PUSTULAR ACNE, STAPHYLODERMA AND ITS TREATMENT WITH TOLBUTAMIDE

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The problem of acne, speaking pathologically, is not very serious, but if we consider the total picture including psychological ramifications which affect the social life of the individual, it becomes a disease of major importance. This aspect has been well documented by Marshall.

The treatment of acne is not a simple "magic bullet" affair. The specific systemic measures usually employed in addition to local therapy depend upon the seriousness of the skin condition. These additional measures include hormone therapy, antibiotic therapy, dietary control, vitamin supplements, ultraviolet and x-ray therapy, and administration of toxoids and vaccines. Local and x-ray therapy is aimed at combating sebaceous gland hyperplasia and seborrhea, and eradicating follicular plugging to prevent new foci.

In severe cases of acute pustular acne, local therapy alone is of little value. The underlying predisposing causes, whether hormone disturbances or metabolic defects, must be taken into consideration. Antibiotics are of doubtful value topically but are of value systemically in some forms of acne.

We agree with other investigators that vitamin A has a definite value, particularly in the comedo-papular type of acne. Clinical evidence of vitamin A deficiency, such as follicular keratosis about the elbows and knees of certain patients, can often be found. We use Aquasol A, 50,000 units once daily for three months. We often combine 50,000 units of synthetic vitamin A with 500 mg. of vitamin C. The role of vitamin A in the treatment of acne has received wide study. When acne is characterized by comedo formation and numerous small papules (especially when the comedo phase is excessive), we employ a dosage of 100,000 units of vitamin A per day for 3-5 months.

The role of hormones in the management of acne has been and still is controversial, but again good results have been achieved by us, as by many workers, with the use of oestrogenic substances.

It has been shown that the urinary excretion of 17-ketosteroids is increased in patients receiving ACTH therapy. In patients with Cushings disease, in persons before puberty, and in eunuchs, 17-ketosteroid excretion is low and acne is not present. The excretion level rises at puberty, especially with the development of secondary sex characteristics, and at this time acne manifests itself. It has also been shown that the excretion of 17-ketosteroids is a reliable guide to the androgen level. It has been our custom to prescribe oestrogens in severe cases, in males and also in females with exacerbations at the menstrual period. We use diethylstilbestrol, 0.25 mg. daily for 12-15 days of the month for males and in females 0.25 mg. once daily from seven days after completion of the menses until the onset of the next period. This avoids disturbance of the cycle of ovulation. Oestrogens inhibit the gonad-stimulating function of the anterior pituitary gland. One must be careful not to use excessive doses because they may inhibit ovulation, and in the male gynaecomastia may result.

Bacteria are an important factor in the development of follicular plugging and pustular lesions with acne. Cocci have been found in the follicles and not in the inflammatory infiltrate about the sebaceous glands. Bacteriological studies in our cases revealed that the organisms cultured from acne pustules included: (1) haemolytic Staph. albus; (2) non-haemolytic Staph. albus; (3) haemolytic Staph. aureus; (4) non-haemolytic Staph. aureus; and (5) mixed forms of diphtheroids as contaminants. In some cases there was no bacterial growth. Sensitivity tests were performed in all cases of staphylococcal infection from the purulent secretion of the pustule, and organisms were tabulated as resistant and sensitive to antibiotics. The following antibiotics were used orally: sulphonamides, penicillin, erythromycin, chloramphenicol, oamycin, tetracycline, novobiocin. Antibiotics were used in the deep, nodular, cystic, pustular types of moderate to severe acne. Isoniazid was also used in some cases. A few patients needed the addition of an antibiotic to control the pustular element of the eruption. All types of antibiotics were used, but the best results were obtained with chloramphenicol and erythromycin. We were never impressed with the end results obtained with any antibiotic, except where we encountered a deep cellulitis requiring incision and drainage. After one week, a favourable response was obtained, only to be followed by a new flare-up in the pustular element of the lesions. Relapses were frequent after discontinuance of the antibiotics. Most of these pustular cases received courses of ascending doses of staphylococcus ambotoxoid injections, 1:5 dilution increasing to the undiluted mixture.

TOLBUTAMIDE THERAPY

Shortly after the introduction of tolbutamide on the Canadian market for the treatment of diabetes, our attention was drawn to the rapid recovery of moderately severe acne in two women who were on this therapy. In view of the rapid improvement in these two patients, a series of 23 additional patients were given tolbutamide therapy and carefully followed up. Some had deep pustular acne, chronic staphyloderma, recurrent furunculosis, sycoasis vulgaris, hidradenitis suppurativa or hidradenitis axillaris, and other resistant pustular infections of the skin.
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Results

The results obtained have been summarized in Table I. All patients experienced a sharp decrease in new pustular and cystic lesions and diminution both in size and soreness. All were greatly improved, in marked contrast to the results obtained with usual methods of therapy. No hypoglycemic reactions were observed. One patient complained of nausea and diarrhoea, and one of headaches and vertigo. The latter was found to be sensitive to sulfonamides.

Method

Only patients who were resistant to therapy by the usual methods of treatment were included in this study. They were instructed to continue taking carbohydrates in their diet, including candy and fruit if desired. All those with severe acne received one tablet (0.5 g. tolbutamide) every 12 hours. The milder cases received one tablet (0.5 tolbutamide) per day. These patients were seen at regular intervals and their blood sugar was determined at frequent intervals. The results were always within normal limits.

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Case Reports

Case 1.—Mr. D.I. (mechanic), aged 22, had been treated for acne for five years at other centres and had received about 1000 r of x-ray therapy. He was first seen here in March 1958, presenting a deep cystic type of acne vulgaris of the face, shoulders and back, with innumerable sebaceous cysts and comedones and deep acne papulo-pustules. The reddened cysts were the size of a hazel nut, and the neck was involved with band-like keloidal lesions. He felt very insecure and afraid to face the public, and required tranquilizers. This patient had been treated by us by all known methods of acne therapy, including diet, Viemintex packs, resorcin, and sulphur lotions, stilbestrol and most of the antibiotics. He responded to acne surgery and chloramphenicol, injections of staphylococcal toxoid, vitamins, and ultraviolet light, but with relapses. In May 1958, he was given tobutamide 0.5 g. (Mobenol) twice daily. He began to show very marked and continued improvement. The purulent lesblons diminished gradually until no evidence of pyoderma was seen, but only acne sequelae with scarring. He is receiving CO₂ therapy and will require facial skin planing.

Case 2.—Since 1954, Mrs. M.N. (a stenographer) had been treated for pyoderma faciale, consisting of intense reddish cyanotic erythema associated with superficial and deep abscesses and cystic lesions. Some cysts were connected with communicating channels and sinus tracts with deepseated pustular and linear scarring. Previous treatment by us consisted of incision and drainage, x-ray therapy, local therapy, injections of penicillin, sulfonamides, many antibiotics including chloramphenicol, ultraviolet light, CO₂ therapy, vitamins, staphylococcal toxoid, and vitamin D₃ (calciferol), and a search had been made for a foci of infection. She had many remissions and relapses with pustular flare-ups. In October 1957, she was given tolbutamide, with a gradual clearance of all pustular lesions. All lesions have cleared except the late sequelae, and the patient is at present receiving CO₂ therapy.

Case 3.—Mr. J.L., aged 29 (druggist), was first seen in January 1957, with a severe papulo-pustular acne vulgaris of face and neck, and acne keloidal lesions of the back, deepseated pustules and many cystic pustular lesions. He also had sycosis vulgaris. This patient had been under the care of other clinicians including dermatologists for many years, receiving x-ray
therapy to the limit of tolerance. Under our care he was given acne surgery, ultraviolet light, CO₂, staphylococcus toxoid and all forms of local therapy, resorcin and sulphur lotions, vitamins A and C, isoniazid, stilboestrol, and a large number of antibiotics, with relapses and remissions. In February 1958, he was started on tolbutamide 0.5 g. twice a day, with a continued clearance of the lesions. He is still taking one tablet daily, and the lesions have cleared, only an occasional one reappearing. He is now being treated for the late sequelæ, with CO₂ for scarring, and continuing with local therapy.

Note: This patient, when taking two tolbutamide tablets daily, at times experienced hunger, mild trembling, and a little sweating—which could have been evidences of hypoglycaemia. This was remedied by increased consumption of carbohydrates.

Case 4.—Mrs. M.C. (practical nurse), aged 50, with a long history of recurrent furunculosis involving groin, external genitalia, breast and nipple areas, was treated by incision and drainage and X-ray therapy, and was allergic to many antibiotics except oleanosymin and erythromycin. She had many recurrent flare-ups. She was first seen in November 1957, with subcutaneous nodular, painful lesions, involving groin and perianal and vulvar regions, as well as a few in the axillae. Some were soft and fluctuating and discharged purulent material which on culture grew a haemolytic staphylococcus. Our diagnosis was: hidradenitis suppurativa, or deep infection of the apocrine glands. Treatment included more X-ray therapy, ultraviolet light, antibiotic compresses and applications, tin oxide tablets, oestrogenic hormone, staphylococcus toxoid, and multiple vaccine therapy. She responded very well to erythromycin and oleanosymin, but with flare-ups of painful and recurrent furuncular lesions. The fasting blood sugar was 95 mg. % and she had no glycosuria. In April 1958, she was started on tolbutamide 0.5 g. twice a day, and gradually showed a marked improvement with only occasional recurrences. The subcutaneous nodules did not develop into abscesses and underwent resolution. She is taking one tolbutamide tablet daily.

Case 5.—Mr. H.D., aged 20 (farmer), was first seen in July 1957, with a very severe and deep cystic and papulo-pustular acne vulgaris, and an associated oily seborræa. Face and forehead were covered with reddened cystic and deep acne pustular lesions, and many indurated papules. Some cysts were the size of a hazel nut and one was the size of a small walnut. He had been under the care of dermatologists for four years, and received much X-ray and local therapy.

Under our care he was given more unfiltered X-ray therapy, Vleminkx’s compresses, detergent soaps, staphylococcus toxoid, sulphur and resorcin cream and lotion, and a variety of antibiotics from sulfonamides to all the “mycins,” responding best to chloramphenicol. There were many remissions and relapses. All therapy was stopped except local therapy and he was started on tolbutamide, 0.5 g. twice a day, in March 1958. We instructed him to take a little extra candy each day, and gave him CO₂ therapy with acetone locally twice weekly. The response was sudden and dramatic. In two weeks, all pustular elements of the lesions disappeared. The active lesions subsided markedly and no new lesions appeared. He is being treated now for the late sequelæ, and a few very superficial pustules still make their appearance. He is taking one tolbutamide tablet daily.

Case 6.—Mr. J.H., aged 22 (school teacher), whose acne began at age 15, presented himself in January 1958, with a severe deep papulo-pustular acne vulgaris covering the entire back, face, shoulders and chest, with scarring and sequelæ. Clinically, this was a case of acne aggregata seu conglobata. Many double comedones with severe perifollicular infection and confluent infiltration, and softening of the lesions with suppuration were present, lesions varying in size from a filbert nut to a marble and requiring many incisions and drainages. Under the care of another dermatologist for 3-4 years previously, he had received maximum doses of X-ray therapy to face, chest and back.

In January 1956, he was given an acne diet and Vleminkx’s packs, resorcin and sulphur lotions, stilboestrol, nearly all known antibiotics, injections of toxoid, and ultraviolet light, and all foci of infection were searched for. He would improve in the summertime with exposure to sunlight, but relapse in the winter with severe and deep pustular lesions. In March 1958, the patient was given CO₂ therapy to the face and ultraviolet light to the body, injections of Pancebrin (multiple vitamins), and one tolbutamide tablet, 0.5 g. twice a day, with a decided and marked improvement of all pustular elements. Local therapy was continued. A few lesions recurred when the patient could not afford medication, but when tolbutamide tablets were supplied to him the lesions gradually subsided. He is now taking one tolbutamide tablet daily with a dramatic subsidence of all lesions, except for the sequelæ. Tolbutamide tablets will be stopped when no new lesions appear, and he will be a candidate for dermabrasion.

Discussion

The modus operandi of the drug is not manifested by any antibiotic action, for it is a sulfonyleurea and not a sulfonamide. The way tolbutamide acts is still debatable. It has no bactericidal effect. A 1.0-g. dosage lowers blood sugar levels about 10% in normal individuals.

What role does tolbutamide play in the management of acne and pyodermic skin disorders? This poses a question which cannot be answered at this time, nor can the question of the mechanism of action of tolbutamide in the management of diabetes. For many years furunculosis and carbuncles have been associated with diabetes.

What is the mechanism of the beneficial action of this drug? The answer is to be found in the theories of the late Dr. Eric Urbach of Philadelphia. He championed the concept that the skin not only serves as a temporary storehouse for dextrose, but also plays an important role in intermediary carbohydrate metabolism. The skin has a capacity to transform glucose into glycogen and possesses glycolytic fermentations. Finally he suggested the concept of “skin diabetes” as a term for the syndrome, including a therapy-resistant skin.
disease, clinically furunculosis, sweat gland abscesses and pruritus. This syndrome is manifested by high fasting skin sugar levels together with normal blood sugar curves and marked improvement of the dermatosis, as well as a fall in high skin sugar levels on a low carbohydrate diet and the use of tolbutamide.

There is of course no connection with a true pancreatic diabetes (diabetes mellitus); the acne patient has normal blood sugar tolerance curves, and no case of this kind progresses to frank diabetes. Cutaneous glyohistechia with apparently normal sugar regulation is merely a hyperglycoterma without hyperglycemia. There is a disturbance of carbohydrate metabolism involving only the tissues of the skin. This pattern of behaviour can be described by the term "skin diabetes".

This theory has much evidence in its favour and opens up a vast field for research in the future. Is the effect of tolbutamide in these skin conditions one of altering the environment of the staphylococci to the point that the natural body mechanisms can cope with the invaders? There is much work to be done, but this thought is offered as a possible explanation of the results obtained in this small series. Further detailed biochemical and bacteriological studies are obviously in order.

CONCLUSIONS

Acne is still one of the greatest problems, and the management of it is still the major activity of most dermatological practices. Tolbutamide has proved to be a good adjuvant in our practice. We are convinced that this is a very useful drug in these cases. The effects on acne patients are much better than those of the broad-spectrum antibiotics and are obtained at a fraction of the cost. Of course, the hypoglycemic effect is more marked in the diabetic than in the normal individual. We have concluded that tolbutamide aids in controlling pyogenic infections of the skin. Repeated routine checks on fasting blood sugar levels in several patients taking two 0.5-g. tablets a day were all within normal limits.

A series of 26 patients with pustular acne vulgaris and other pustular dermatoses, resistant to the usual forms of therapy, were treated with 0.5-1.0 g. tolbutamide from one to four months, and all improved. In six patients the improvement was fair; the rest had good or excellent results. There was one failure, in a woman allergic to sulfonamides.

The results obtained so far warrant continued broader investigation of this compound and its relationship to dermatological conditions.

SUMMARY

Twenty-six patients with severe forms of acne vulgaris and other forms of pustular dermatoses were treated with tolbutamide when all other forms of therapy had been disappointing. All patients, except one, experienced fair to excellent improvement.

REFERENCES


OVARIAN SURGERY DURING PREGNANCY*

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Ovarian surgery during pregnancy has always carried an implied and actual threat towards the integrity of the pregnancy in the mind of the gynaecologist. This trepidation is based on three physical facts:

1. The trauma involved to the uterus and the adnexa.
2. The surgical shock and sequelts attendant on any laparotomy.
3. The dislocation of the corpus luteum from its position in the ovary, with all its associated endocrine implications.

The importance of each of these factors is still controversial, particularly in relation to the part the corpus luteum plays in the economy of pregnancy. From a limited experience, we would feel that the factors of trauma and so-called "surgical shock" are most important.

Surgery, carefully performed, should not be postponed, because of the age of the pregnancy. When pain is severe and persistent, unrelieved by bed rest and sedation, and a definite mass is felt, little is to be gained by waiting, as operation is nearly always inevitable.

OVARIAN PHYSIOLOGY IN PREGNANCY

Samson Wright stated that if the corpora lutea are removed from rabbits 20 hours after mating—that is, when the fertilized ova have been in the tube for 20 hours—no progational changes will take place in the uterus. Furthermore, none of the embryos will live after the fourth day. However, if