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Synovial pathology in Behcet's syndrome*

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SUMMARY Eight specimens of synovial membrane from 6 patients with 'definite' Behcet's syndrome were available for histological examination. Only the superficial zones of the synovia were affected, all except one being replaced by dense inflamed granulation tissue composed of lymphocytes mingled with macrophages, vascular elements, fibroblasts, and neutrophils. There was a marked plasma cell infiltrate and lymphoid follicle formation in one synovium only, and there was no evidence of infection. Pannus and erosive change were present in the three specimens which included the articular surface, the erosive change being visualised radiologically in two of these. It is suggested that these appearances are characteristic of Behcet's syndrome and should be added to the list of diagnostic criteria.

Several accounts of the clinical manifestations of Behcet's syndrome have been published (Mason and Barnes, 1969; Cooper and Penny, 1974; Moll *et al.*, 1974; Chajek and Fainaru, 1975) together with suggestions of criteria for the diagnosis of this syndrome (Mason and Barnes, 1969). However, the pathology of the synovial membrane of inflamed joints in Behcet's syndrome has previously been briefly described in only 2 cases in the English literature (France *et al.*, 1951; Currey *et al.*, 1968). We report the histological appearance of the synovial membrane from 8 joints in 6 patients with Behcet's syndrome.

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Clinical material

Synovium from 1 female and 5 male patients was studied. The clinical features of these patients are given in Table 1, indicating that all 6 satisfied the criteria for 'definite' Behcet's syndrome as suggested by Mason and Barnes (1969). The joints affected in these patients are shown in Table 2, together with the results of tests for rheumatoid factor and radiographic findings. Radiological erosive change was present in 2 cases: of the hip in Case 3 (Fig. 1), and of the manubriosternal joint on a review of the radiographs in Case 4 (Fig. 2), although the latter

Table 1 *Summary of presenting features and clinical signs*

Case no.	*Sex*	*Age at onset (years)*	*Presenting feature*	*Mouth ulcers**	*Genital ulcers*	*Eye lesions*	*Skin lesions*	*Arthritis*	*GI*	*CVS*	*GU*
1	M	35	Fever; arthritis (episodic)	+			Pustules	+			
2	M	43	Mouth ulcers; genital ulcers; skin pustules	+	+		Pustules	+		DVT	
3	M	19	Arthritis	+		Uveitis		+	UC		NSU
4	M	20	Mouth ulcers; skin ulceration	+	+	Corneal ulcer	Ulcers; pustules	+	D&V	Raynaud's	
5	F	27	Skin pustules; arthritis	+	+		Ulcers; pustules	+			
6	M	Child	Mouth ulcers; arthritis	+	+		Pustules	+		DVT	

*Mouth ulcers in 4 relatives of Case 1. GI=gastrointestinal; CVS=cardiovascular system; GU=genitourinary; DVT=deep vein thrombosis; UC=ulcerative colitis; NSU=nonspecific urethritis; D&V=diarrhoea and vomiting.

Table 2 *Summary of radiographic findings and joints involved*

Case no.	*Radiographs*		*Rheumatoid factor*	*Wrists*	*Shoulders*	*Knees*	*Feet*	*Other joints*
	Loss of cartilage	*Bony erosions*						
1	+	−	Negative	+	+	+	MTP	Elbow, ankle
2	+	−	,,	+		+		
3	+	+ (hip)	,,			+		Hips
4	−	+ (manubriosternal)	,,		+	+	MTP	PIP, manubriosternal
5	±	−	,,	+		+		
6	−	−	,,			+		

MTP = metatarsophalangeal joints; PIP = proximal interphalangeal joints.

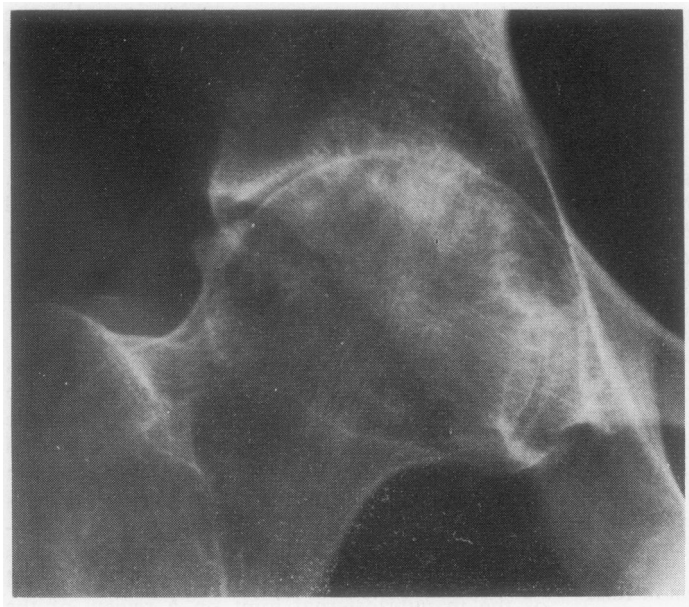


Fig. 1 *Case 3. Radiograph of the hip showing severe loss of cartilage joint space around the femoral head with erosive change.*

had previously been reported as nonerosive (Currey *et al.*, 1968; Mason and Barnes, 1969).

Synovium was obtained from 8 joints in the 6 patients, all of which were the site of clinical inflammatory disease; from 1 wrist, 5 knees, 1 hip, and 1 manubriosternal joint (Table 3). Bacteriological examination of joint fluid was performed in specimens from Cases 1 and 3 (Table 3).

Results

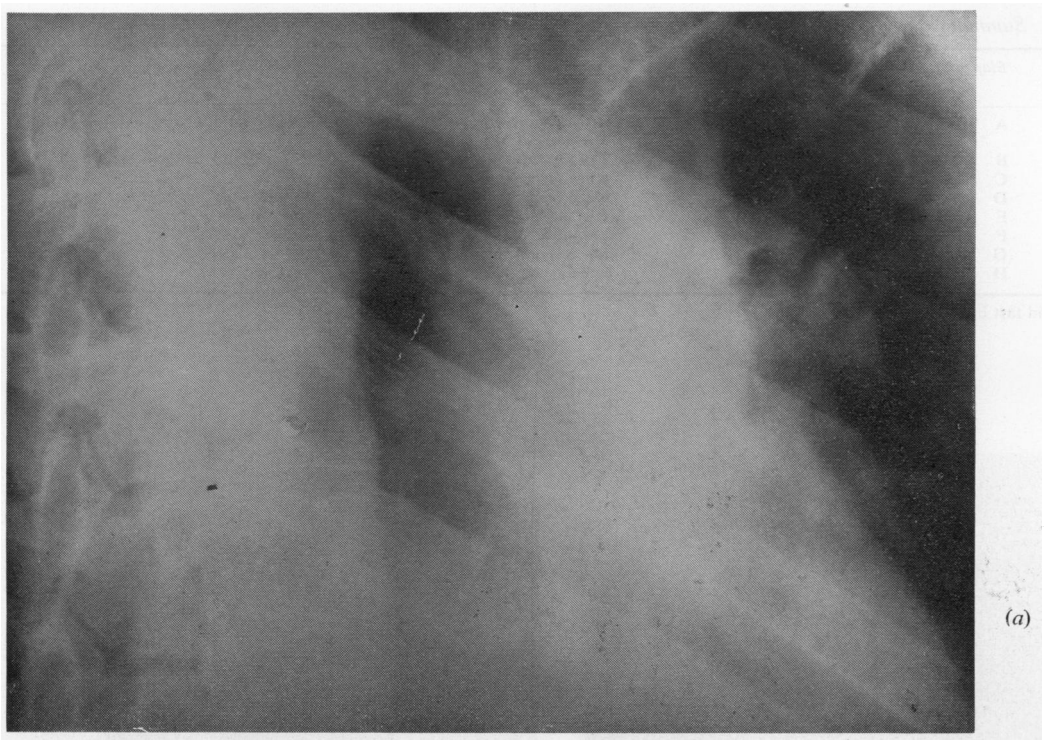
BACTERIOLOGY

Joint fluid obtained from Cases 1 and 3 at the time specimens A, B, and D (Table 3) were obtained was sterile during routine culture and two specimens (B and D) were examined for acid-fast bacilli with negative results.

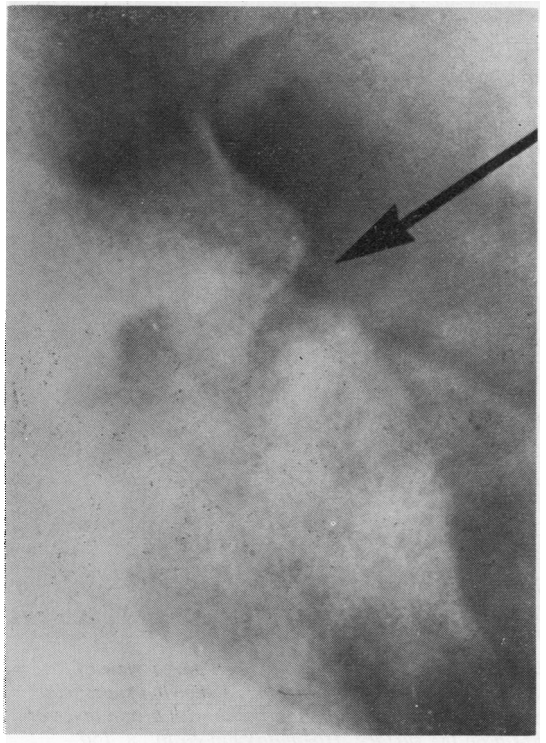
HISTOLOGY

Case 1—specimen A (head of ulna and synovial membrane of the wrist)

Pannus containing numerous neutrophils extended across the surface of the articular cartilage and replaced it in several areas (Fig. 3). There was widespread loss of the synovial lining layer and the superficial zone of the synovial membrane was heavily inflamed with numerous neutrophils (Fig. 4) and was replaced by granulation tissue in many areas. The granulation tissue contained a moderate number of lymphocytes but no plasma cells.



(*a*)



(*b*)

Fig. 2 *Case 4. Radiograph of the manubriosternal joint showing erosion (a) on oblique chest radiograph; (b) by photographic enlargement of a detail from an oblique chest radiograph.*

Fig. 3 *Case 1—specimen A (see Table 4). Granulation tissue (pannus) extending over and into articular cartilage of distal end of ulna. Haematoxylin-eosin* × *18.*

Table 3 *Summary of disease duration before biopsy, joints biopsied, and bacteriological findings*

Case no.	*Biopsy*	*Duration of diseases in joint before biopsy (years)*	*Joint*	*Bacteriology*
1	A	17 (episodic)	Wrist (synovectomy) + excision of distal end of ulna	Sterile fluid
	B	0·25	Knee (needle biopsy)	Sterile fluid; no acid-fast bacilli
2	C	7	Knee (synovectomy)	—
3	D	0·5	Knee (needle biopsy)	Sterile fluid; no acid-fast bacilli
	E	3·5	Hip (arthroplasty)	—
4	F	1·25	Manubriosternal (biopsy)	—
5	G	3	Knee (synovectomy)	—
6	H	3·5	Knee (synovectomy)	—

AFB = Acid fast bacilli.

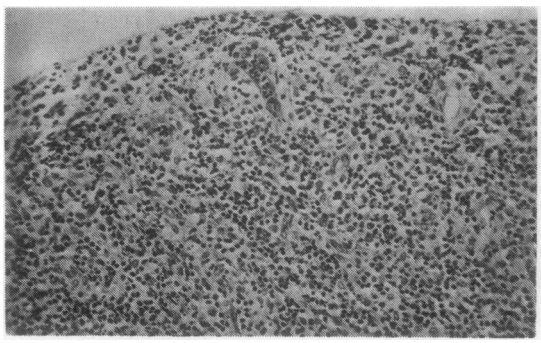


Fig. 4 *Case 1—specimen A. Synovial membrane from wrist joint. Shows absence of lining cells and presence of heavily inflamed granulation tissue. Haematoxylin-eosin.* × *150.*

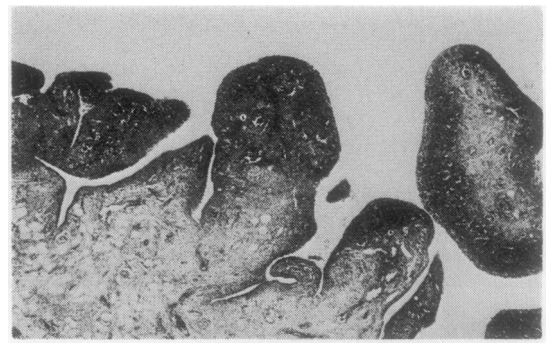


Fig. 5 *Case 2—specimen C. Synovial membrane from knee joint. Shows bulky villi with heavy accumulation of inflammatory cells in superficial zone and absence of inflammatory infiltrate in deeper synovial tissue. Haematoxylin-eosin.* × *18.*

Case 1—specimen B (knee synovium)
There was complete loss of the synovial lining layer, and the synovium was composed of heavily, actively and chronically inflamed granulation tissue with numerous neutrophils.

Case 2—specimen C (knee synovium)
The synovium was thickened with the formation of bulky villi in places (Fig. 5). There was marked synovial cell hyperplasia in some areas. Villous and nonvillous synovium exhibited marked vascularity adjacent to the surface, and marginated neutrophils were a prominent feature in these surface vessels. There was heavy neutrophil infiltration of the superficial synovium with a moderate number of lymphocytes but no plasma cells. In places the villous and nonvillous synovium was ulcerated and had a superficial zone composed of heavily inflamed granulation tissue without a surface synovial layer (Fig. 6). The deeper layers of the synovial membrane and the capsule were normal.

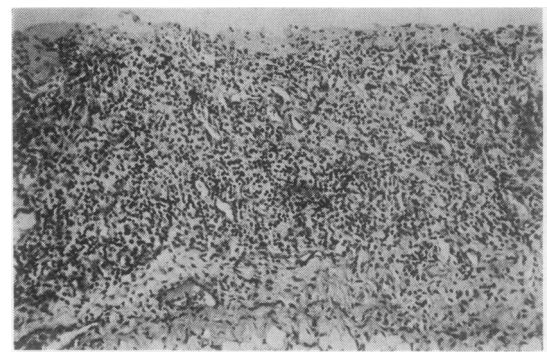


Fig. 6 *Case 2—specimen C. High power view of synovial tissue illustrated in Fig. 3 showing superficial zone replaced by granulation tissue with a thin layer of fibrin on the surface. Haematoxylin-eosin.* × *150.*

Case 3—specimen D (knee synovium)
The superficial layer of ulcerated areas of the synovial membrane was composed of granulation tissue with numerous macrophages and neutrophils, without lymphoid cells (Fig. 7). In those areas where a residual lining layer was present there was marked synovial cell hyperplasia. The deeper layers of the synovium are not affected by the inflammatory process.

Case 3—specimen E (head of femur, capsule, and synovium)
The head of the femur showed advanced osteoarthrosis with extensive cartilage loss and eburnation of bone but without cyst formation. At one edge inflammatory pannus extended into residual cartilage and into bone. The synovial membrane had a lining layer present in a few areas only and the superficial zone contained sparse macrophages, neutrophils, and few lymphocytes. The capsule was thickened but had no remarkable features.

Case 4—specimen F (cartilage and synovium from manubriosternal joint)
A brief description of the histological findings in this case has been reported by Currey *et al.* (1968). The material available for examination for this, and the previous report, consisted of tissue obtained by open biopsy of the joint which was performed 7 months before radiotherapy was started and 20 months before surgical fusion of the joint. The material taken at fusion comprised a few small pieces of bone and cartilage only. Examination of the material taken at open biopsy showed pannus containing numerous neutrophils and macrophages extending into hyaline and fibrocartilage (Fig. 8). The synovial tissues contained numerous neutrophils and macrophages and there was replacement of the lining layer by granulation tissue containing fragments of cartilage.

Case 5—specimen G (knee synovium)
Abundant surface fibrin was present without a recognisable synovial cell layer over most of the surface. The subsynovial tissue consisted of vascular granulation tissue containing young fibroblasts with a moderate lymphocytic infiltrate. There were a few scattered plasma cells and moderate numbers of neutrophils. There was no evidence of lymphoid aggregation, perivascular cuffing, or vasculitis. The deep synovial fat and fibrous tissue was normal but was separated from the granulation tissue by collagenous fibrous tissue (Fig. 9).

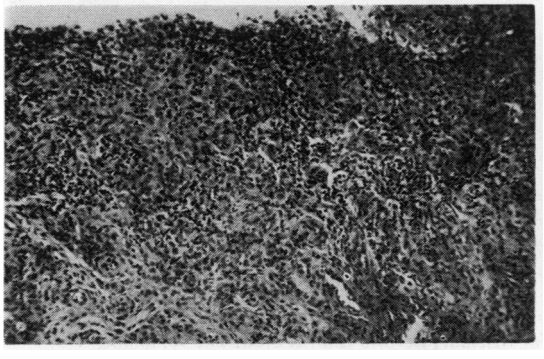


Fig. 7 *Case 3—specimen D. Synovial membrane from knee. The superficial zone shows heavy inflammation and marked macrophage proliferation. Haematoxylin-eosin.* × *150.*

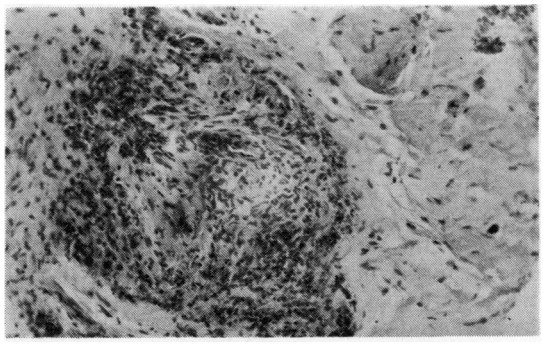


Fig. 8 *Case 4—specimen F. Tissue from manubriosternal joint. The fibrocartilage (right) is being replaced by inflammatory pannus containing many macrophages and neutrophil polymorphs (left). Haematoxylin-eosin.* × *150.*

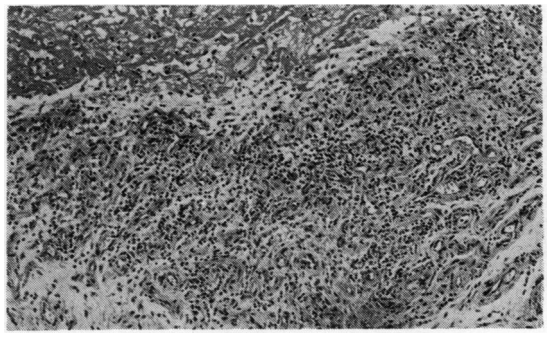


Fig. 9 *Case 5—specimen G. Synovial membrane from the knee showing vascular granulation tissue with a lymphocyte infiltrate containing some polymorphonuclear leucocytes. There is a large amount of surface fibrin present (top left) and the synovial cell layer is absent. Haematoxylin-eosin.* × *210.*

Case 6—specimen H (knee synovium)
A small amount of surface fibrin was present and a mild degree of hyperplasia of the synovial cell layer. The subsynovial tissue comprised fibrous tissue with marked concentric perivascular distribution and an increase in the vascularity of this region. Moderate numbers of lymphocytes and focal areas of heavy plasma cell infiltration were present (Fig. 10). Several lymphoid aggregates, without germinal centre formation, were seen. The deeper subsynovial tissue comprised normal fat and was fairly sharply demarcated from the fibrotic areas. Polymorphonuclear leucocytes were present in relation to the surface synovial cell layer and the superficial part of the synovium.

Discussion

Similar histological features were present in seven of the eight synovial membranes (Cases 1–5; specimens A–G; Table 4). These were variable loss of the synovial lining layer (ulceration) and the replacement of the superficial zone of the synovium by heavily inflamed granulation tissue. There was marked deposition of fibrin on the surface of the synovium in one specimen (Case 5—specimen G), and mild deposition in one other (Case 1—specimen B). Such lymphocytes as were present were intermingled with other components of granulation tissue, namely macrophages, vascular elements, fibroblasts, and neutrophils. There was no marked plasma cell infiltration or lymphoid follicle formation in these specimens.

In the eighth specimen (Case 6—specimen H) there was also only patchy mild synovial lining cell hyperplasia, the linings cells being absent, in some areas. In this specimen there was a marked plasma cell infiltrate and lymphoid follicles were present without germinal centre but some neutrophils were also present in the superficial zone together with a marked increase in vascularity.

These changes occurred solely in the superficial zone of the synovial membrane, the deeper layers and the capsule not being affected by inflammation, lymphoid cell accumulation, or fibrosis. The findings were similar to those briefly described in the knee and ankle in a single case of Behcet's syndrome by France *et al.* (1951).

In the three specimens where articular surface was available for examination there was evidence of inflammatory pannus, with cartilage erosion in two and extension into bone in one (specimen E). The arthritis of Behcet's syndrome has previously been described as nonerosive radiologically (Mason and Barnes, 1969). In the cases now reported, however, radiological erosive change was present of the hip in Case 3 (Fig. 1), and of the manubriosternal joint in Case 4 (Fig. 2) which has been confirmed histologically, and pannus destroying cartilage confirms the radiological appearance of loss of 'cartilage joint space'.

Conventional staining techniques gave no evidence of infection by micro-organisms in any specimen. Although some examples of septic arthritis may produce changes similar to those described above

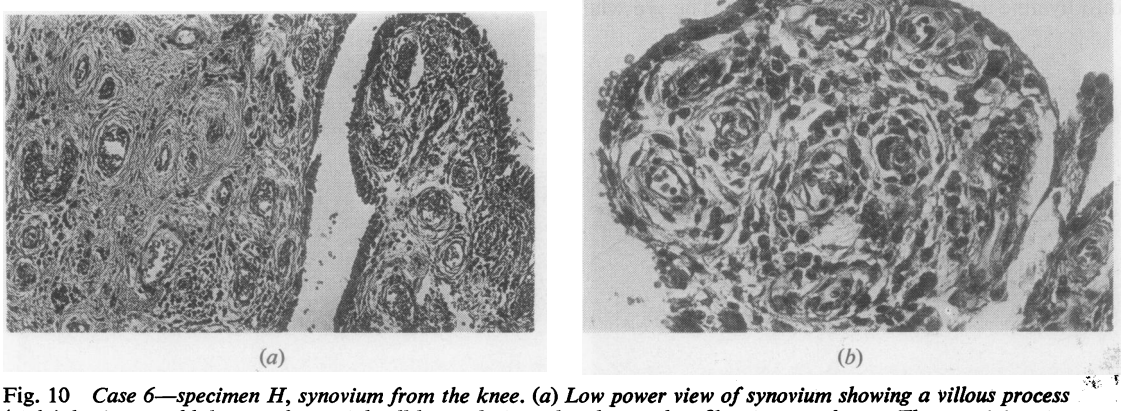


Fig. 10 *Case 6—specimen H, synovium from the knee. (a) Low power view of synovium showing a villous process (right) having a mild degree of synovial cell hyperplasia and with vascular, fibrotic central area. The remaining synovium (left) shows fibrosis with a tendency to a concentric perivascular distribution and plentiful small blood vessels. A moderate chronic inflammatory cell infiltrate is present. Haematoxylin-eosin. × 210. (b) High power view of a villous process containing numerous small vessels, some fibrosis, and a moderate plasma cell infiltrate. Haematoxylin-eosin. × 550.*

Table 4 *Summary of histological findings*

Case no.	*Specimen*	*Joint*	*Villi*	*Synovial lining cell hyperplasia*	*Superficial zone granulation tissue and loss of lining (ulceration)*	*Neutrophils*	*Plasma cell excess*	*Pannus + cartilage erosion*	*Lymphoid follicles*
1	A	Head of ulna + wrist synovium	++	0	++	++	0	+	0
	B	Knee	+	±	++	++	0	N/A	0
2	C	Knee	++	+	++	++	0	N/A	0
3	D	Knee	0	+	++	++	0	N/A	0
	E	Head of femur +synovium	+	0	+	+	0	+	0
4	F	Manubriosternal	0	0	+	+	0	+	0
5	G	Knee	0	0	+ (±profuse surface fibrin)	+	0	N/A	0
6	H	Knee	+	+	0	±	+	N/A	+

N/A=not applicable

there was no evidence of bacterial infection of the synovium in these 8 specimens. Ulceration and the replacement of the superficial zone of the synovial membrane by heavily inflamed granulation tissue, without involvement of the deeper layers and in the absence of infection, seem characteristic of Behcet's syndrome; although one specimen showed little neutrophil infiltration and moderate plasma cell infiltration and lymphoid follicle formation. It is suggested that these appearances would be helpful in diagnosis and should, therefore, be added to the criteria already described, probably as a minor criterion in the scheme recommended by Mason and Barnes (1969).

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