BEHCET'S SYNDROME

BY

G. W. CSONKA

Belfast City Hospital

The literature on Behcet's Syndrome has been reviewed by Curth in America (1946), Katzenellenbogen (1946), and Ephraim (1944) in Palestine, and in this country by Prosser Thomas (1947). Though cases of this kind were described by several authors before Behcet, he was, nevertheless, the first to recognize the clinical unity in one patient of the three cardinal symptoms, and he called it the triple-symptom complex (Behcet, 1937).

The reported instances of the fully developed syndrome are not many, but since the diversity of the presenting symptoms must have led many patients to various medical specialists, it is likely that many cases have been reported under the symptoms and signs pertaining to the system in which the specialist in question was most interested. The fully developed disease presents oral and genital ulcers with various, sometimes grave, eye lesions. These signs may appear simultaneously or successively in any order, e.g. with lag periods of up to twenty-one years between the ulcers and the eye lesions (Whitwell's case, 1934), and may be of any degree of severity. Recurrences are frequent, but without predictable regularity. Single attacks have occurred, although the possibility of late recurrences must be remembered in prognosis. None of the lesions by themselves are sufficiently diagnostic—but the combination of two or three symptoms in the course of one attack or as recurrences may give a fairly sure indication of "Behcet's syndrome."

Case Reports

The obscure ætiology may justify the following notes on two cases referred to

venereal disease and skin departments of a military hospital as ? secondary syphilis and ? Vincent's stomatitis respectively.

CASE 1

A cadet, aged 18, single, was referred to a venereal centre by his medical officer with the diagnosis of ? secondary syphilis.

On admission.—A healthy man had had painful ulcers of mouth and penis for one week; he denied sexual intercourse. There had been no previous major illnesses, and in particular no indication of previous venereal disease, skin disease, or aphthosis.

Examination.—There were small, shallow ulcers in the mouth, especially the inside of the lips. Tonsils, teeth, and gums appeared healthy. There were similar ulcers on the glans penis and sulcus coronæ. Dark-ground examination for *T. pallidum* gave negative results. Direct smears and cultures from the lesions showed no pathogens. Kahn, Wassermann, and gonococcal complement fixation tests were all negative, and there was no pyrexia.

Progress.—Two days after admission the patient developed bilateral conjunctivitis and ciliary injection. No pathogenic organisms were found in the conjunctival secretions. The eyes were improving slowly after a week, when he developed pyrexia of 103° F. and complained of pain in his nose. An early furuncle was found in his nasal passage, and soon afterwards he began to have œdema of the face. The ulcers of mouth and penis began to show signs of regression (two and a half weeks after their first appearance). He was given three-hourly intramuscular injections of 20,000 units of penicillin for his furuncle, which burst shortly afterwards with subsequent disappearance of the constitutional symptoms. Smears and cultures from the nasal boil showed *Staph. aureus*.

The oral and penile ulcers had maintained their improvement in the meantime, and the eyes were almost entirely clear; but one gained the impression that the course of penicillin had not contributed to this event as the regression had started before penicillin therapy and had progressed very slowly during treatment. The patient was discharged to duty four weeks after admission.

CASE 2

A lance-corporal, aged 30, married, was admitted to a venereal disease and skin department with a history of ulcers in the mouth. These had started a week before as small erosions and became painful as they progressed. He was treated by his medical officer and a dental surgeon, but the condition became worse. A provisional diagnosis of Vincent's stomatitis was made.

On admission.—The man was very depressed and pale, with painful sores in his mouth. There was nothing relevant in his personal medical history, and no tuberculosis or allergic diathesis in the family history.

Examination.—Widespread ulcers were seen in the patient's mouth, their average size being 2 to 4 mm. with a tendency to coalesce; both buccal membranes and the hard and soft palates were affected, and in particular the lower lip, which showed some oedema. There was slight cervical adenitis. Teeth, tonsils, and tongue appeared healthy. There was some folliculitis on the face and shoulders.

The glans penis showed numerous discrete sores, and on the shaft were two larger, deeper, and more irregularly outlined ulcers. There was no inguinal adenitis. The patient asserted that he had not noticed the genital sores until the day before admission.

Repeated dark-ground examinations were negative for *T. pallidum* and also for Vincent's spirochaetes from both sites. Repeated smears and cultures failed to show any pathogens. Weigert-stained films were searched without success for inclusion bodies. Kahn test was negative. The red blood count was 4,800,000 per 100 c.mm. of blood, and the white 4,800; the differential count was normal.

Progress.—Next morning the condition had become more painful and the patient was able to take nothing but a little fluid; the genital ulcers had increased in extent. He was now given 100 mg. tablets of nicotinic acid five times a day for six days, making 3,000 mg. in all. No other treatment was given. His diet consisted of milk and, later, ordinary hospital diet. After the third tablet the patient volunteered the information that the pain had almost vanished, and by next day the ulcers of mouth and genitals appeared to be healing. His mental attitude was euphoric, in

great contrast to his former dejection. On the fourth day of treatment there were only dusky areas to indicate the former sites of ulcers. A few days later he was discharged and was asked to report any recurrence of symptoms, but he has not done so yet.

Discussion of Cases

The first patient showed the triad of stomatitis, genital ulcers, and eye lesions (conjunctivitis and mild iritis), which is characteristic of the fully developed Behcet's triple-syndrome complex. In addition there was the intercurrent furunculosis, a feature often noted in this condition.

The second case was an incomplete form of the same disease. Similar "formes frustes" have been described previously (Whitwell, 1934; Popoff, 1938; O'Leary, 1933; Michaëlis, 1937; Gray, 1924; Berlin, 1944) and appear to be more common than the fully developed triad.

Diagnosis

It is not necessary to wait for recurrences before a diagnosis is established, as single attacks of the disease are well known (Pils, 1925; Kumer, 1930; Talalov, 1934; Carol and Ruys, 1928; Chauffard and others, 1923).

Combinations of two symptoms of the triad, such as oculo-genital and oculo-oral, have been observed by Blobner (1937), Cavara (1940), and Franceschetti and Valerio (1940). In our present state of knowledge any two symptoms of the triad are the minimum needed to make a diagnosis; thus recurrent or single aphthosis of mouth or genitals or non-specific irido-cyclitis by themselves are insufficient; nor is there any specific laboratory or therapeutic test known to aid in diagnosis.

Treatment

All treatments, including administration of penicillin and sulphonamide compounds, have failed; only two patients, treated by Knapp (1941) and Schultheiss-Linder (1941) with nicotinic acid, appear to have reacted promptly. Knapp's therapy had little success with other workers. Benadryl has been tried in a case of aphthosis without effect (Lynch, 1947).

Aetiology

Behcet's belief in a specific virus has not been confirmed, nor his contention that focal sepsis plays a part in producing and

maintaining the disease. Tuberculosis as an ætiological factor is now discounted (Curth, 1946). A similarity to herpes has been noted by Katzenellenbogen (1946). Allergy, particularly in connexion with the *S. aureus*, is considered by Weve (1923) and Foss (1941) to play a part in causation. Several authors have noted a peculiar skin sensitivity which produces reactions to all intradermal tests and has even reacted to physiological saline injections and the prick of a sterile needle. Blobner (1937) likened this non-specific reactivity of the skin to the so-called "pathergy" of Urbach, which is not based on an antigen-antibody reaction. Cavara (1940) believes that a virus induces sensitivity to the staphylococcus.

In one necropsy on a patient who had died with progressive central nervous symptoms, perivascular round-cell infiltration of the brain was found, as well as œdema of the liver (Berlin, 1944). Liver enlargement was noted by Carol and Ruys (1928) and by Michælis (1937). Apart from Berlin's fatal case, symptoms of the nervous system were observed by Prosser Thomas (early neuritis) and Knapp (? disseminated sclerosis). Mental depression was noted several times (as in my second patient). Arthritis was found in several cases, and chronic dysentery, ileitis, and ulcerative colitis preceded a few.

It is clear from the many careful and competent laboratory investigations that no known infective agent can be held responsible for the disease. Biochemical findings of the blood, urine, fæces, cerebrospinal fluid, and gastric secretions were normal. The positive skin reactions to a great diversity of unrelated substances, ranging from physiological saline, tuberculin, and staphylococcus toxoid to Frei's antigen, appear to emphasize the non-specificity of the disease. There is, however, a similarity between the symptom pattern of Behcet's syndrome and that of other better known diseases, and the former could be a deficiency disease. In the Table the main characteristics of Behcet's disease are set out, together with those of a group of deficiency diseases.

Stomatitis, eye lesions, balanitis, various skin affections, late mental symptoms, and the chronic relapsing course can be found in the Behcet syndrome groups as well as in the deficiency diseases listed. It is also noteworthy

that a few of these cases were preceded by chronic bowel disorders, and that nervous symptoms did occur late in the disease, this making for greater similarity to the deficiency diseases mentioned in the Table. Moreover no causative agent of infection has been found in the triple syndrome.

How may one reconcile the favourable results with nicotinic acid in Knapp's, Schultheiss-Linder's and the present second case, with the negative reports by other workers? Have different conditions been grouped under the same diagnostic heading, in which case nicotinic acid might be used as a therapeutic test aiding differentiation? Has nicotinic acid been given in too low a concentration? This is possible in the case of some workers who gave 100 to 150 mg. nicotinic acid daily for a few days and recorded failure. For the treatment of the mental confusion of acute nicotinic acid deficiency, Sydenstricker (1943) suggested 100 mg. of nicotinic acid (or 30 mg. of nicotinamide) hourly for ten doses in the first two days, then 500 mg. daily for several days. It might be relevant to mention the recent work by Ellinger and Benesch (1945), in which it is suggested that sulphonamide compounds destroy intestinal organisms which synthesize nicotinic acid. These drugs should, therefore, not be administered concurrently. There is also some evidence that a low carbohydrate intake enhances the activity of the vitamin.

I am of the opinion that the variations in the symptomatology of Behcet's syndrome suggest various deficiency factors, but that the general picture fits well within the frame of the complex syndromes of avitaminosis B. Secondary invasion by organisms, in particular the staphylococcus, modifies the clinical picture.

Summary

Two cases of Behcet's triple syndrome are described. One patient conformed to the classical description of the disease; the other showed severe oral and genital ulceration and was considered to have the incomplete form of the same syndrome.

Ætiology is discussed; neither infection nor allergy is thought to be the primary cause. Deficiency disease (vitamin B complex) is suggested.

TABLE
COMPARES BEHCET'S SYNDROME WITH AVITAMINOSIS B

Disease	Signs	Associated Signs	Course	Aetiology	Treatment
Behcet's Syndrome (full)	Recurrent genital ulcers ; stomatitis ; eye lesions.	Non-specific skin sensitivity ; pyoderma ; acne ; erythema nodosum. Arthritis ; colitis ; dysentery. Various nervous disturbances.	Chronic, with recurrences. May lead to blindness and encephalopathy.	?	All treatments have failed, a few successes with nicotinic acid therapy.
(incomplete)	Any two of the above.	Milder, often less complicated.	Often single attack.	?	As above.
Pellagra	Recurrent stomatitis, dermatitis, dementia, and diarrhoea.	Amblyopia and atrophic gastritis. Previous disease of alimentary tract associated.	Chronic, with recurrences.	Deficiency of nicotinic acid and riboflavin.	Reduced carbohydrate intake, massive nicotinic acid and riboflavin therapy.
Sprue	Recurrent stomatitis, glossitis, fatty diarrhoea, irritability, and anaemia	Conjunctivitis, depression. Previous disease of alimentary tract associated.	Chronic, with recurrences.	Deficiency of ? folic acid and vitamin B complex.	Vitamin B complex as folic acid and liver ; low fat and carbohydrate diet.
Ariboflavinosis	Glossitis ; cheilosis ; conjunctivitis ; corneal vascularization ; keratitis.	Seborrhoea. Often associated with sprue, pellagra etc.	Chronic, with recurrences.	Deficiency of vitamin B ₂ .	Massive riboflavin therapy.
Diabetes Mellitus complications	Glossitis ; intertrigo ; pyoderma ; balanitis ; often mental depression.		Insensitive to insulin if carbohydrates high in diet. Relieved by nicotinic acid.	Deficiency of nicotinic acid (Rudy and Hoffmann, 1942 ; Sydenstricker 1943).	Massive nicotinic acid therapy and low carbohydrate diet.

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