1 to 2% of all patients sensitive to insulin exhibit general manifestations. There can be little doubt that this patient's symptoms of general malaise, nausea, anorexia, and heartburn, with irregular vomiting, coinciding in onset and offset with the cutaneous reactions, were part of a general allergic reaction. This case is also interesting for the severity of the local cutaneous reaction (there does not appear to be a record of a local cutaneous reaction with bulla formation following subcutaneous injections of insulin) and the very short period of hypersensitivity.

Gastineau and Leavitt (1946) reported a case of allergy to insulin with a generalized reaction which was improved by treatment with diphenhydramine hydrochloride. In their case the reaction recurred when that drug was discontinued. In our case spontaneous desensitization probably occurred, as promethazine hydrochloride was given for only three days, and there was no recurrence when it was discontinued.

Wilder, in the discussion of the case of Gastineau and Leavitt (1946), draws attention to insensitivity to the anti-diabetic activity of insulin as a form of allergy to insulin. In this case no increase in the dose of insulin was necessary during the period of allergy.

In most of the reported instances of allergic reactions to insulin it has been shown that the reactions are diminished or abolished by the use of insulin recrystallized several times, and it has been suggested that minute traces of secondary protein contaminating the purified insulin are responsible. This was probably the mechanism in our case, as a comparison of the two insulin solutions used has shown that crystalline insulin is the only substance common to both.

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TREATMENT OF ANOGENITAL WARTS WITH PODOPHYLLIN

BY

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The treatment of soft warts in the anogenital region with podophyllin was first described by Kaplan (1942), who wrote: "The treatment . . . consists of the application of 25% podophyllin in mineral oil to all the condylomatous masses, care being taken not to make the application too liberal. Within 6 to 8 hours after the application the patient begins to experience pain over the area of application and usually requires codeine sulphate or even morphine for relief. During the next 12 hours there is a marked local reaction, with inflammation and oedema throughout the tissues near the site of application. On the second and third days the condylomata begin to slough off and the pain eases. On the fourth or fifth day the tissues return to normal. . . . A weaker solution requires repeated applications and the pain is almost as severe."

Review of Literature

Eleven years have elapsed since that paper was published, and numerous reports have confirmed the efficacy of the treatment but stressed the frequency of reactions. Culp *et al.* (1944) treated 100 cases in the U.S. Army and 13 developed balanitis or proctitis, three of them severe enough to necessitate a dorsal slit or circumcision. Macgregor (1945) reported 25 cases in which the excess podophyllin was cleaned off with soap and water after six to eight hours,

the area dried, and a dusting powder applied. In his opinion, this greatly reduced the incidence of severe reactions. Lipman Cohen (1946) treated 30 Service cases, all as in-patients. In some there was much swelling and discharge under the foreskin, which could not be retracted. This subsided with baths and 12.5% aqueous sodium sulphate dressings. The scrotum became superficially ulcerated if left for long in contact with the podophyllin. A dorsal slit and later circumcision were required in one case. In a further small series, in which the Macgregor technique was used, Cohen reported that the reactions were rather less, and remarked that "this method . . . is much less painful than Kaplan found originally, but more so than Macgregor stated."

Sullivan and King (1946) followed a similar routine, and reported that "balanitis and phimosis occur in some patients. . . . The frequency of this complication depends on the amount of podophyllin which comes into contact with the glans penis and foreskin, and also probably on individual sensitivity to the drug. The balanitis and phimosis subside in a few days if the preputial sac is irrigated daily with a mixture of equal parts of distilled water and 3% hydrogen peroxide. It is not necessary to perform a dorsal slit or circumcision except in extreme cases." Flagg and Powell (1947) experimented with various strengths of podophyllin, and recommended the use of the 25% suspension for meatal lesions, 10-15% for lesions on the glans or prepuce without phimosis or a redundant foreskin, and 5-10% for lesions under a redundant phimotic prepuce. They reported reactions in 27% of cases (non-meatal) treated with the 25% suspension. Nobis (1948) tried the effect of suspension in 96% alcohol instead of liquid paraffin, in an attempt to localize the applications to the warts and avoid the seeping which is inevitable with the oily base. Ronchese (1949) stressed the importance of ringing the area with soft paraffin, while Willcox (1948) suggested that more harm than good may result from this manoeuvre.

It will be seen from this review that, although the efficacy of podophyllin has been established beyond doubt, local reactions from its use are far from negligible. Cases of severe conjunctivitis have been caused by accidental transfer of the irritant material to the eyes. There is a considerable risk that the patient who attends as an out-patient will forget or be unable to report again six to eight hours later for the removal of the podophyllin. It may perhaps be possible to avoid severe reactions by careful in-patient supervision, such as was reported by Cohen (1946). A stay in hospital, however, of between 4 and 29 days (average 12 days) seems hardly justified in the management of a comparatively minor complaint, and in civilian practice would be quite impracticable.

New Method

It is for these reasons that the development of a safer method of treatment seems imperative. Wurm (1950) described a method in which he used a much weaker preparation, 1.5% podophyllin being dissolved in hexaethylene polyglycol, in order to get better penetration. A modification of this method has been used for the past 18 months on over 100 cases in the skin and venereological out-patient departments attached to the Royal Naval Barracks at Portsmouth.

To start with, 1.5% podophyllin in propylene glycol was used, but it has since been found that a 3% concentration is more effective, and does not cause any inflammatory reaction. The area is first cleaned with 1% cetrimide, and dried. The application is then made with an orange stick and cotton-wool, followed by profuse powdering with talc. The prepuce, if present, is then adjusted to cover the glans penis and the patient warned not to interfere with it. After 24 hours the procedure is repeated, and again on subsequent days. By the second, third, or fourth application the lesions start to melt away, and it is very seldom that more than four or five applications are required. If there is the slightest reaction, the treatment is not carried out until

it has settled, the area being kept well powdered. It is, however, very seldom that any discomfort is reported by the patient, and in no case has an oedematous balanitis developed. This really does seem, in fact, to be a safe and yet most reliable form of treatment, that can be carried out even by an untrained assistant.

It has been our experience that the harder and more chronic lesions are generally resistant to podophyllin, and usually require destruction by diathermy or electrocautery.

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Medical Memoranda

Löffler's Syndrome Occurring During Streptomycin and P.A.S. Therapy

Toxic reactions encountered during treatment with sodium *p*-aminosalicylate (P.A.S.) include fever and pruritus (Hemming and Stewart, 1949), skin eruptions (Horne, 1949), haematuria (Nagley and Logg, 1949), hypoprothrombinaemia (Swanson, 1949), potassium deficiency (Cayley, 1950), and jaundice and enlargement of lymph nodes (Cuthbert, 1950). In the following case of Löffler's syndrome combined therapy with streptomycin and P.A.S. was given, the latter drug being held responsible. This is the first time, so far as I am aware, that this complication of P.A.S. therapy has been described in this country.

CASE REPORT

An unmarried girl aged 18 suffered from tuberculous endometritis (chest x-ray film clear). Previous illnesses were pneumonia in 1945, and mumps and measles in childhood. There was no personal or family history of allergy. Out-patient treatment with streptomycin (1 g. daily) and P.A.S. (12 g. daily) was begun on November 18, 1952. On December 13 she complained of general malaise of three days' duration associated with anorexia, vomiting, and vertigo. She had received 25 g. of streptomycin and approximately 290 g. of P.A.S. Specific drug therapy was discontinued. After admission to hospital later the same day she had a rigor and vomited. Her temperature was 99.6° F. (37.6° C.). Her face was flushed, and the conjunctivae were injected. An intensely itching maculopapular rash quickly developed on her trunk and forelimbs. The occipital, deep-cervical, epitrochlear, and axillary lymph nodes were enlarged. There was no icterus. The liver and spleen were not palpable. Diphenhydramine hydrochloride, 200 mg. daily, was given and lotio calaminae cum menthol applied locally. For three days she had low irregular pyrexia—99.6° F. (37.6° C.). The itching gradually subsided and the rash faded.

On December 17 she was well; the rash had gone; the liver-function tests were normal; Hb, 13.3 g.; white cell count, 8,200 per c.mm. (differential count not performed). On December 22 the white cell count was 5,640 per c.mm. (polymorphs 53%, eosinophils nil). Diphenhydramine hydrochloride was discontinued. On the 26th streptomycin, 0.1 g. intradermally, produced generalized reaction with vertigo, tinnitus, and vomiting. Her face was flushed, there was no rash, and her temperature was not elevated. An area of induration and erythema, 3 cm. in diameter, at the site of injection later became ulcerated and persisted for two weeks.

Test doses of P.A.S., 1.5 g., 3 g., and 6 g., were given by mouth on successive days without ill effect. On January 2, 1953, a test dose of P.A.S., 6 g., was given by mouth. In the evening she complained of feeling hot, and developed a dry irritating cough. Her temperature was 105° F. (40.6° C.), pulse 120, respirations 30. Her face was flushed but there was no rash. Glands were palpable in the neck, axillae, and epitrochlear regions. The respiratory and cardiovascular systems were normal. Diphenhydramine was resumed.

Next day her temperature was normal, she felt well, and the cough was easier. X-ray examination of the chest revealed extensive coarse mottling throughout both lung fields, resembling a widespread bronchopneumonia. On the 4th she had no complaint; the cough was gone, and the drug was discontinued. Chest x-ray examination was repeated on January 8 and no pulmonary disease was seen.

Next day the Hb was 13.7 g.; white cell count, 9,800 per c.mm. (polymorphs 70%, including eosinophils 4%). Desensitization to P.A.S. was begun according to the schedule recommended by Madigan *et al.* (1950).

January 14, P.A.S., 1.5 g.: rise of temperature in evening—100.4° F. (38° C.); shivery, but no other complaint. January 15, P.A.S. withheld; temperature normal; chest x-ray film showed no pulmonary disease. January 16, P.A.S. resumed at 500-mg. dose; E.S.R., 12/19 mm. (Westergren). January 18, P.A.S., 1.5 g.: well; white cell count, 10,200 per c.mm. (polymorphs 70%, including eosinophils 8%). January 22, P.A.S., 3 g.: white cell count, 10,480 per c.mm. (polymorphs 61%, including eosinophils 10%). January 29, P.A.S., 6 g.: no ill effect; cold agglutinin titre 1 in 28. February 5, P.A.S., 9 g.: no complaint; cold agglutinin titre, 1 in 16.

COMMENT

The syndrome of acquired sensitivity to P.A.S.—namely, constitutional upset with fever and pruritic skin eruption—was first reported by Horne (1949) and has since been described and amplified by many workers. More recently (Jeffry *et al.*, 1952) it has become apparent that a similar syndrome occurring in patients receiving combined streptomycin-P.A.S. therapy may be evidence of acquired sensitivity to both drugs. The allergic nature of these reactions is indicated by the positive results of skin tests with the appropriate drug, by the eosinophilia reported by several authors, and by the effectiveness of desensitization.

There is no doubt that the above case was one of acquired sensitivity to both streptomycin and P.A.S. The main interest in the case centres on the reaction which occurred after the initial flare-up had subsided and which followed the administration of test doses of P.A.S. alone. The outstanding feature of this reaction was the absence of significant constitutional upset despite high fever (105° F.—40.6° C.). The only symptom complained of was an irritating cough which lasted nearly three days. The temperature returned to normal on the second day and remained at that level. Radiologically there was extensive patchy consolidation in both lungs, which had cleared completely five days later with no treatment other than diphenhydramine. The eosinophil count was not carried out at the height of the reaction, but one week after the onset of the reaction—that is, after resolution of the pulmonary infiltrations—eosinophils numbered 4% of 9,800 white cells per c.mm. and rose subsequently during P.A.S. desensitization to 10% of 10,480 white cells per c.mm. The occurrence in an allergic individual of such transient pulmonary infiltrations without significant general upset seems to justify a diagnosis of Löffler's syndrome.

This syndrome, as Löffler himself has pointed out, represents an allergic response of the body to an antigen, the lung being the shock-organ. In most of Löffler's cases the antigen was *Ascaris lumbricoides*, but, as Crofton *et al.* (1952) have shown in their very extensive review of the subject, a wide variety of other antigens have been incriminated from time to time. It is perhaps surprising that Löffler's syndrome is not seen more often in acquired sensitivity reactions to P.A.S. The not infrequent occur-