the corticotropin fails to reduce the salt excretion and especially if it fails to induce eosinopenia and hypokalemia. Ten patients who had been receiving steroids (for seven years, in one instance) underwent orthopedic surgery. The above test was carried out in nine and revealed adrenal insufficiency in six. The diagnosis was borne out by the occurrence of shock in four of the patients and the effectiveness of hydrocortisone given intravenously in combating it. In cases of elective surgery the operation can be postponed for several months to permit weaning, but, when emergency surgery is required in a patient who has been receiving cortisone, increased amounts of steroid will be needed during and after the operation.*

Hypoadrenocorticism is increasing in frequency because of the increased variety and use of steroids in the treatment of a number of diseases. This has produced a growing problem for those of us who are called on to operate on such patients for injury or reconstruction of their bones and joints.[1] Orthopedic surgeons in particular should be cognizant of the symptoms and management of sudden adrenocortical insufficiency during and after surgery or injury, since a number of patients who receive cortisone acetate or other steroids come under their treatment for reconstruction.

Hypoadrenocorticism may result from several conditions. It may be induced by the administration of steroids. It results from adrenalectomy or hypophysectomy, procedures in vogue today for treatment of certain cancers, from hyperplasias of the pituitary adrenal system, and from hypertension. It occurs in adrenal cortical hypofunction (Addison's disease). Finally, it may occur as a result of adrenal tuberculosis, amyloid disease, and other pathological conditions of the adrenals.

## Effect of Long-term Use of Steroids

There are many corticosteroids on the market today. Among them are cortisone, hydrocortisone, fludrohydrocortisone acetate, prednisone (Meticorten), prednisolone (Sterane), Co-Deltra (buffered prednisone), and Co-Hydeltra (buffered prednisolone). Other preparations, which include salicylates (such as Sigmagen [tablets containing prednisone, aspirin, ascorbic acid, and aluminum hydroxide] and Salcort [tablets containing cortisone acetate, sodium salicylate, dried aluminum hydroxide gel, calcium ascorbate, and calcium carbonate]), are also being widely used. Some confusion has been produced among doctors and patients alike by the variety of trade names for the identical steroid. The fewer side-effects these steroids have, the more widely they are used. However, one side-effect that has not been diminished is induced hypoadrenalism, which may result from therapy with steroids over a long period of time. That these steroids are potential adrenal suppressors, causing functional and pathological adrenal atrophy, has been well established by Bennett [2] and others.[3]

## Diagnosis of Hypoadrenalism

Patients with hypoadrenalism who must undergo surgery may be classified into two categories. First, they may have adrenocortical insufficiency but their operation may be classified as elective. It can be put off until the appropriate time. Second, they may have adrenocortical insufficiency at a time when injury or disease requires an emergency operation. The diagnosis of hypoadrenalism in each of these cases is a difficult problem.

*Elective Cases.*—When faced with the problem of operating on a patient in whom he suspects adrenocortical insufficiency, the surgeon would like to know whether this condition actually is present. Adrenal insufficiency may not be provoked until a very major stress occurs, such as an operation of great magnitude. It also may occur, however, with a far less stressing incident, such as a simple manipulation of the knee with the patient under anesthesia.[4]

We have had difficulty in determining whether the patient who has been receiving steroids for some length of time is actually devoid of adrenocortical function. One of the indicators we have been studying is the measure of salt conservation after an intravenous infusion of corticotropin (ACTH). The amount of salt excreted in the urine per 24 hours is measured for 48 hours, during which time the salt intake is calculated and restricted to not over 3 Gm. per 24-hour period. During this time blood electrolytes as well as the 24-hour urinary potassium and sodium excretion are measured. After the 48 hours have passed, an infusion is given of 50 mg. of corticotropin in 500 cc. of dextrose and water over a 4-hour period. Thereupon, in the next 24 hours, at 12-hour and 24-hour periods, the total uri-

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nary salt excretion is recorded as well as the blood electrolytes. If the patient has normal adrenal function, the amount of salt excreted in the urine in the 24 hours after this test will decrease by 50 to 75% of that in the control period. Since the average person normally excretes about 100 mEq. of salts a day per liter of urine, usually the excretion in the urine will not exceed 40 or 50 mEq. per liter over the 24 hours after the infusion. Therefore, if the amount excreted fails to decrease, this failure to conserve salt after the test with corticotropin should alert one to the possibility of hypoadrenalism. This condition is especially likely to exist if the patient also fails, after the infusion of corticotropin, to develop hypokalemia, a slight rise in the plasma level of 17-hydroxycorticoids, and a transient eosinopenia, all of which occur in the normal person. The long-term treatment with cortisone, received no supplementary steroids and tolerated surgery without difficulty.

*Emergency Cases.*—A second problem, which is difficult to evaluate, occurs in the patient who must have emergency operation or treatment due to injury and in whom there may be some deficiency in pituitary or adrenal function. In this instance, one is not able to examine the patient elaborately prior to surgery, and, consequently, we have found that a regimen similar to that described recently by Perlmutter[5] has been of some help to us in the subsequent management. In such cases, where a history of cortisone therapy has been given, the simultaneous examination of a specimen of voided urine and of blood for sodium concentration will be useful. A high degree of salt excretion and

*Occurrence and Treatment of Adrenocortical Insufficiency in Ten Orthopedic Patients Undergoing Elective or Emergency Surgery*

| Case No. | Surgery | Age, Yr. | Sex | Diagnosis | Steroid Used Previously | Operation | Supplementary Management | Shock | End-Result, Time After Surgery |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Elective | 43 | M | Pemphigus, 2½ yr. (osteoporosis; avascular necrosis, hip) | Cortisone acetate, 35-1,000 mg. (av. 200 mg. daily) | Replacement of head of femur | Cortisone, salt, blood | 9 times in 72 hr. | Living and well, 4 yr. |
| 2 | Elective | 37 | M | Adrenal cortical hypofunction (Addison's disease); arthritis, lumbosacral and sacroiliac joints | Desoxycorticosterone acetate (Doca) pellets, 150 mg.; cortisone, 25 mg., 7 yr. | Spinal fusion and sacroiliac fusion; removal of plate (4 mo. later) | Desoxycorticosterone, cortisone, hydrocortisone I.V., saline solution, blood | none | Wound infection, living and well, 2 yr. |
| 3 | Elective | 60 | M | Rheumatoid arthritis; protrusio acetabuli | Cortisone, 75 mg., 18 mo.; hydrocortisone, 20 mg. (stopped 3 wk. prior to surgery) | Angulation-resection osteotomy, hip | Hydrocortisone I.V., cortisone, prednisone (Meticorten), blood | none | Living and well, 4 mo. |
| 4 | Elective | 36 | M | Rheumatoid arthritis (severe contractures) | Hydrocortisone, orally, 20 mg. daily, 2 yr. | Femoral osteotomy | Cortisone, hydrocortisone I.V., blood | none | Living and well, 18 mo. |
| 5 | Elective | 68 | F | Rheumatoid arthritis; intracapsular fracture, nonunion (osteoporosis) | Hydrocortisone orally, 20-40 mg., 4 mo. | Smith-Petersen nailing; Fred Thompson prosthetic replacement, 6 wk. later | Cortisone, hydrocortisone, prednisone, blood | twice | Living and well, 18 mo. |
| 6 | Elective | 54 | M | Rheumatoid arthritis; fracture of right hip, nonunion | Hydrocortisone; cortisone, 50-100 mg., 3 yr. | Prosthetic replacement, right hip | Hydrocortisone I.V., cortisone I.M., blood | none | Living and well |
| 7 | Emergency | 56 | M | Rheumatoid arthritis; ruptured appendix (fistula [fecal], sepsis, osteoporosis) | Cortisone, 50 mg. I.M.; hydrocortisone intra-arterially, 18 mo. | Appendectomy; closure evisceration (2 wk. later) | Hydrocortisone I.V., cortisone, saline solution, blood | 3 times in 24 hr. | Death (adrenal atrophy and sepsis) |
| 8 | Emergency | 78 | F | Rheumatoid arthritis (osteoporosis); intracapsular fracture of hip | Prednisone, 20 mg., 8 mo. | Smith-Petersen nailing of hip | Hydrocortisone I.V., cortisone, prednisone, blood | twice | Living and well, 6 mo. |
| 9 | Emergency | 78 | F | Idiopathic thrombocytopenic purpura; intracapsular fracture of hip; osteoporosis | Prednisone, 40 mg., 6 mo., 10-40 mg. | Knowles pins, hip | Cortisone, prednisone, blood | none | Death, 4 mo. (autopsy showed normal adrenals) |
| 10 | Emergency | 48 | F | Osteoarthritis; intracapsular fracture of hip | Prednisone, 20-30 mg., 9 mo.; hydrocortisone | Smith-Petersen nailing of hip | Prednisone, hydrocortisone I.V. | none | Living and well |

absence of these particular changes in response to corticotropin provides a useful indicator that supportive steroid therapy may be required. Clinically, the presence of asthenia and hypotension is doubly significant, especially if the patient has received adrenocortical steroids for over three months.

We have used this method of assay in nine patients, and we have been able to demonstrate to our satisfaction, prior to surgery, the need for supplementary treatment during stress in six patients. The successful treatment of these six patients with supportive therapy indicates either that this method of assay was useful or that the administration of corticosteroids did not harm the patient in the recovery from stress even if the supplementary steroid was not actually needed. The three patients in whom the preliminary tests disclosed salt conservation after infusion of corticotropin, despite a low serum sodium level should suggest the possibility of hypoadrenalism and alert the surgeon to the need for treatment in the event of shock. In emergency cases, the presence of eosinophilia, unexplainable hypotension, and a high urinary volume and salt excretion indicates adrenal insufficiency.

## Present Series

We have collected the data on 10 patients requiring operations on the bones and joints (see table). All of the patients had been receiving cortisone or other steroids for at least four months prior to surgery. One of them had also been receiving desoxycorticosterone acetate (Doca) pellets for seven years because of adrenal cortical hypofunction. Two of the patients had been receiving prednisone and two, hydrocortisone orally. Three additional patients were suspected of having adrenal insufficiency because of long-term corti-

sone therapy, but they did not demonstrate this condition in response to the test with corticcotropin. They are not included in this study.

It was of great interest to note the preoperative conditions that required treatment with steroids. Six persons were afflicted with rheumatoid arthritis of advanced degree, one had pemphigus, one had idiopathic thrombocytopenic purpura, one had adrenal cortical hypofunction, and one had been receiving cortisone for osteoarthritis. None of the patients had received corticosteroids for less than four months. Dosages ranged anywhere from 20 mg. of prednisone a day for four months to 1,000 mg. of cortisone a day over two years. Two patients died: one directly as a result of adrenal insufficiency and treatment, the other four months later of other causes. We have been able to examine the adrenals of both of these patients. The autopsy of the patient who died soon after operation disclosed adrenal atrophy, with both adrenals weighing less than 3 Gm. There were thin cortices, with loss of the lipid substance. However, in the patient with thrombocytopenic purpura who died four months after operation, the adrenals appeared normal despite the patient's having received heavy doses of prednisone for over six months up to the time of death.

Six of the patients thought to have induced hypoadrenalism underwent elective surgery and four underwent emergency surgery. Three of the four undergoing emergency surgery required open treatment for fractures, while the fourth, with arthritis, developed a silent ruptured appendix. Operative procedures performed on the patients included insertion of Knowles' pins and Smith-Peterson nails, spinal fusion, osteot-

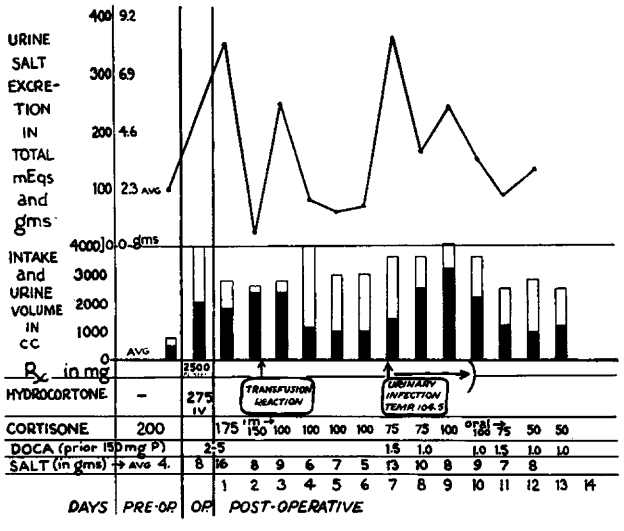


Fig. 1.—Salt loss and treatment in patient with adrenal cortical hypofunction (Addison's disease) undergoing spinal fusion.

omy, resection-angulation osteotomy, and prosthetic replacement of the head of the femur. The ages ranged from 36 to 78 years.

Treatment consisted of increasing the amounts given of steroids in various forms and, in some cases, of salt administration during surgical stress and shortly thereafter. One patient also received desoxycorticosterone. Details of management varied, depending on the particular time these patients were studied. For example, in 1952 a patient was carried through simply with intramuscular administration of cortisone every four hours and with salt, whereas the last patient was given cortisone intramuscularly before, hydrocortisone intravenously during, and prednisone after surgery. In only one case, because of adrenal cortical hypofunction, was it necessary to use desoxycorticosterone. In this pa-

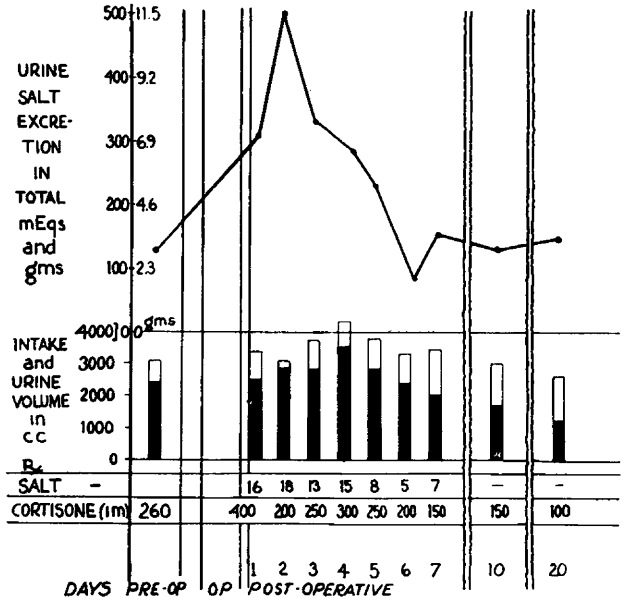


Fig. 2.—Salt loss and treatment in patient with induced adrenal insufficiency undergoing replacement of head of femur.

tient, after a spinal fusion, a transfusion reaction and a urinary tract infection produced a sharp increase in salt excretion, requiring the use of additional desoxycorticosterone, salt, and cortisone. Figure 1 illustrates the rise in urinary salt excretion and the need for supplementary steroids in this patient.

Follow-up of these patients varies from six months to four years. In no instance after convalescence has there been any evidence of further adrenocortical insufficiency. Except during periods of stress, practically all the patients were receiving low maintenance doses or no steroids whatsoever when last seen.

*Clinical Response During Early Postoperative Period.*—Shock occurred in 4 of the 10 patients postoperatively. (This was defined as blood pressure under 80/50 mm. Hg, pulse rate over 120 per minute, and clinical appearance of shock.) The first patient we studied, who had pemphigus, had nine separate bouts of shock within 72 hours postoperatively, requiring heroic, constant treatment. Undoubtedly, in this patient shock was due to frank insufficiency as well as to poor management. The fact that this patient's urinary salt excretion was excessive can be seen in figure 2. One patient died despite all attempts at therapy. Within three weeks this patient had had three separate bouts of shock. Death was due to sepsis and overwhelming infection as well as to adrenal atrophy. One patient, who had undergone an uncomplicated Smith-Petersen nailing, had two separate bouts of shock 24 hours after operation. A second patient had two separate bouts of shock within the first 24 hours after replacement of the head of the femur. The intravenous

use of hydrocortisone in both of the last-mentioned patients was effective in restoring blood pressure to normal. All of the patients operated on received adequate blood transfusions. In none of the patients was hemorrhage the cause of shock. Particular care was taken to maintain blood volume. It was interesting to note that in no instance was shock present while the patient was under anesthesia; it occurred only after the patient had awakened. The shock would come on in a matter of minutes and lasted, in one case, as long as two hours. Usually, marked improvement was noted within a half-hour after administration of hydrocortisone. In addition, each of the four patients in whom shock developed had eosinophilia and an unusually high salt excretion for a number of days after surgery. This, to us, was significant evidence that there was a defective adrenocortical response to the stress of surgery or injury. In no instance was there evidence of renal disease or water intoxication.

### Treatment

The hypotensive state may come when one expects it least, namely, during the first 24 to 48 hours postoperatively. It comes on with great speed and requires definitive treatment. One cannot wait for corroboration by the laboratory in such cases. The treatment of adrenocortical insufficiency with a corticosteroid is most important. Even if one is not certain in such an emergency that the hypotension is due to adrenal depletion, we feel that hydrocortisone should be given intravenously along with other supportive treatment. A high eosinophil count in the presence of severe stress (with a high amount of urinary salt excretion), as well as persistent tachycardia and hypotension despite adequate blood replacement therapy, is an indication that adrenocortical insufficiency is present. We feel that the treatment of induced adrenocortical insufficiency can proceed along three lines.

1. Patients undergoing emergency surgery should receive 100 mg. of hydrocortisone intravenously in 500 cc. of saline solution, supplementary blood, and cortisone intramuscularly in 50-to-100-mg. doses. 2. Patients undergoing elective surgery who require cortisone up to the time of surgery should be treated as follows: Preoperatively, they should receive 100 mg. of cortisone at 9 p. m. the evening before and at 7 a. m. the morning of operation. During operation, they should receive 100 mg. of hydrocortisone in addition to blood. Postoperatively, they should receive, every 12 hours, 50 to 100 mg. of cortisone the first day and 25 to 50 mg. the second day. Then, if the course is satisfactory, prednisone should be substituted on the third day and given daily in 20-mg. doses for three days, and the doses should then be tapered off. 3. For patients undergoing elective surgery who do not require steroids, the surgery should be put off for three months while steroid administration is tapered off and the patient's adrenal function is studied.

Response to the first two regimens described indicates that the assumption of adrenocortical insufficiency is correct, although actual proof of this may be difficult. However, we feel that, since it is only a short-term method of treatment bolstered by continuing intramuscular administration of steroids, the danger of infection or failure in wound healing is quite remote. This is particularly true in operations on extremities, where sepsis is less catastrophic, rather than in operations on the intestine. However, high doses of cortisone will interfere with repair, and, therefore, one should take the patient off this regimen as quickly as possible.[6] In this particular series, infection occurred in only one patient, when pyelitis, cystitis, and wound infection developed in the patient with adrenal cortical hypofunction.

Long-term prednisone therapy did not produce pathologically detectable adrenal atrophy in the patient with idiopathic thrombocytopenic purpura, who came to autopsy. Whether functional atrophy was present is not known, as this patient was operated on for a fracture and was not studied preoperatively.

### Summary and Conclusions

There are a great many steroids on the market today that may cause adrenocortical insufficiency if they have been used for a long time prior to surgery. It is important to know whether adrenocortical insufficiency occurs, as it produces shock and is easily manageable. Therefore, each patient should be closely questioned for pretreatment with a corticosteroid. The use of a salt-excretion test after infusion of corticotropin has been of some value preoperatively as an indicator of adrenocortical insufficiency and, thus, of the need for supplementary treatment.

Ten patients who had been receiving cortisone acetate for a sufficient amount of time to produce in some of them adrenocortical insufficiency underwent operation. In six of nine patients in whom a preoperative test with corticotropin was utilized, the failure to conserve salt in addition to the failure to develop eosinopenia indicated the need for supportive therapy, and these patients were managed on such a program during surgery with a minimum of discomfort. One patient on long-term corticosteroid therapy did not present evidence of adrenocortical insufficiency at autopsy, while still another did produce evidence of this. Accordingly, adrenocortical insufficiency often, but not always, results from prolonged administration of steroids.

One should test for adrenocortical insufficiency rather than take its presence for granted prior to surgery. Operations on any patients undergoing elective procedures on the bones and joints should be postponed, therefore, until an assay to rule out adrenocortical insufficiency has been undertaken. A patient who has been receiving cortisone or another corticosteroid for any length of time and who requires surgery should be weaned away from the steroid for several months and then have surgery performed. When a patient has been receiving cortisone, however, because of other factors and when emergency surgery is required, treatment should consist of administration of increased amounts of cortisone and hydrocortisone during and after surgery, as needed, until the patient's condition becomes stable.

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Dr. Robert Kaufman, New York, gave permission to report case 9.

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# THE NATURAL HISTORY OF HERPES ZOSTER

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• *The course of herpes zoster was studied in a series of 206 patients that included infants and octogenarians. There were 32 patients under the age of 20; in 30 of these (94%) the condition cleared up in 14 days or less. The infection was more severe and prolonged in older patients. In four elderly patients symptoms persisted six months or longer. The relative frequency with which the various parts of the nervous system were involved varied from youth to old age. No instance of involvement of the ophthalmic division of the trigeminal nerve was observed in patients under the age of 20, but ocular complications did not appear to be related to the aging process. Postherpetic neuralgia did not occur in patients under 20 but was frequent in patients over 50. Sex, race, and season did not perceptibly influence the incidence of infection in this series.*

Herpes zoster is an acute, self-limited disease of infectious origin. It is characterized by grouped vesicular lesions on an erythematous base distributed over several dermatomes as well as, in some cases, by a systemic reaction. This study of the incidence, duration, distribution, and complications was undertaken to establish clearly the natural history of the disease. Impressions gained from the more severe reactions associated with herpes zoster have tended to color the picture unfavorably. As a result of these impressions, the literature is crowded with many reports of treatments advocated to alleviate pain and shorten the course of the infection. Jadassohn [1] suggested the benign nature of herpes zoster in his review, but, until recently, no attempts have been made to chart its natural course. It is hoped that this study will serve as a yardstick to evaluate the future claims for therapeutic success in patients with this infection.

The majority of the 206 cases for this analysis were chosen from the dermatology and ophthalmology departments of a general hospital (Hospital of the University of Pennsylvania, Philadelphia) and the outpatient department of a pediatric hospital (Children's Hospital of Philadelphia) over a 15-year period. By surveying a pediatric hospital and an ophthalmology clinic, we naturally increase the number of children and the incidence of ophthalmic involvement. We felt that this would give a more valid picture of the infection than a study of cases selected from a dermatology clinic alone, and that this was a valid assumption is shown by a comparison of the age groups in our series with the percentage of the population of Philadelphia in the various age groups.

In analysis of the data, the number of cases in the study of any one facet of the infection varies according to the information that was available on the various cases. The infection was considered to have cleared when all crusts had fallen off leaving erythematous, macular lesions. The postinfectious inflammatory reaction on the skin was not considered part of the acute infection in the evaluation of the length of the infection. Neuralgia following herpes zoster was defined as any subjective, painful sensation that persisted after the acute phase of the infection. Treatment consisted of a number of nonspecific measures and, therefore, did not enter into the data.

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## Etiology

Virological studies have established clearly the similarity of the infectious agents in chickenpox and herpes zoster. The elementary bodies seen under the electron microscope are rounded or brick-shaped and measure approximately 210 by 243 mμ. They are most numerous during the first 12 to 24 hours and decrease rapidly, so that by 72 hours they are practically nonexistent. The virus particles from chickenpox and herpes zoster are indistinguishable in all physical appearances. Von Bokay [2] suggested the close relationship between the two after observing cases of chickenpox arising after contact with herpes zoster. Since then, many reports of chickenpox occurring in persons who are in contact with patients with herpes zoster have been reported, while the reverse has been much less commonly observed. In this connection, the British medical research council reported 20 outbreaks of chickenpox instituted by cases of herpes zoster in boarding schools for boys during a five-year period.