In the same way that a depressant concentration of regional analgesic produces a low R.R.F., so also systemic analgesics with a central depressant overlay result in a poor ventilatory performance. Pethidine and intravenous xylocaine have this disadvantage, which is shown clearly when contrasted with the relative purity of action of amideone. Local analgesics administered systemically can be effective if the speed of infusion is carefully regulated (Gordon, 1943; McLachlin, 1945), but the margin between effective analgesia and depression is narrow, and a drip rate that suddenly accelerates can rapidly lead to profound depression and dangerous convulsions. This lability in the balance between depression and analgesia is shown by the jagged peaks and valleys of the xylocaine series in Fig. 5. It would seem illogical to use local analgesics by the systemic route, unless the superior quality of analgesia provided were such as to warrant the close supervision required. This series shows no evidence of such superiority.

Clearly, the spirometric method of comparison would have to be modified if used for analgesic drugs having a direct respiratory stimulating effect of their own, for otherwise an abnormally high R.R.F. would be obtained, unrelated to the analgesia produced (something akin to the improvement of respiration found in the epidural series). This source of error could be eliminated by carrying out control vital capacities with a test dose of the drug before operation. The improvement of vital capacity that occurred following epidural block in patients with pulmonary congestion suggests that greater accuracy would be obtained by employing only patients with normal cardio-respiratory function in this type of investigation.

Lastly, it must be emphasized that the results of this method of comparison, based upon wound pain, may not be applicable to other types of pain. The method is deliberately designed to measure relief of pain in an inherently painful situation, whereas many analgesics act by removing the painful situation and not by dulling the pain. For example, a correctly applied Thomas's splint relieves the pain of a fractured femoral shaft, and the methonium drugs (although innocent of any essential analgesic action) may yet be most effective in the pain of acute pancreatitis (Davies *et al.*, 1953; Pyke, 1953). Similarly, although pethidine scores poorly in this series, it may be very valuable in pain from smooth-muscle spasm, such as ureteric colic, for then relief of pain is partly due to a direct antispasmodic action.

Summary

There is a need for comparing analgesic drugs quantitatively under clinical conditions. A quantitative method is described, based on vital capacity measurements. After an upper abdominal operation breathing is restricted by pain; analgesic drugs are assessed by the amount they restore the vital capacity towards normal.

The method is illustrated by comparing four analgesic procedures in 20 patients.

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UVEOPAROTID SARCOIDOSIS WITH CEREBRAL INVOLVEMENT

A CASE REPORT

BY

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Heerfordt (1909) first indicated that the nervous system might be affected in sarcoidosis, and since then the occurrence of neurological complications has been widely affirmed. The attack is recognized to be usually upon cranial or peripheral nerves, and sarcoid of the brain or spinal cord is a distinct rarity. The following case of a man personally observed at intervals for over twenty years, and only recently dead, is therefore of interest, for he had a cerebral lesion at one stage of his illness. This presented as a slowly growing intracranial tumour which was surgically removed some 13 years ago.

Case Report

The patient, a van driver, was first seen when aged 24 as an out-patient in the ophthalmic department of the Cumberland Infirmary, Carlisle, on November 3, 1934. He complained that the sight in his right eye had begun to fail early in June that year, and the left eye six weeks later. In August he had developed bilateral parotid swellings, first on the right and three weeks later on the left, which had persisted since, and in October he had noticed a transient swelling on the left shin. On questioning it appeared that he had had an attack of left-sided chest pain, with shortness of breath, for some weeks in April and May, 1934, and a similar episode in 1931. There were no other significant points in the previous medical or family history.

On examination both eyes showed ciliary injection, fine keratic precipitates, a number of small pale nodules in the iris (eight in the right, four in the left: Fig. 1), and many posterior synechiae. The fundus was obscured by vitreous opacities. His visual acuity was less than 6/60. Both parotid glands and the right submaxillary gland were enlarged and hard. No other abnormal physical signs were found.

FIG. 1.—Showing relative size and position of iris nodules.

The fundus was obscured by vitreous opacities. His visual acuity was less than 6/60. Both parotid glands and the right submaxillary gland were enlarged and hard. No other abnormal physical signs were found.

The patient was admitted to the ward under the care of Dr. T. McL. Galloway, the results of whose special investigations were as follows:—chest x-ray examination: hilar glands enlarged bilaterally, lung fields clear; tuberculin tests: negative at 1/10,000, 1/1,000, and 1/100; blood W.R. negative; full blood count: red cells, 6,150,000; Hb, 125%; white cells, 4,700, normal differential count; urine: no albumin or sugar, no casts or cells, no tubercle bacilli; B.P., 138/80; no cough, no pyrexia. When discharged from hospital on January 30, 1935, the parotid swellings had subsided, the ciliary injection and the iritic nodules had gone, though some keratic precipitates and many vitreous opacities remained. Radiologically the hilar masses were still present, but were thought to have decreased somewhat in size. The diagnosis was chronic uveoparotitis.

The patient was seen at intervals during 1935 and once in 1936. The ocular signs regressed further, but he continued to complain of shortness of breath on exertion and easy tiring. Early in 1940 he had severe headaches; these increased in severity, and in consequence he had to stop

work in May of that year. On July 11, 1941, he again attended the ophthalmic department of the Cumberland Infirmary, now complaining of headache, fits, loss of memory, and failing vision. The fits were apparently

FIG. 2a

FIG. 2b

FIG. 2a.—Operation specimen. Sarcoidosis in brain with epithelioid tubercles, calcification and giant-cell formation, but no necrosis. ($\times 40$.) FIG. 2b.—Same as FIG. 2a ($\times 180$), showing centrally placed giant cell inside epithelioid tubercle.

generalized and had started in November, 1940. On examination bilateral chronic papilloedema, with some secondary atrophy, was discovered. His visual acuity was 6/18 right and left. The visual fields showed right homonymous upper quadrantic loss. The pupils were irregular owing to posterior synechiae; there was patchy loss of iris pigment. The eyes were quiet and free from vitreous opacities. A diagnosis of cerebral tumour was made, and the patient was referred to Professor Geoffrey Jefferson on August 1, 1941.

On October 4 he was admitted to the Manchester Royal Infirmary under Professor Jefferson, who has kindly allowed me access to his case records. In addition to the signs previously noted, there was now a slight right-sided pyramidal disorder of movement in the arm and leg, and the patient's apparent loss of memory was found to be really due to nominal dysphasia. Skull x-ray films showed erosion of the posterior clinoids and dorsum sellae,

FIG. 3.—Radiograph of chest done on August 17, 1950, showing hilar enlargement and egg-shell calcification of the gland.

no increase of vascular markings, and no intracranial calcification. A preoperative diagnosis was made of left temporal tumour—probably slowly growing glioma—and on October 14 an osteoplastic skull flap was turned. The temporal lobe was seen to be whitish, its gyri were widened and flattened. An avascular tumour was exposed in its substance, which had the macroscopic appearance of an astrocytoma. The tumour was excised by temporal lobectomy and sent for histo-

logical examination. The late Dr. Eugen Pollak, of the department of neuropathology, Manchester University, reported that it was not a neoplasm, but a conglomerate tuberculoma, showing "small heaps of epithelioid cells surrounded by lymphocytes and in some places single giant cells; miliary eruptions in different places with formation of more or less well-defined tubercles. In places there are the beginnings of cellular condensations, often of epithelioid character, in relation to vessel walls, and inflammatory lymphocytic infiltrations around vessels are also scattered through the specimen" (Figs. 2a and 2b).

In view of this report, it was feared that tuberculous meningitis might develop post-operatively, but convalescence passed uneventfully. A further chest x-ray examination showed the hilar shadows still prominent and what was thought to be a little fluid at the mediastinal end of the right interlobar fissures, but no evidence of disease in the lung parenchyma. The Mantoux test was also repeated, and found negative.

The patient returned home on November 2; neurologically, he now had a complete right homonymous hemianopia as the result of the temporal lobectomy, and right-sided weakness and dysphasia as before. His case was thought to exemplify the thesis that uveoparotitis was a form of tuberculosis, and for the next five years (until October, 1946) he was kept under review by Dr. J. A. Guy, Westmorland County Medical Officer of Health.

In 1950 I showed the slides from the cerebral lesion to Dr. J. Steven Faulds, pathologist to the Cumberland Infirmary, Carlisle. He commented that whilst the sections looked, superficially, like a tuberculous lesion in brain tissue, the histological characters were unquestionably those of a typical sarcoid granuloma. The appearance was of a mass of tuberculoid follicles, composed of endothelial cell systems with central hyaline necrosis, and containing giant cells of tuberculous type. The chief points of differentiation from tubercle were, firstly, the absence of caseation in the follicles, the centres of which still retained visible cell outlines, and, secondly, the central, rather than peripheral, situation of the giant cells.

In view of this new light on the patient's case he was readmitted to the Cumberland Infirmary in August, 1950. On examination abnormal physical signs were restricted to the eyes and nervous system. His visual acuity was 6/9 right, 6/6 left. Complete right homonymous hemianopia was present with sparing of the maculae. There was consecutive bilateral optic atrophy. Each eye showed atrophy of the iris stroma and thinning of the posterior pigment layer with radial dehiscences, but no scars at the site of the nodules seen in 1934. The pupils were irregular, with posterior synechiae; the vitreous was clear. Dr. Geoffrey Scott Harden reported:—Chest radiograph: areas of calcification and pleural thickening at apex of right lung; massive enlargement of hilar gland shadows bilaterally, with egg-shell calcification (Fig. 3). This type of calcification supports the diagnosis of sarcoidosis; it is not found in tuberculosis. X-ray films of the hands showed no evidence of bony sarcoid deposits. Blood count: Hb, 102%; white cells, 7,300 (polymorphs 59%, lymphocytes 24%, monocytes 3%, eosinophils 14%). Mantoux test: 1/1,000 weakly positive, 1/100 positive. The patient was well in himself.

Shortly after his return home it was noticed that he tired more quickly and movements and speech were more laboured. Towards the end of 1952 his interest in things and his power of concentration began to wane and he fell asleep during the day. In March, 1953, following a fit, his right arm and leg were considerably affected; so he was taken into Westmorland County Hospital, Kendal, under the care of Dr. G. M. Barrett, the consulting physician, to whom I am indebted for information about investigations carried out. These included a blood count which disclosed that the marked eosinophilia present in August, 1950, had completely disappeared, that the plasma proteins, including the albumin/globulin ratio, were normal, and that a liver biopsy revealed no change suggestive of sarcoidosis.

During that summer he had improved so much that he was able to take a daily walk of 500 yards. In January, 1954, after a similar attack, he was unable to clothe himself, to get about, or to take part in conversation, but remained cheerful and enjoyed company. On November 11, 1954, he had another fit, and on the 15th died in coma.

Dr. I. G. McGregor, who attended him, was able to arrange for a necropsy. This was done by Dr. Geoffrey W. Storey, assistant pathologist, Group Hospital Laboratory, Kendal, to whom I am indebted for a copy of his findings. Summarized these were:

Cause of Death.—Bilateral haemorrhagic necrosis of adrenals.

Adrenals.—No evidence of sarcoidosis present.

Brain.—Surrounding the site of the left temporal lobectomy there was softening, with a large number of pinkish miliary bodies. A similar area of infiltration in the right occipital cortex. Both areas confirmed histologically as active sarcoidosis (Fig. 4).

Thorax.—Enlargement of hilar and mediastinal lymph nodes—firm and rubbery, with patchy calcification and dense white areas, suggesting old tuberculosis. No evidence of old or recent tuberculosis in lung parenchyma. Histological examination confirmed that all glands showed active or old-standing sarcoidosis with calcification but no necrosis (Fig. 5).

Liver.—A few small foci of softening microscopically; these were found to be active sarcoidosis, but scanty in amount.

Discussion

This case was originally diagnosed in 1934 as one of uveoparotitis, a condition which at that time was generally believed to have a tuberculous cause (Souter, 1929; Garland and Thomson, 1933). The identity of the disease as a common presenting form of generalized sarcoidosis, later established by Waldenström (1937), Bruins-Slot *et al.* (1938), and others, was of course still unknown, but in retrospect it is now clear that the patient already had generalized lesions when he was first seen. In addition to the characteristic ocular and salivary gland involvement, he had had an attack of pleurodynia three years earlier which may have been significant; he had more definitely related pulmonary symptoms of chest pain and breathlessness some weeks before his eyes were affected, with enlarged hilar glands radiologically demonstrated later; and, further, the transitory painless lump on one shin, which was not seen, may well have been a dermal sarcoid.

In regard to the later development of cerebral symptoms, it appears that a neurological semeiology is far more often met with in the uveoparotid variant of generalized sarcoidosis than in the Boeck-Schaumann form of the malady (Jefferson, 1952), though the significance of this fact is obscure. Whether it is due to subtle variations in the agent which provokes the disease or whether it reflects differential tissue susceptibility of individual hosts is unlikely to be solved until the prime cause of sarcoidosis is discovered. At present there are three main hypotheses about the nature of the malady (Cowdell, 1954). The first, whose popularity is now distinctly on the wane, accounts it an atypical (anergic) form of tuberculosis infection. The second, which is of fairly recent origin, regards it as a diffuse tissue reaction of fixed pattern, which may be set in motion by any of a number of factors, and so considers it a syndrome rather than a disease proper. The third holds that it is unquestionably a true morbid entity, having a single cause as yet unidentified, but which may prove to be viral (Löfgren and Lundbäck, 1950). The present case provides no clues which bear on aetiology.

Mention has already been made of the infrequency of central nervous as compared with peripheral affection in sarcoidosis. From the reviews of Roos (1940) and Colover (1948), it is evident that only a relatively small number of

such cases have found their way into the literature, and in most of them pathological proof has been lacking. Exceptions are the case described by Lenartowicz and Rothfeld (1930), in which there was very extensive sarcoid infiltration of the base of the brain, including the left temporal lobe,

FIG. 4.—Necropsy specimen of left temporal lobe area, showing active sarcoidosis, with calcification. ($\times 50$.)

a case with brain and brain-stem lesions described by Zollinger (1941), and a case with hypothalamic involvement (Aszkanazy 1952); Tillgren (1935) and Wahlgren (1937) reported an intracranial sarcoid lesion restricted to the pituitary gland, and Naumann (1938) and Colover (1948) reported sarcoidosis of the intracranial meninges; but no

FIG. 5.—Hilar lymph node showing extensive fibrosis and calcification. ($\times 80$.)

others are known to me. The histology of sarcoid deposits in the neural substance is identical with the general pattern of sarcoid follicles in other tissues, and the microscopical appearance of the cerebral hemisphere lesion in the present instance conforms fully to this plan.

Lastly, it is remarkable how long a course the illness ran in this patient, for he lived 24 years after his first attack of

pleuritic pain in 1931 and over 20 years after the first proved evidence of sarcoidosis. One case is known to have survived over 40 years, but very few over 20 (Cowdell, 1954).

Summary

The case of a man with generalized sarcoidosis, personally observed for 20 years, is described. First seen in 1934 on account of uveoparotid symptoms, which afterwards subsided gradually, he presented himself again in 1941, now with signs of cerebral tumour. Diagnosis of a slow-growing glioma was made by Professor Geoffrey Jefferson, who excised the left temporal lobe. After histological examination, the tumour was pronounced to be an intracerebral tuberculoma, but re-examination of the histological sections nine years later by Dr. J. S. Faulds led to recognition that the microscopical appearances were, in fact, typically sarcoid in character. The necropsy revealed that the sarcoid changes were limited to the brain, the thoracic lymph nodes, and the liver. The eyes could not be reported on. Proved cerebral sarcoidosis is a very rare condition, and a brief review of the literature is given.

I gladly acknowledge my indebtedness to various colleagues, in particular to Sir Geoffrey Jefferson, to Dr. J. S. Faulds, and to Dr. J. M. Jefferson (University of Birmingham) for their interest and valued help. The photomicrographs were taken by Dr. Faulds.

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HYPERTONIC DEHYDRATION

BY

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The principles upon which fluid and electrolyte therapy are based are sound but often empiric. This empiricism applies particularly to the assessment of depletion when the patient is first seen and when data are minimal for subsequent treatment. The most reliable measures at this stage depend on our knowledge of the extracellular concentration of sodium and on our estimate of the total body water. When both these variables are known the total amount of each extracellular electrolyte can be calculated and the deficiency estimated.

In clinical practice Marriott (1947) has gone far to clarify our knowledge by insisting on the separate identity of "pure water" and "pure sodium" deficiency, though briefly mentioning a mixed type of deficiency. This mixed deficiency has been called by Darrow and Pratt (1950) hypertonic dehydration, and it is with this hypertonic dehydration that we are here concerned. It would appear from the observations of physicians examining the problems of water and electrolyte deficiency that hypertonic dehydration is not common (Marriott, 1947; Black, 1953). In surgical

practice, however, it seems that hypertonic dehydration is common, not readily recognized, and but rarely treated.

Hypertonic Dehydration

It need scarcely occasion surprise that, in fact, water and electrolyte are rarely lost in proportion to their concentration in the extracellular fluid. Table I shows the simple

TABLE I.—*Electrolyte Content of Some Body Fluids*

Secretion or Effusion	Na (mEq/l.)	K (mEq/l.)	Cl (mEq/l.)
Stomach	60	12	130
Ileum	135	7.5	94
Peritoneal effusion ..	138	5	105
Sweat	50	15	50
Serum	140	5	103

arithmetic mean of the electrolyte content of various body fluids obtained in some of my own patients. The figures for invisible perspiration are taken as the upper limits of normal suggested by Darrow and Pratt (1950). The loss of pure water via the lungs and of hypotonic sweat, in conjunction with the loss particularly of gastric contents by vomiting, leads rapidly to a state of water and electrolyte depletion in which the water depletion is much more extensive than the electrolyte loss. This is only partly correct, in that the potassium loss by some of these routes represents a considerably larger fraction of the body store than would be lost if the potassium content were only that of the extracellular fluid. It is not intended, however, to treat at length with potassium deficiency, and attention is confined here mainly to the chief extracellular ions.

This loss of water in excess of electrolyte leads to a rise in the concentration of sodium and chloride in the extracellular fluid, although in fact the body store of these electrolytes has been depleted. In the case of a substance such as urea, which is diffused through all the body water compartments, this is not of importance, but in the case of the chief extracellular electrolytes, such as sodium and chloride, the extent of the space may be more important than the concentration of the ion. Haemoconcentration leads also to a rise in the haemoglobin and plasma protein content, often masking a concomitant deficit of these colloids.

As in a pure water deficiency, the excessive loss of water leads to a hypertonicity of the extracellular fluid, thereby resulting in a withdrawal of cellular water, though the extent of the changes is not so marked as in pure water deficiency. In the early stages this hypertonicity can also be offset by an increasing excretion of electrolyte in a concentrated urine. When, however, maximal renal concentration has occurred and the renal plasma flow continues to decrease, the kidney is no longer able to correct the increasing extracellular hypertonicity, and renal compensation is lost. If the maximal renal concentrating power is diminished—and this is not uncommon in the elderly male with prostatic symptoms—the onset of the clinical state is hastened. Hypertonic dehydration is seen particularly, therefore, in the older age group of male subjects.

This apparently simple explanation of hypertonic dehydration is unfortunately at variance with experimental observations. In particular, the experiments of McCance (1936) on salt deprivation have shown that the water loss parallels the sodium loss, and only at a much later stage does the serum sodium concentration fall. It appears from these experiments that osmotic tonicity is a consideration of greater importance to the body economy than is the regulation of the total body water. The relatively inaccurate observations of clinical practice, if they contradict these findings, must be viewed with suspicion. The fact, however, that such contrary results are observed is the justification for reporting the condition here.

Clinical Features

It has been variously reported that the symptoms of this state combine those of both pure water and pure sodium deficiency. It has been my own experience, however, that