BEHÇET'S DISEASE

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OTO-LARYNGOLOGISTS sometimes meet with cases of ulcerations of the mouth and pharynx and may miss examination of the genitalia and eyes. If they keep in mind the triad of oral ulceration, genital ulceration and hypopion iritis they may pick out many cases of Behçet's disease which would have otherwise been overlooked.

Hippocrates in his third book of Endemic Diseases, described a similar symptom complex which could have been Behçet's disease.

Jacobini in 1894 described a similar manifestation.

Adamantiades in 1930 recorded a case with the same complex. In 1937 Halusi Behçet, Professor of Dermatology in Istanbul, described this triad in detail, suggested a new clinical entity and proposed the theory of being infective in origin due to a certain virus. Since then the disease took his name and many investigators studied it from different angles.

Sezer in 1953 succeeded in the isolation of a virus from some of his cases but many other investigators could not.

Incidence:

It was described that the disease is more prevelant in the Mediterranean and Near East; France *et al.* in a review of 32 cases in the literature found 57 per cent. of them to occur in this region, 36·1 per cent. occurred in Europe and 6·1 per cent. in the U.S.A.

On the other hand Dowling in a report on 128 cases found hardly more than a moderate preponderance in the Middle East as compared with other parts of the world.

No race or colour is immune. Commonly the disease affects males more than females and the ratio varies from 2 : 1 to 9 : 1 in different reports.

Age:

Usually the disease starts between 20 and 30 years. One case was reported at the age of 13. Case No. 4 of our series is 18 years old.

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Clinical Picture

The fundamental clinical picture is the triple complex of recurrent ulcerations in the mouth and pharynx, ulcers in the genitalia and hypopion iritis.

Curth in 1946 and Phillips and Scott in 1955 said that it is enough to diagnose the case if two features out of the three are present and most probably the third one follows after some time. Usually the mouth and pharyngeal lesions appear first, then the genital lesions and lastly the ocular ones after many years, maybe after 10 years.

Mamo and Baghdassarian (Beirut) in 1964 found out that the triple complex forms only part of the clinical picture and they are usually preceded and followed by other manifestations. The disease runs a chronic course with remissions and exacerbations.

The onset is usually indefinite and it is common that the case presents by the oral or genital lesions. In some cases the onset is manifested by an initial stage of a low grade fever, malaise, general weakness accompanied sometimes by muscle or joint pains. This initial stage usually subsides after a few weeks.

The patient may remain apparently free from symptoms for a variable period which may be from 6 months to 5 years after which he gets typical attacks of ulceration of mouth and genitalia and eye affection.

The attack remains for 1 to 4 weeks and then subsides. Recurrence occurs after a few weeks and usually the patient gets about four to five remissions per year. With every attack the eye condition becomes worse until ultimately the patient becomes blind. Later in the course of the disease, maybe after many years, cerebrospinal complications may appear and with their occurrence the prognosis becomes gloomy.

The attack as a rule occurs without prodromata and no precipitating factor is known. Russel recorded in his case psychogenic and emotional factors which precipitated the attack. The attack may start with some fever, pains in the muscles and joints and then ulcers appear.

The Oral and Pharyngeal Manifestations:

Ulcers may appear on the fauces, cheek, gums, lips, tongue and pharynx. They are usually multiple and vary from 2 to 18 mm. in diameter. The edge of the ulcer is usually punched out, the floor is covered by a white or greyish slough. There may be a small red areola or there may be no reaction at all around it. The rest of the mucous membrane around the ulcer is normal.

These ulcers give rise to variable degrees of pain and dysphagia, may remain for some days or a few weeks and heal but other crops appear again. Extension to the œsophagus has been described.

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The Genital Manifestations:

The scrotum is the most common site for the lesions but the shaft of penis or glans may be affected. The lesion usually starts as a vesicle or papule which ulcerates rapidly and the diameter of the ulcer is from 4 to 16 mm. The edge of the ulcer is also characteristically punched out, the floor is covered by a whitish exudate and there is little or no induration around. The skin around the ulcer is almost normal and the ulcer appears as if nibbled out.

In females ulcers usually appear on the labia and rarely in the vaginal walls or cervix. A bartholin cyst may be found. Sometimes ulcers appear on the perineum.

The ulcers heal spontaneously after a few days or weeks leaving some scarring then recurrence occurs in other areas in the next attack.

Other genital lesions have been reported as chronic epididymitis, hydrocele and orchitis.

The Ocular Manifestations:

The characteristic lesion is hypopion iritis but in early cases mild iritis or uveitis only may be present. Some authors claim that the disease affects first the posterior segment of the eye as macular œdema, retinal hæmorrhages and perivasculitis. Sezer reported narrowing of the retinal vessels with signs of periarteritis and endarteritis. Zeavin reported vitreous hæmorrhage in one case. It is possible that in the past the diagnosis was not made until the disease was advanced and the iritis was marked and the anterior chamber pathology masked the posterior segment changes. Nowadays with the early diagnosis and the early treatment with steroids the hypopion is less common and it is possible to diagnose fundus changes better.

Later the vision deteriorates and the patient becomes blind. One eye may precede the other and usually both are affected. The eye may become atrophic and in some cases secondary glaucoma may need enucleation.

Skin Manifestations:

Katzenellenbogen and Berlin observed abnormal non-specific skin reactivity. A prick of a needle or intradermal injection of saline may produce an erythematous papule or pustule at the site of the prick. This reaction may be present in other unaffected members of the family.

Franceschetti made a Behçetin skin test by preparing an antigen from the scrotal lesions.

Erythema nodosum is common and may appear in any part of the body. It is present in about one third of the cases. Other lesions such as folliculitis, acniform eruptions, pustules, furunculosis, pyoderma and abscesses may be present.

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Neurological complications:

Recently the frequency and severity of involvement of the central nervous system in this syndrome has been emphasized. These complications usually appear late in the course of the disease after 2 to 5 years from onset. Some cases appeared as early as the third month and some as late as 15 years. With the appearance of these complications the prognosis as regards life is serious. The disease becomes fatal only when the nervous system is involved. There appears to be a particular predilection for the brain stem but any part may be affected and the patient may get headache, fever, loss of consciousness and meningitis, a picture of meningoencephalitis. Other affections are reported such as cranial nerve palsies, hemiparesis, quadriparesis, pseudobulbar palsy, organic mental syndromes, aphasia, cerebellar signs and spinal cord involvement with spastic paraplegia or Brown-Sequard syndrome.

Pericardial complication:

Sigel and Larson in February, 1965, reported a case in which a pleuro-pericardial friction rub was heard over the left anterior chest. An electrocardiogram showed serial changes in repolarization forces compatible with pericarditis. The symptoms and signs of pericarditis disappeared after 1 week but the electrocardiographic abnormalities persisted.

Thrombophlebitis:

The disease is famous for its thrombophlebitic complications which probably form an essential part of its pathology. Thrombosis of the central retinal vein, thrombophlebitis of the dural sinus, leg, thigh and calf veins were described.

Thomas reported thrombosis of the inferior vena cava and Boolukas reported a case with thrombosis of the superior vena cava.

Pathology

Biopsies from the oral and genital ulcers revealed non-specific inflammation with preponderance of polymorphonuclear cell infiltration around the ulcer. A lymphatic reaction may be seen deep underneath it. Perivascular infiltration with lymphocytes and plasma cells can be found. France *et al.* observed cell infiltration around the venules and capillaries which spared the arteries.

In the eye the pathology is essentially a perivascular infiltration with polymorphs, monocytes and macrophages. In Sezer's cases severe necrosis of the ciliary body and the peripheral choroid of non-specific nature was found.

In the nervous system round cell infiltration occurs in the meninges and brain tissue with small areas of softening. There may be loss of myelin and some vascular cuffing in the white matter.

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Laboratory Investigations

The blood picture usually shows a moderate leucocytosis, about 12,000, and an increase in the sedimentation rate is present. Blood cultures and serological tests are negative. Cultures from the throat and genitalia usually show the ordinary organisms.

Skin tests by intradermal injection of distilled water or saline may reveal the non-specific reactivity.

The Behçetin skin test using an antigen obtained from the genital ulcers may give a positive reaction.

The cerebrospinal fluid is normal except in cases with neurological manifestations.

Ætiology

Up till now the ætiology of this disease is not definite and many theories are put forward.

The infective theory is the most accepted one although it is still not well established. Behçet suggested that the disease is due to a virus relying on the presence of elementary bodies in smears of hypopion fluid and exudate from the oral lesions.

Alm and Oberg in 1945 succeeded in producing uveitis, keratitis bullosa, focal encephalitis and optic neuritis in rabbits by intracisternal injection of cerebrospinal fluid of patients having the disease.

Sezer in 1953 could isolate a virus from his cases and the virus displayed the same cultural and serologic properties. This virus caused encephalitis in mice and produced in the eyes of rabbits lesions similar to those in man. Positive complement fixation and neutralization tests indicated that special antibodies against the virus are present in the blood of patients having the disease. He grew the virus on chorioallantoic membrane of fertile eggs.

In 1956 Sezer reported the disease in three brothers and this indicated that the disease is communicable. He said that viræmia is present in the patients and can be correlated with the clinical manifestations. As the viræmia increases the titre of the complement fixation reaction decreases and *vice versa*, when the viræmia diminishes the titre of the complement fixation reaction increases.

Evans *et al.* in 1957 inoculated undiluted "aqueous" on the chorioallantoic membrane of fertile hens' eggs. Specimens of brain tissue were homogenized, diluted and injected in other eggs. Intense congestion of the chorioallantois and scanty pock formation occurred. The pocks were 5 mm. in diameter, tough and white. Death of the embryo occurred on the sixth day. After 21 passages the virus could be transmitted at a titre of 10^{-4}. In six cases out of 11 he found in their serum a neutralizing antibody for the virus at a titre of 1/32 or more. This antibody was absent in

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control cases. Attempts to transmit the agent to mice, guinea-pigs and rabbits failed.

On the other hand many other investigators such as Katzenellenbogen, Curth, France *et al.*, Braley, Breslin, etc., could not get positive results by virological examination.

Other theories are put forward but lack enough proof.

The allergic theory depends on the presence of recurrent attacks, the erythema nodosum but the eosinophilia is absent.

The vascular theory: This depends on the frequent occurrence of the thrombophlebitis and the perivascular infiltration but the mechanism is unknown.

Some people such as Shikano think that the disease may be a collagen disease.

As to the special localization in the mouth and genitals Berlin (1960) said that these are the sites for the simultaneous predilection of other diseases of various pathogenesis such as Syphilis, ulcus vulvae acutum, pellagra, drug eruptions, erythema exudatum multiforme, lichen ruber and pemphigus vulgaris. In the last three dermatoses the Koebner phenomenon is very evident, characterized by the appearance of identical lesions after a trauma. If a simple needle prick is able to produce a papule or pustule, other insignificant injuries may also act in the same way. In orientals the mouth and genitals are prone to trivial trauma, the mouth because of the strong food and poor unhygenic habits, the genitals especially in the males because of the perspiration. This may perhaps explain some of the epidemiologic and clinical features of the disease, the incidence in the Middle East, the preponderance in the poor class, the males and the oral and genital involvement.

We have a personal feeling that the disease may be related to foot and mouth disease of cattle. One case has been reported in the fever hospital which had the typical multiple ulcers and was a contact of diseased animals. The character of the ulcers and the multiplicity of the lesions are analogous to those found in the cattle. An epidemic of foot and mouth disease of cattle occurred in Egypt in August, September, October in 1964. Case No. I of our series works as an agricultural engineer in a farm in which cattle are bred and were the victims of the epidemic last autumn. Anyhow, this is still a suggestion and is in need of extensive virological research.

Treatment

Since the ætiology of the disease is not yet established all sorts of treatments have been tried. Removal of septic foci, courses of old tuberculin, streptococcus vaccine injections, fever therapy using Typhoid vaccine or milk injections, autohaemolysis, penicillin, chlortetracycline, sulfonamides, salycilates, large amounts of vitamins and even placental

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implantation. Other lines of treatment such as blood transfusion, antihistaminics, œstrogens, chloramphenicol, streptomycin, oxytetracycline, superficial and deep X-ray therapy and stovarsol have also been tried but all failed to give satisfactory results.

For the thrombophlebitis anticoagulants were given but also without beneficial effect.

Due to the failure of all these lines of treatment adrenal steroids and corticotropin (ACTH) were used and sometimes in large doses and for prolonged courses. They gave more favourable results although no cure or even arrest of the disease occurred. There is diversity of opinion about their value and even Sezer said that they are contraindicated as he found that they increased the clinical manifestations and decreased the titre of antibodies in the blood. On the other hand Phillips and Scott, Wadia and Williams, Borrie, Breslin and many others observed good results with their use and it is possible that the unfavourable results were due to small dosage or short duration of the treatment.

Case Reports

Case No. I.

M.S., a male, aged 31 years. He works as an agricultural engineer in a big farm, presented on January 20th, 1965, with pain in the throat and dysphagia. The pain started 20 days before and received antibiotics. Examination of his mouth showed no abnormality. The posterior pharyngeal wall showed the upper part of a big ulcer which extended down in the hypopharynx and using the mirror it was found extending down to the postcricoid region. The ulcer was about 18 mm. wide and 24 mm. from above downwards. Its floor was covered by greyish slough and the edge was vertical and punched out resembling the syphlitic one. The rest of the mucous membrane of the pharynx, larynx, mouth and nose were free of ulceration.

Small discrete tender glands were found enlarged in the upper deep cervical group on both sides. A biopsy was taken from the edge of the ulcer and it showed non-specific inflammation with round cell infiltration (Fig. 1).

As no diagnosis could be made, Syphilis was suspected and the patient was referred to a dermatologist for further investigation. Luckily the dermatologist found ulcers on the genitalia and the diagnosis of Behçet's disease was suggested. A big ulcer was present on the root of the penis on its lower surface. It was about 16 mm. in diameter with punched edges. The skin around the ulcer was dusky and minimal induration could be felt. Two small similar ulcers were present on the scrotum. No glands were enlarged in the groins (Fig. 2).

Examination of the eyes revealed no pathological changes in the iris or in the fundus. His vision was 6/9 and 6/12 with glasses. Swab from the throat showed no specific organisms other than the normal flora. The patient was given dexamethasone in the form of decadron tablets 1·5 mg. daily for 10 days and then 1·0 mg. daily for another 10 days and then 0·5 mg. daily for another 10 days. Locally the ulcer was painted with Collubiazol (a local sulfonamide paint) and it gradually subsided leaving a scar in its place but other small

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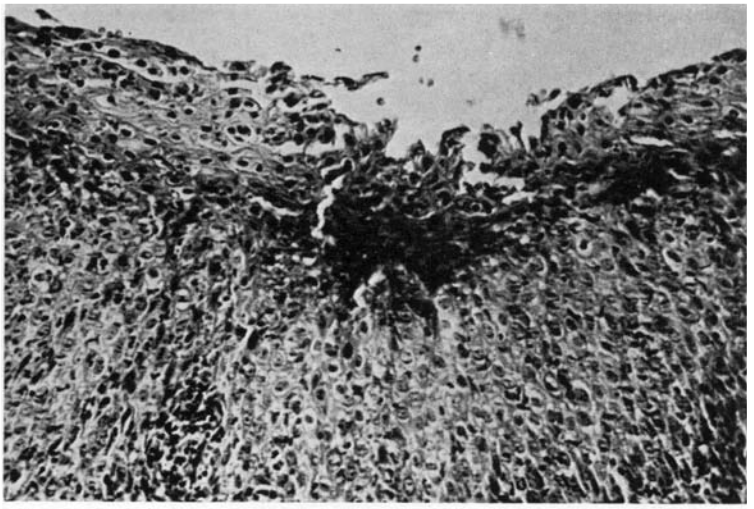


FIG. 1.
Case I. Microscopic picture of ulcer of Posterior Pharyngeal wall.



FIG. 2.
Case I. Ulcers on root of penis and scrotum.

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ulcers on the cheek appeared. They were from 5–8 mm. in diameter, superficial and one of them showed a red areola but the rest did not have any reaction around. The surrounding mucous membrane was normal. Some of these ulcers healed and others appeared and the condition remained quiescent for about 6 weeks.

On April 18th, 1965, the patient got a new attack manifested by severe dysphagia and hoarseness of the voice. His temperature was 37·8. Examination of the larynx and hypopharynx showed a big ulcer in the left pyriform fossa extending on the aryepiglottic fold. The arytenoid, aryepiglottic fold and epiglottis on the left side were swollen and red. The movement of the arytenoid was sluggish and the left vocal cord could not be seen because of the overhanging aryepiglottic fold. The right cord and rest of the larynx were free. There were small ulcers on the cheek (Fig. 3).

The ulcer on the root of the penis was still present but the two small ones on the scrotum were healed (Fig. 2).

The eyes did not show any change. The patient was given oxytetracycline, to avoid secondary infection, for 6 days. He was given another course of steroid as in the previous attack. The ulcer in the pyriform fossa resolved gradually but still there was some œdema of the arytenoid and aryepiglottic fold. The cord movement was slightly sluggish. No neurological disturbances were found.

Case No. II.

S.M.M., a male, aged 42 years, referred from a dermatologist on February 12th, 1965, with ulcers on the palate, posterior pharyngeal walls, lips and cheek (Figs. 4 and 5).

No affection of the larynx was present. On the genitalia an ulcer was found on the lower surface of the shaft of penis just below the glans (Fig. 6). Scars were present in the scrotum. The patient was blind. He had advanced iritis and uveitis in both eyes. The patient had had the disease for 13 years with recurrent attacks of ulcerations. His vision gradually failed and he became blind 2 years ago.

Case No. III.

K.M.P. is a female aged 30 years. She came on March 18th, 1965, complaining of dysphagia, otalgia, burning sensation in the mouth and tongue. The patient said that the disease started 3 months before by fever, rigors, excessive salivation, pain in the mouth and hoarseness of voice. She received antibiotics and the fever subsided after 1 week. The ulcers in the mouth improved. Then ulcers appeared on the upper lip and were covered by scabs which sometimes separated and bleeding occurred. A biopsy was taken and the result was hyperkeratosis with non-specific ulcer.

Ulcers of the mouth appeared again on the cheek (Fig. 7), gums and lower lip (Fig. 8).

On examination the temperature was 37·6° C.

The lower lip showed hyperkeratosis, fissuring and scab formation. Ulcers were present on the inner surface of the lip, cheek, gums and tongue.

Gynæcological examination showed ulcers on the labia and vaginal walls.

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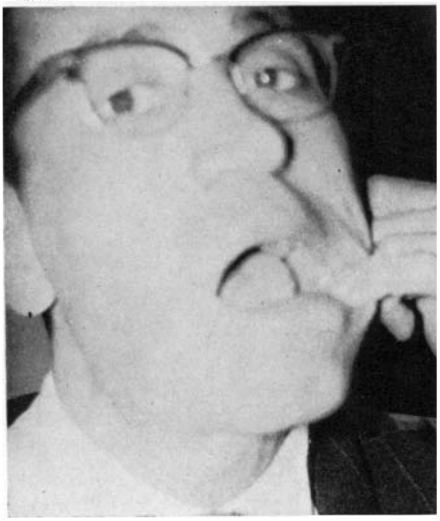


FIG. 3.
Case I. Ulcer on the cheek.

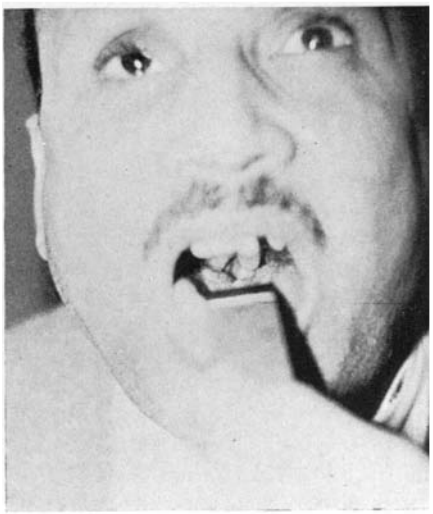


FIG. 4.
Case II. Ulcers on palate and pharynx.

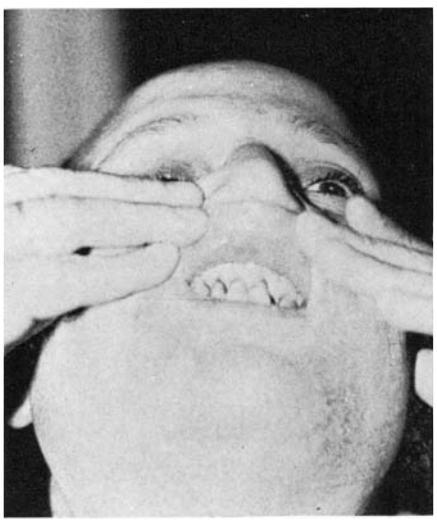


FIG. 5.
Case II. Ulcers on lips.

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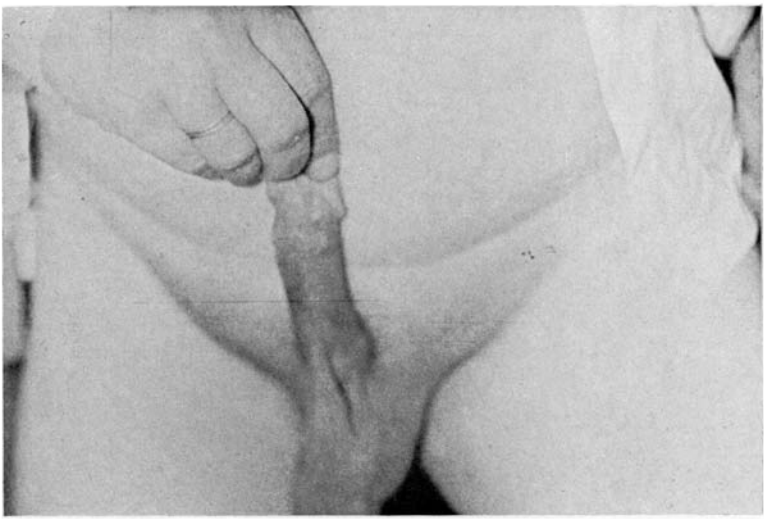


FIG. 6.
Case II. Ulcer on penis.

No eye manifestations were present and the vision was 6/6 and 6/9. Electrocardiogram revealed no evidence of pericarditis. The patient received a course of dexamethasone for 1 month. The ulcers on the lip improved but those on the tongue, gums and cheek improved to a less extent and new ulcers appeared.

Case No. IV.

F.A., a male, aged 18 years, was referred to our section from the Ophthalmology section where he was admitted complaining of pain in his left eye with marked diminution of vision and ulcers in mouth and on scrotum. Last year he had a similar trouble with his right eye and felt severe pain and headache, most probably due to secondary glaucoma, and enucleation of the eye was necessary. Examination of the left eye showed that there was conjunctival and ciliary injection, the cornea was clear, the anterior chamber was shallow, the iris was muddy and its pattern was lost but no hypopion was present, the pupil was sluggish, he could see only hand movement, the tension was 12 mm mercury. The fundus showed patches of choroiditis.

The mouth showed small multiple ulcers in the cheek (Fig. 9), tongue (Fig. 10) and lips.

On the scrotum there was a rounded ulcer about 12 mm. in diameter, the edges punched out and no skin reaction around (Fig. 11). The patient was given steroid treatment as in the previous cases, the ulcers subsided to some extent but still there are a few ulcers on the cheek and the eye condition is quiescent but the vision is bad.

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FIG. 7.
Case III. Ulcers on cheek.



FIG. 8.
Case III. Ulcers on lips.

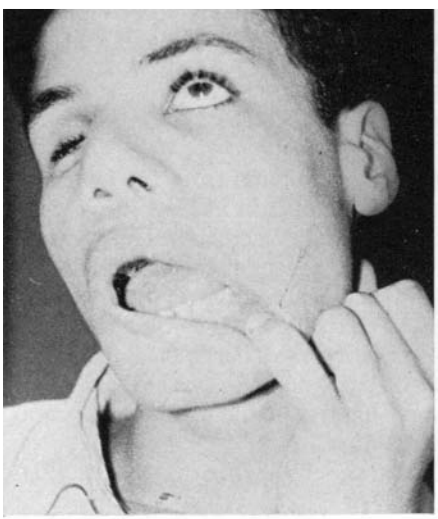


FIG. 9.
Case IV. Ulcers on gums.

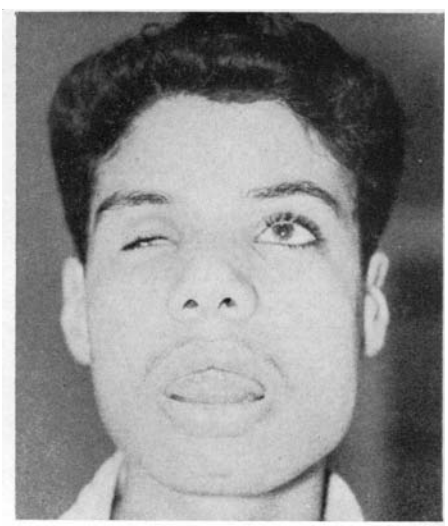


FIG. 10.
Case IV. Ulcers on tongue.

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FIG. 11.

Case IV. Ulcer on scrotum.

Summary

The triple complex of ulcers of mouth, genitals and iritis has to be considered in the differential diagnosis of ulcers of the mouth and pharynx.

The disease runs a chronic course starting with an initial stage and followed by irregular attacks in which the classical ulcers appear. The disease is protracted and usually ends in blindness. Neurological complications may occur later in the disease and may be fatal. The ætiology of the disease is not yet definite and the most accepted theory is virus infection. The only treatment of some benefit is steroid. Four cases are reported with laryngeal and pharyngeal affection in the first case. Cases No. 1 and 3 did not show ocular manifestations probably due to the early affection. None of these cases showed neurological or pericardial complications.

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LABORATORY INVESTIGATIONS FOR CASES I, III AND IV.
(*Done in N.A.M.R.U. Laboratory*)

Laboratory test	Case No. I	Case No. III	Case No. IV
Leucocytic count	5,100	6,500	4,500
Neutrophiles	56 per cent.	21 per cent.	49 per cent.
Lymphocytes	40 per cent.	67 per cent.	39 per cent.
Monocytes	2 per cent.	5 per cent.	5 per cent
Eosinophiles	2 per cent.	11 per cent.	2 per cent.
Platelets	492,000	335,000	750,000
Sedimentation rate	50	43	35
RBC	4,950,000	5,660,000	5,600,000
C. Reactive Protein	P + +	P +	P + + +
Antistreptolysin "O"	125 TU	166 TU	250 TU
Cold agglutinins	Negative	1 : 32	1 : 4
VDRL	Negative	Negative	Negative
Blood culture	No growth	No growth	No growth
Urea N	12·3	14	11·6
Glucose	73	89	71
Cholesterol	179	253	187
Bilirubin (Total)	0·45	0·75	0·6
Bilirubin (Direct)	0·25	0·45	0·15
Thymol Turbidity	4·6	13·5	4·0
Cephalin Flocculation 24 hr.	1 +	Negative	Negative
Protein Total	6·7	8·6	8·4
Albumen	3·8	4·6	4·7
Alkaline phosphatase	1·4	2·1	3·7
Transaminase SGOT	33	108	25
Transaminase SGPT	16	75	9

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