

## BRAIN-STEM ENCEPHALITIS\*

### FURTHER OBSERVATIONS ON A GRAVE SYNDROME WITH BENIGN PROGNOSIS

BY

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[WITH SPECIAL PLATE]

In 1951, in collaboration with Professor P. C. P. Cloake and under the title "Mesencephalitis and Rhombencephalitis," I published three examples of a syndrome the exact counterpart of which I had failed to find previously described. In these cases, after a prodromal period of general malaise and mild pyrexia, there developed gradually signs of mid-brain disturbance, followed by a progression suggesting downward extension of the disease until, in two cases, there was almost total suppression of all functions having brain-stem innervation, but no respiratory or cardiac embarrassment. After a stationary period, in which two of the cases appeared moribund, there was a gradual recovery, the patients finally attaining total and absolute normality. The condition was thought to be a virus encephalitis, but without any pathological support for this view. From correspondence in the press, personal communications, and discussions following this paper it became apparent that other physicians and neurologists had seen rare isolated cases almost exactly similar, and having had an equally favourable outcome so that no pathological studies have become available. Two of the cases described by Espir and Spalding (1956) and given the diagnosis of encephalitis lethargica were very comparable at one stage, but their subsequent course differed.

In the last three years I have seen four further examples of this clinical syndrome, and have kindly been allowed to refer to another under the care of Dr. William Goody and Dr. J. Hamilton Paterson (Paterson, 1953). My last patient died at the height of the attack and pathological study was possible. Though no claim to be describing a specific disease entity is made, it seems justifiable to group together cases of such great clinical similarity and to draw attention again to this grave condition, from which total recovery is possible.

#### Reports of Cases

In order to give a complete picture of the group as a whole, the clinical histories already published *in extenso* are briefly summarized as Cases 1 to 3.

##### Case 1

Female aged 24. In January, 1949, two weeks of headache and muscular pains were followed by drowsiness, ptosis, left facial paralysis, and ataxia developing over one week, and succeeded by diplopia, dysarthria, dysphagia, and numbness down the left side of the body. The patient was easy to rouse, but dozed on cessation of stimulation. Conjugate eye movements were impaired, with coarse nystagmus; masseters and facial muscles were weak; hearing was impaired; there were left hemihypalgesia, a left extensor plantar response, and left cerebellar ataxia. Cerebrospinal fluid (C.S.F.) contained 26 lymphocytes per c.mm. and gave a paretic Lange reaction. For four weeks the signs extended

until there was complete ptosis and total bilateral ophthalmoplegia, with total paralysis of jaw muscles and facial muscles, gross deafness, total aphagia, aphonia, and inability to lift the head or move the tongue. The remainder of the body was unchanged.

After three weeks a recovery began which was rapid at first, but later typical Parkinsonism of the head and limbs developed and lasted two months. This, in common with all other signs, totally and completely recovered, so that in ten months the patient was normal in all respects and has remained so for eight years.

##### Case 2

Male aged 36. In March, 1950, one week of malaise and headache was followed by drowsiness, ptosis, diplopia, and ataxia. Four days later bilateral ptosis, fixed dilated pupils, and weakness of eye movements developed. He was drowsy but easily roused, rapidly dozing again. In another three days there were gross bilateral ptosis, total palsy of all but downward eye movements, bilateral ataxia of limbs, and absent reflexes. One week later total right and partial left facial palsy developed. The C.S.F. contained 77 mg. protein per 100 ml. and showed a mildly paretic Lange reaction. Recovery began three days later, and was total and complete in two months. The patient has remained entirely normal for seven years.

##### Case 3

Female aged 24. Admitted in June, 1950, for ovarian cystectomy. Had headache for one week, followed by transient loss of consciousness; operation then performed, but patient remained drowsy afterwards with mild pyrexia and developed diplopia and dysarthria. Drowsiness increased for one week, then a major convulsion occurred. C.S.F. contained 153 mononuclear cells per c.mm. and gave a paretic Lange reaction. Gradual deterioration over three weeks to severe drowsiness, bilateral ptosis, total bilateral ophthalmoplegia, bilateral paralysis of jaw muscles, palate, pharynx, and tongue. There were slight deafness and slight ataxia in arms and legs. Recovery began after one week and continued over two months, accompanied by a maniacal psychosis. This last feature and all other signs completely recovered, and the patient has been entirely normal for seven years.

##### Case 4

(Under the care of Dr. William Goody and Dr. J. Hamilton Paterson)

A female aged 47 developed numbness of the left side of the body, followed three days later by vertigo, vomiting, ataxia, and weakness of the left side. After a stationary period of approximately three weeks, vomiting recurred, blurred vision developed, and left-sided ataxia increased. A week later there was further deterioration, and over the space of two weeks she progressed to a state in which she was very drowsy, there was total bilateral ophthalmoplegia, her jaw and facial muscles were paralysed, she was unable to speak or swallow, and there was a gross flaccid weakness of all limbs. The C.S.F. was normal throughout the illness.

After one week in this state she began to move her eyes and monosyllabic speech returned; two weeks later speech, swallowing, and eye movements were normal, but tremor of the head and a myoclonic tremor of the palate had developed. She then made a steady recovery except for some emotional lability, and twelve weeks after admission was able to return home. She remained entirely well, and on examination by Dr. Goody four years later the only abnormality found was a dubious plantar response on the left side.

##### Case 5

A boy aged 11 had mumps in the spring of 1954, and on getting up was giddy and unsteady for a few days. He recovered from this and throughout the summer was well except for some emotional lability. In November, 1954, he complained of headache and general malaise, which persisted for four days, when he became drowsy and confused.

\*Based on a paper read in the Section of Neurology and Neurosurgery at the Annual Meeting of the British Medical Association, Brighton, 1956

One day later the drowsiness increased and gross slurring of speech and marked weakness of facial muscles developed. For three further days his condition deteriorated, and when seen at the height of the illness he was drowsy but easily rousable; there was gross paralysis of conjugate ocular movement in all but a downward direction; the jaw muscles were paralysed and there was a bilateral facial paralysis. He was unable to swallow or speak, but the tongue movement appeared little affected. There was a flaccid weakness—but not paralysis—of all movements of arms and legs, with absent tendon reflexes, equivocal plantar responses, and bilateral ataxia of limbs. His C.S.F., at normal pressure, contained 12 mononuclear cells per c.mm. and 80 mg. protein per 100 ml.

He remained in this state for about five days. Speech then began to return, followed by swallowing and later—over a period of about two weeks—by normal ocular movements. Three months after the onset there was only very slight ataxia of the legs as a residual physical sign, but there had been considerable emotional lability, and during the next year he showed marked impairment of learning capacity and had several bouts of aggressive and violent behaviour. Examination in November, 1955, a year after the onset, showed a very slight ataxia of the legs, but no other abnormal sign, and he is known to have remained physically normal for two and a half years.

#### Case 6

In November, 1954, a boy of 10 developed slight general malaise, which lasted for three weeks and was followed by headache and, after two days, by fever, photophobia, and vomiting. He was found then to have a mild pyrexia, minimal neck stiffness, but no abnormal neurological signs. His C.S.F. contained 28 lymphocytes per c.mm.; biochemistry normal. There was apparent improvement for six days, and then over a period of 24 hours he became drowsy, developed paralysis of facial muscles on both sides, and was apparently unable to swallow or speak or to sit up. This state of affairs persisted for four days, when he became less drowsy, facial movements, swallowing, and speech began to return, and the rigidity of arms and legs decreased. *Pari passu* with this, however, there developed a Parkinsonian tremor of the right hand and arm and slight tremor of the head, which persisted in diminishing degree for two weeks. By the beginning of February, 1955, he was entirely normal, and has remained so for two and a half years.

#### Case 7

In early November, 1954, a boy of 10 developed frontal headache and general malaise, which persisted for two weeks and was accompanied by some abdominal pain. He then began vomiting, his headache increased, and he became drowsy and suffered intermittent delirium. Three days later the drowsiness increased, diplopia developed, the eyelids drooped, and he had difficulty in swallowing. His C.S.F. at this stage contained 65 leucocytes per c.mm. (mainly polymorphonuclear) and 60 mg. protein per 100 ml. Over the next three days there was general deterioration, the eye movements became more restricted, the speech slurred, facial muscles weak, and swallowing more affected. Examined after a further 24 hours, he was very drowsy but easily roused, dozing off again when stimulation ceased. There was bilateral ptosis, and almost total ophthalmoplegia in all but a downward direction. The jaw muscles were very weak, the facial muscles weak on both sides, and the palate and pharynx weak. Speech was grossly slurred, and there was generalized hypotonia with absent tendon reflexes and bilateral extensor plantar responses.

Two days later total ophthalmoplegia, total facial, palatal, and pharyngeal paralysis, and complete aphonia had developed. After two further days he improved; swallowing and ocular movements returned, and speech became intelligible. Over the next two weeks there was steady recovery, and by the end of December he was neurologically entirely normal. He showed at this time, and for

some weeks afterwards, undue lability of emotions and some impairment of intellectual capacity. The former has persisted, but otherwise he has been entirely normal for two and a half years.

#### Case 8

In early March, 1956, a boy of 14 developed vague muscle pains and general malaise and became drowsy; three days later he complained of headache, some abdominal pain, and vomiting. The next day the headache increased and the drowsiness became profound; he had periods of restlessness and confusion and was incontinent of urine. The C.S.F. at this time contained 70 mg. protein per 100 ml., but showed no other abnormality. His condition slowly deteriorated over the next two days, his conscious level fluctuating according to the degree of stimulation; there were slight weakness of facial muscles, gross slurring of speech, difficulty in swallowing, and ataxia of the arms and legs with marked reduction of tendon reflexes. The C.S.F. contained 10 mononuclear cells per c.mm. and 70 mg. of protein per 100 ml.

At this stage he developed an extrapyramidal tremor of the head, neck, and right arm, which disappeared as further deterioration occurred in the next 24 hours; by then he was drowsy but could easily be roused, and there was bilateral ptosis and almost total bilateral ophthalmoplegia. Jaw muscles were paralysed on both sides, and there were bilateral deafness and marked paralysis of palate, pharynx, and tongue. He was unable to speak, to swallow, or to raise his head. There was abolition of tendon reflexes, but it was impossible to get sufficient co-operation to test other functions of the nervous system. Twenty-four hours after this examination he had a sudden fit, which was said to consist of extreme rigid extension of all four limbs, and in this he died.

Necropsy was carried out next day by Dr. E. W. N. Trounson. The brain was removed and fixed. No abnormality was seen with the naked eye in the brain or any other organ. The brain and portions of liver, kidney, spleen, and suprarenals were examined histologically by Dr. A. L. Woolf, who reported as follows.

In the liver there were marked periportal accumulations of lymphocytes (Special Plate, Fig. 1) with some pyknosis of adjacent liver cells. The spleen, kidneys, and suprarenals were normal.

Abnormalities in the brain were remarkably scanty. In the brain-stem there was widespread swelling and ballooning of the myelin sheaths in the less compact fibre tracts as is seen in cerebral oedema; these are illustrated in Special Plate, Fig. 2, taken from the ventral tegmental decussation through which pass the oculomotor fibres. Also in the brain-stem there was astrocytic hyperplasia (Plate, Fig. 3), the astrocytes showing "twinning" and bulkiness of cytoplasm—also seen in cerebral oedema. The nerve cells were not strikingly affected in any part of the brain, but an occasional nerve cell in the third-nerve nucleus showed a wrinkling of the nuclear membrane and commencing cytolysis. In the cerebellum there was a diffuse but slight loss of Purkinje cells, though some folia were completely devoid of these cells. The blood vessels were distended in all areas, but in the frontal lobes, around some of the vessels, there were eccentrically placed perivascular aggregations of lymphocytes.

### The Clinical Syndrome

**Geographical Distribution.**—The number of cases is too small to attach any real importance to this, but the 1949–50 cases all occurred in Birmingham, and Cases 5, 6, and 7 all in the same month of 1954 in closely neighbouring districts of Shropshire and Herefordshire at a time when various presumed systemic virus infections were abundant amongst the local children.

**Age.**—One patient, with the longest course, was 47, and another 36, but all the remaining patients were below 25 years of age.

*Sex.*—There were five males and three females.

*Prodromal Symptoms.*—There was a period of from one to three weeks of general malaise and headache in all cases, and of muscular aching in some.

*Onset of Central Nervous Involvement.*—This was gradual in each case, and in six cases drowsiness was the first symptom. Vomiting and ataxia were presenting symptoms in the remaining two.

*Early Symptoms and Signs.*—Headache, present in all cases, was mild, but drowsiness was marked. Six cases had double vision and six vomiting, while five complained of unsteadiness of gait. Drowsiness was present in all cases. The patients appeared to be asleep, but were easily roused to full co-operation, though if stimulation was relaxed they would quickly slip back into sleep again. Ptosis and defective conjugate eye movements were present in all cases, while attempts at lateral or upward eye movement resulted in a coarse large-amplitude nystagmus. Downward movement was usually normal. Dysarthria was marked in six cases. Seven cases ran a low-grade pyrexia.

*Period of Progression.*—The time from the earliest signs to maximal disability varied: it was one week in two cases, two weeks in two cases, three to four weeks in three cases, and eight weeks in one case. In all except one the progression was slow and unremitting, and in none was it abrupt.

*Signs of Maximal Disability.*—In seven of the eight cases there was a total or almost total ophthalmoplegia, and in the eighth a partial ophthalmoplegia. If any eye movement remained, it was in a downward direction. Six cases had total bilateral paralysis of the motor supply of the fifth nerve, and all had total bilateral facial paralysis at some stage. Deafness was present in six; six had a total or gross paralysis of the ninth, tenth, eleventh, and twelfth nerves, and six had complete anarthria. There was loss of tendon reflexes in five cases, but with extensor plantar responses. Long-tract sensory signs were present in four.

It was striking that in no case was cardiac or respiratory distress present; muscle tenderness and signs of meningeal irritation were found only to a minimal degree in one.

*Period from Maximal Disability to Total Recovery.*—Excluding the fatal case, this lasted one month in three cases, three months in one, ten months in two, and seventeen months in one.

*New Signs During Recovery.*—Five patients developed an extrapyramidal type of rigidity and four a typical Parkinsonian tremor. In all except one case these developed during the stage of return of neurological function, but in the fatal case the signs were apparent just preceding maximal disability. Six cases, during recovery, showed emotional lability, particularly the tendency to spontaneous, inappropriate laughing and giggling. Two showed aggressive and violent behaviour.

*Sequelae.*—It is notable that neurological recovery has been total in six cases, the seventh having a minimal ataxia. Any extrapyramidal or Parkinsonian features have also totally disappeared. In two cases there has been some intellectual deficit, which was severe enough to interfere with education in one.

*Laboratory Investigations.*—These gave comparatively little information. Negative findings are not listed, but all available agglutination tests were carried out in all except one patient, with no positive result. The C.S.F. pressure was normal in all cases; there was a pleocytosis, predominantly lymphocytic, of 10–153 cells per c.mm. in five cases; the protein content was over 60 mg. per 100 ml. in four cases, the maximum being 80 mg. Three showed a paretic Lange reaction, but no abnormality in the level of sugar or chlorides was found. A blood leucocytosis of 12,000 to 16,000 cells per c.mm. was present in four cases.

Electroencephalography was performed in two cases only (Cases 1 and 3); this showed widespread delta and theta abnormality in all leads, appearing in bursts, and in the first case predominantly in right temporal leads.

## Discussion

The outstanding feature of these cases has been the subacute development of disturbed brain-stem function so gross that at some stage in all except one case survival for even a few days seemed impossible. It is difficult in a scientific communication to convey the gravity of the patients' condition when at its worst and the drama of the degree of recovery possible.

In our original communication (Bickerstaff and Cloake, 1951) we employed the term "mesencephalitis and rhombencephalitis" in default of anything which better indicated the part of the central nervous system bearing the main brunt of the abnormality. The disease process, however, is probably widespread throughout the brain, the clinical manifestations of brain-stem involvement being so much more dramatic than other features tend to be obscured. We discussed previously the differential diagnosis and the reasons for excluding many well-known conditions capable of producing transient brain-stem disturbance. These reasons have not changed and they will not be repeated.

The pathological process must be one capable of producing suppression of function without destruction of tissue—for recovery has taken place so rapidly and so completely. It is therefore not very surprising that histological examination of the fatal case has shown so little demonstrable abnormality. It seems probable that the loss of Purkinje cells was an anoxic, terminal manifestation. The vascular distension was certainly referable to the fit in which the boy died. However, the beading and swelling of the myelin sheaths and the "twinning" and swelling of the astrocytes are of greater significance, for if such a process of oedema were widespread throughout the stem function could be suppressed, but not destroyed, and could remain in abeyance until such time as the oedema receded, when rapid recovery would be possible.

Whether or not a process of brain-stem oedema is responsible for the neurological manifestations in this condition, the fundamental cause of the syndrome remains obscure. It has always been attractive to incriminate some unknown neurotropic virus, and the similarity to some cases of encephalitis lethargica has been mentioned several times since our original paper, but the pathological details available now, though scanty, give little direct support for this view and reveal practically none of the perivascular cuffing considered so typical of virus infections of cerebral tissue. An alternative possibility is that the cerebral changes may be a secondary effect—perhaps allergic in nature—to some systemic disease. No overt clinical evidence of generalized disease was manifest to support this in these cases, but the marked periportal round-cell infiltration in the liver of the fatal case was at least suggestive of virus infection.

Taking the clinical pattern of this syndrome as a whole, there are certain similarities to the course of the so-called infective polyneuritis—the mode of onset and progression, the stationary state at maximal disability, and the rapid recovery of gross paralysis with slower final extinction of all abnormality. Indeed, several patients had lost all tendon reflexes even at a time when neither hypotonia nor paralysis of the limbs was marked. There is growing support for the view that infective polyneuritis results from an allergy or hypersensitivity to some agent or variety of agents, as yet undetermined, and the cases considered here may equally well be the clinical end-result of a variety of causal factors rather than a specific disease caused by a specific organism. This fact does not minimize the importance of recognizing the syndrome, for in view of its potentially benign outcome no effort should be spared to maintain the patient's general condition, to control fits, and to prevent inhalational bronchopneumonia, even at a stage when it appears that death must inevitably follow within a matter of hours.

The burden of care will fall upon the nursing staff. Their efforts will be even further stimulated if they realize the probability of a favourable outcome, and for the parents and relatives of the patient the hope sustained by the

medical attendants during the intensely distressing period of maximal disability is invaluable. Once deterioration appears to be checked a reasonably confident prognosis can be given—though a warning should be issued of the possibility of personality changes during the convalescence and the rather more remote danger of permanent impairment of intellectual capacity.

**Summary**

A description is given of eight examples of a clinical syndrome of gradual onset in which develops almost total paralysis of all motor function, originating first in the mid-brain and later in the whole brain-stem, accompanied by only mild pyramidal or long-tract sensory disturbance, and no cardiac or respiratory abnormality.

From a stationary stage of extreme gravity, dramatic total recovery has occurred in seven cases, with no neurological sequelae.

The pathology of the fatal case is described, and a state of transient cerebral oedema, possibly related to a systemic virus infection, is suggested as the basic cause.

I wish to express my thanks to Dr. William Goody and Dr. J. Hamilton Paterson for allowing me to refer to Case 4; to Drs. Hugh Fisher, J. Macaulay, and A. C. Kendall, consultant paediatricians, for referring to me Cases 5-8; and to Dr. A. L. Woolf and Dr. E. W. N. Trounson for the pathological studies on Case 8.

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**RETICULOHISTIOCYTOSIS (LIPOID DERMATO-ARTHRITIS)**

BY

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[WITH SPECIAL PLATE]

This paper describes four patients with a similar and unusual syndrome of a widespread papular and nodular eruption and multiple arthritis. Circumscribed areas of destruction in bone were present, and in two cases this progressed to a "concertina" deformity of the fingers. Tendon-sheath swellings and patches of xanthelasma palpebrarum occurred in two of the cases. Histological examination of all involved tissue in every case showed the same type of giant cells, the cytoplasm of which appeared granular and in places finely "foamy." An unusual type of lipoid has been demonstrated in these cells. Two patients died, and in both, apart from widespread infiltration of tissues by the giant cells, a fibrinous pericarditis was present.

Twelve cases showing a similar clinical picture and histology have been described in the literature under various headings, and are summarized in the Table.

**Personal Cases**

**Case I**

Mrs. E. P., a housewife. Apart from a hysterectomy for fibroids when aged 40 she had not had any previous illnesses of note. No relevant condition had occurred in the family, and her only brother and sister were alive and well. The patient had been married for 25 years, but was childless. In December, 1949, at the age of 49, she developed painful swelling of the finger, shoulder, and knee joints. At the same time an eruption appeared on the fingers, elbows, both pinnae, the radial aspects of both forearms, and over the manubrium sterni. She came under our observation in July, 1950, and was seen at regular intervals until she died in 1952. When she was first seen there was a widespread papulo-nodular eruption, sheets of yellow-brown papules 0.2-2 cm. in diameter and associated with erythema being present over the forehead, ears, neck, naso-labial furrows, outer aspects of forearms and upper arms, the nail folds, the sacral region, and the anterior aspects of the thighs and lower legs. At the periphery of the involved patch of skin they were occasionally in linear distribution. The larger nodules were present on the scalp, both pinnae, bridge of nose, chin, elbows, dorsum of most fingers, sacral area, and knees. These tended to be purplish in colour. They were well raised from the skin surface and some were confluent (Fig. A). Local heat and pressure did not increase or decrease the number or size of the nodules. The teeth were healthy, but a few papules were present on the lips and gingival margins (Fig. B), the fraenum and posterior part of the tongue, and extending into the tonsillar recesses. There was widespread involvement of the joints associated with moderate pain and often considerable swelling and limitation of movement. Shoulders, elbows, wrists, finger-joints, knees, and ankles were involved. The axillary and inguinal lymph nodes were slightly enlarged. Blood pressure 180/100 mm. Hg.

*Clinical Course.*—Many of the larger nodules remained unchanged, but a few new ones appeared. At times the sheets of papules became less prominent and the erythema faded, but for periods of a few weeks they were more marked and itching occurred. Seven months after the onset four or five large, typical xanthelasma palpebrarum patches were observed. In 1951 an irregular swelling developed in front of the wrists and appeared to be arising from the tendon

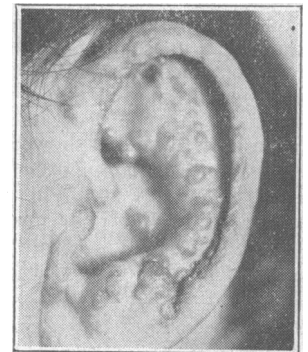


FIG. A.—Case I. Nodules and papules on ear.



FIG. B.—Case I. Papules on upper lip.

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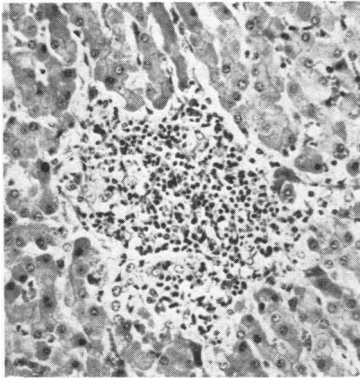


FIG. 1.—Case 8. Section of liver, showing marked round-cell infiltration of portal tract with commencing pyknosis of adjacent liver cells. (Stained haematoxylin and eosin.  $\times 158$ .)

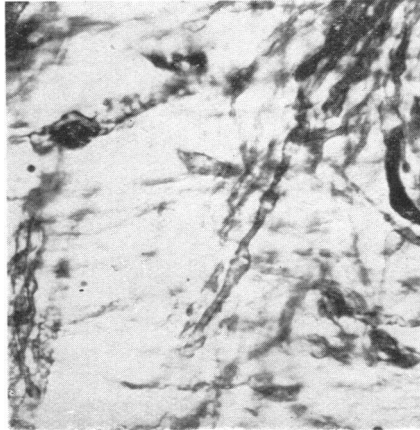


FIG. 2.—Case 8. Section from mid-brain, showing swelling and beading of myelin sheaths. (Woelcker stain.  $\times 565$ .)

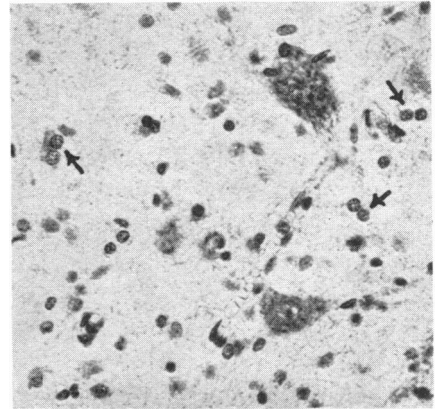


FIG. 3.—Case 8. Section from region of third-nerve nucleus, showing swelling and "twinning" of astrocytes (arrowed). (Nissl stain.  $\times 264$ .)

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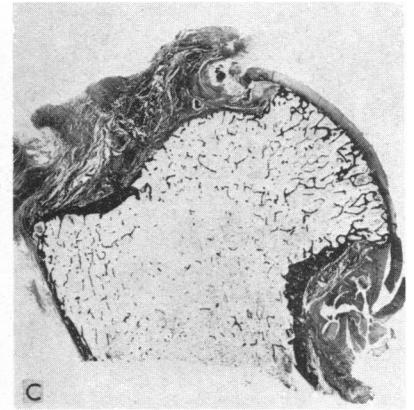
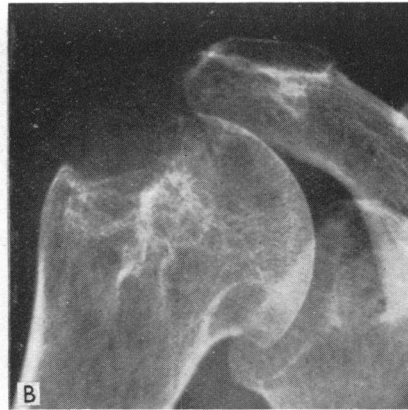
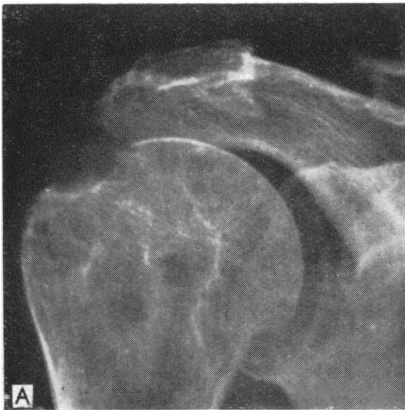


FIG. 1.—Case I. Head of right humerus, showing progressive destruction: (A) January, 1951; (B) August, 1951. (C) Post-mortem section showing replacement of spongiosa by swollen synovial tissue.

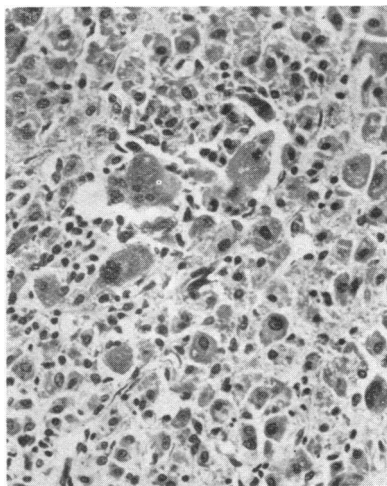


FIG. 2.—Case II. Photomicrograph taken from the edge of an eroded area in the head of the humerus, showing replacement by synovial granulation tissue packed with giant cells similar in morphology to those of the skin lesions. ( $\times 200$ .)

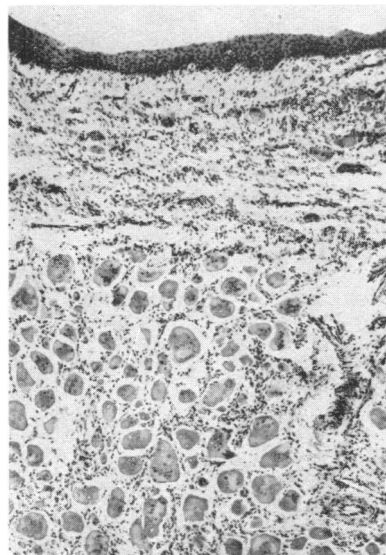


FIG. 3.—Case III. Photomicrograph of skin nodule, showing abundant multinucleate giant cells. ( $\times 40$ .)

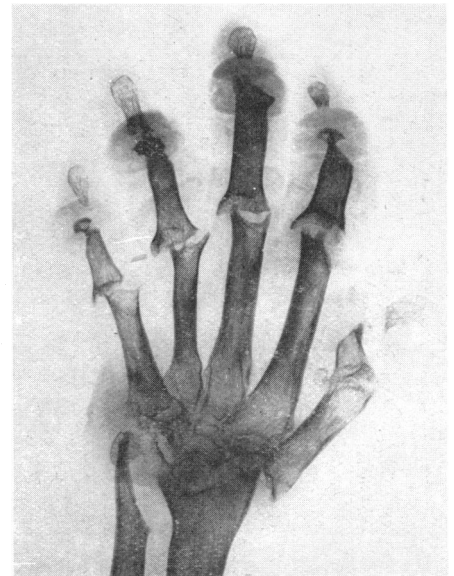


FIG. 4.—Case IV. Radiograph of hand, showing gross bony destruction.