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.

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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

the presenting symptoms are almost entirely those of a pure water deficiency. Patients with hypertonic dehydration present with marked thirst, an adequate peripheral circulation, a fairly full pulse, and a blood pressure just a little lower than would be expected for their age. The urine output is scanty, and the urine is highly concentrated and of high specific gravity, provided the kidneys are healthy. The most notable feature is that the concentration of sodium and chloride in the serum is near normal or above normal. In spite of the fact that these patients appear reasonably well, they are in a dangerous state, precariously balanced on the edge of peripheral circulatory insufficiency, and are quite unfit to undergo major surgical procedures. Table II shows the results of serial blood examinations in the following case.

Case 1.—A man aged 56 was admitted to a medical ward on November 2, 1952, suffering from organic pyloric stenosis. He was treated by gastric wash-out, but not with parenteral fluid or electrolyte therapy. Even on November 4 there was evidence of hypertonic dehydration, but this had become considerably

TABLE II.—*Hypertonic Dehydration (Case 1)*

Plasma or Serum Concentration	Nov. 4	Nov. 10	Nov. 15	Nov. 18
Cl_2 (mEq/l.) ..	102·5	114	92	90·6
Na ,, ..	132	148·5	123·5	127
K ,, ..	—	—	4·3	4·6
Urea (mg./100 ml.)	—	87	50	26
Hb	51%	70%	—	48%
Plasma proteins (g./100 ml.) ..	4·8	5·7	4·6	4·4

more marked by November 10. By this time the patient looked dehydrated, was very thirsty, but there was no evidence of peripheral circulatory insufficiency. He was transferred to a surgical ward on the 10th, and the evidence of hypertonic dehydration noted—namely, thirst, a rising serum sodium and chloride, a moderate increase in blood urea, and a rise in haemoglobin and plasma protein concentration. To uncover the true electrolyte insufficiency, sodium and chloride were replaced only in proportion to their loss by gastric suction and in the urine. In addition a 5% glucose infusion of 4 litres was given during the next few days and the blood again examined. It will be observed that the concentration of the extracellular electrolytes (except potassium) fell to subnormal levels although no new deficit of sodium or chloride had occurred. The urea and plasma protein concentration were also reduced as a result of the dilution effect. A further 2 litres of 5% glucose was then supplied, and the results on November 18 are shown.

It will be seen, therefore, that hypertonic dehydration presents clinically as one of a pure water deficiency, and that an examination of the extracellular electrolytes would suggest to the unwary that nothing is amiss. The electrolyte deficiency can be unmasked by giving a liberal supply of water by mouth if possible, and, if not, parenterally. In the case just described, the calculated sodium deficiency after hydration amounted to the equivalent of 4 litres of saline, a deficiency which would have remained unsuspected if adequate hydration had not been attempted.

Dangers of Untreated Hypertonic Dehydration

The dangers encountered when hypertonic dehydration is neither suspected nor treated are seen mainly in surgical patients and only infrequently in the unoperated. Study of Table II will show that an anaemia and a hypoproteinaemia of considerable degree have been uncovered during the process of hydration. The example demonstrated did show evidence of anaemia before hydration, but frequently the anaemia is not uncovered until the hypertonicity is corrected. Under these circumstances the haemoconcentration remains unsuspected, and at operation is intensified by the present practice of using 5% dextrose as the vehicle for anaesthetic drugs. It has become almost axiomatic that, provided renal function is reasonable, no harm can result from the giving of excess water. What is not required will be excreted. In unsuspected hypertonic dehydration, however, the water will be retained, and a sudden post-operative fall in concentration of haemoglobin, plasma proteins, and electrolyte results. To the danger of an unsuspected anaemia, an unsuspected hypoproteinaemia is added.

Before operation it is only rarely possible to produce oedema, even in an example such as Case 1, by this dilution phenomenon unless saline is given. It will be observed from the protocol in that case that even on November 18 a marked hypoproteinaemia was produced. The next step in treatment is to correct this by supplying plasma or, as in this particular instance, to correct the hypoproteinaemia and anaemia by blood.

When the hypoproteinaemic state is not uncovered until the post-operative phase, however, oedema is very apt to occur simply by supplying water. As the adequate supplement of water is thought to be without danger in the post-operative phase the danger is not readily appreciated. In other cases water intoxication may occur, and it is possible that the rare cases of water intoxication encountered in the post-operative period are due to an unsuspected pre-existent hypertonic dehydration which has not been corrected before operation, and which has led to water retention in the post-operative phase. A water retention of slight degree is normal after even uncomplicated operation (Moore and Ball, 1952; MacPhee, 1953), but the water retention here discussed is much greater and must be regarded as a danger to the patient. Such an unfortunate result is all too common, and may be represented by the following example.

Case 2.—A man aged 60 was admitted to a surgical ward on September 7, 1952, with a gastric carcinoma. Gross dehydration was present, the blood analysis being shown in Table III. The progress on September 9 and 10 is demonstrated. The low serum protein concentration, however, went unmarked, and operation

TABLE III.—*Blood Analysis in Case 2*

Plasma or Serum Concentration	Sept. 8	Sept. 9	Sept. 10		Sept. 11	Sept. 12
Cl_2 (mEq/l.) ..	104	106	113	Opera-	99	89
Total protein (g./100 ml.)..	5·2	—	—	tion	—	—

was carried out on the 10th. The daily sodium and chloride loss was corrected each day in the post-operative phase, but in addition 1 litre of 5% dextrose was supplied daily in excess of requirements. By September 12 the patient had become grossly oedematous, and, although no sodium had been given in excess, a condition of water-overload had been established. Plasma was then ordered, but it was too late, and the patient died that day. Necropsy showed extensive tissue oedema, pulmonary congestion, and oedema.

The features in this case are complicated by an uncorrected metabolic alkalosis, but this would not have led to a fatal outcome. The fact that a degree of hypertonic dehydration remained unsuspected, and that the plasma protein concentration, though initially low, was never re-estimated, permitted a dangerous hypoproteinaemia to result in the post-operative phase.

Conclusions

It has been suggested, therefore, that the concentration of extracellular electrolytes may be no guide to the actual state of the body economy. Decrements in total body water may occur at a different rate, and to a different extent, from losses of sodium and chloride. When time is available before surgical treatment becomes necessary, adequate hydration of the thirsty patient should be undertaken and serial haematocrit readings should be obtained.

Many methods of assessing extracellular electrolyte deficiency in the depleted patient have been published, and most are reliable. They depend, however, on the assumption that changes in water volume and electrolyte concentration march together. Where doubt arises, however, it should always be possible to supply the patient with a loading

dose of water and then repeat the serum electrolyte examinations. If the water is not required in the pre-operative state it will rapidly be excreted, but if required it will be retained and the dilution effect described will take place.

Summary

If water is lost in excess of extracellular electrolyte a state of hypertonic dehydration may be induced.

In this condition the concentration of extracellular electrolytes may be normal or even above normal when the total quantity of electrolyte is decreased.

In the post-operative phase oedema may result if water is given in excess.

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EARLY IMMUNIZATION AGAINST WHOOPING-COUGH

BY

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Whooping-cough has rightly been described as one of the most prevalent and certainly the most lethal of acute specific infections of childhood (Parish, 1952): it caused 9,401 deaths in England and Wales in the ten years preceding 1951, 50% of which were in babies under 1 year old. American workers noted that approximately half their deaths from pertussis occurred in infants who had not yet reached the accepted age for immunization (Fox and Snartemo, 1949). It is also generally agreed that the younger the victim the greater is the severity of the disease and its attendant complications and sequelae.

Although the prophylactic uses of pertussis vaccine had previously been demonstrated (Madsen, 1925; Kendrick and Eldering, 1936; Sauer, 1933), immunization at an early age did not yield what appeared to be favourable results till 1947 (Sako, 1947). It was observed that infants under 3 months of age developed agglutinins as satisfactorily as those in any age group, and that 75% of infants under 6 months developed agglutinins.

Di Sant' Agnese (1949) recommended active immunization against pertussis as soon as possible after birth. In his series inoculations of combined pertussis, diphtheria, and tetanus antigen were completed at nine weeks after birth, and at 13 weeks 60% of these babies had pertussis agglutinin levels which were considered to be protective. It should be stated, however, that agglutinin titres are not accepted by all workers as an index of protective function.

Some investigators suggested that the variable response to early immunization might depend on the type of vaccine used; it was also thought that a more prolonged stimulus was required in young babies, and that this was provided by alum-precipitated vaccine (Sako, 1947). Disappointing results in young infants followed the use of fluid (suspended) vaccine (Sauer, 1941) and many more febrile reactions were observed with it. Howard (1950), in a progress report, noted the alum-precipitated vaccine to have fewer side-effects, but it has been stated that severe or serious reactions occur with it because it causes more local trauma than the other types (Cockburn, 1951).

In the M.R.C. trial (1951) good clinical results were obtained with all five types of vaccine used, but great variability was disclosed. Suggested reasons for this included: (*a*) the selection of strains; (*b*) the medium on which the organisms for vaccine were grown; (*c*) the methods of harvesting the growth; or (*d*) the nature of killing and preserving agents.

With the foregoing facts in mind, we proceeded to investigate the results of immunizing babies at an early age with two different sorts of vaccine, and, further, we felt it would be of interest to observe whether there was an appreciable antibody level in babies at birth, and whether the naturally occurring antibody bore any relationship to the one produced by immunization.

Methods and Materials

All sera were tested against six antigenic suspensions. One was kindly supplied by Glaxo Laboratories Ltd., and consisted of a formolized suspension of two strains of *H. pertussis* containing $2,000 \times 10^6$ organisms per ml. in saline. The remaining five suspensions, of approximately the same number of organisms, were prepared from strains grown according to the technique described by Lacey (1953, personal communication). These were *H. pertussis* H5 and *H. parapertussis* 15 grown in both X and C modes, and *H. pertussis* H16 in the X mode only.

A high-titre rabbit serum prepared against the Glaxo antigenic suspension was used as a positive control.

The material for immunization was obtained as a commercial vaccine in two forms—an aluminium phosphate adsorbed preparation and a simple suspension. These were labelled A and B respectively for the purpose of the investigation.

Titration Technique.—Tests were made in 0.5 by 5 c.cm. tubes. Doubling dilutions of serum were made in saline, starting at a titre of 1:8 and concluding at 1:512. An equal volume of antigen was added to each dilution, and the tubes after mixing were placed in a water-bath at 37° C. for two hours. The final readings were made after allowing the tubes to stand overnight at room temperature. Only definite agglutination was read as positive, faint granularity and similar reactions being disregarded. Figures were recorded as serum dilutions; that is, the final dilutions were in fact double these. Dry, clean tubes were used to collect cord blood at delivery and maternal venous blood shortly after. Blood from the babies at 6 months of age was obtained by heel pricks and collected in Wright's capsules. Sera were separated and stored at −20° C. until tested.

Selection of Cases.—Cases were selected by choosing at random mothers who came to the antenatal clinics between certain fixed dates; these had the nature of the experiment explained to them, and 90 volunteers were divided into three groups of 30 each. Their case records were labelled A, B, and C. Group A babies received aluminium-adsorbed vaccine, Group B had suspended vaccine, and Group C had no immunization before 6 months and served as a control group: they were offered immunization at 6 months.

The basic plan of the investigation consisted in determination of the antibody level against the strains of *H. pertussis* and *H. parapertussis* described above, in mothers and babies at delivery, and in the babies at 6 months. Unfortunately there were defections. Some mothers changed their minds and refused immunization after their babies had been delivered, and some babies were excluded because of illness or congenital defects. There were also a few cases with incomplete injection records.