Results

The results of the experiment are shown in the Table. Twenty-one children completed the trial. During the first two weeks the children gained between ½ and 5 lb. (227 and 2,270 g.) in weight, with an average of about 2 lb. (907 g.). While receiving phenmetrazine 18 children

Result of Double-blind Controlled Trial of Phenmetrazine

Case No.	Weight Gain During Preliminary Two Weeks (in lb.)	Weight Gained or Lost While Receiving Phenmetrazine (in lb.)	Weight Gained or Lost While Receiving inert Tablets (in lb.)
1	+1	−½	+1½
2	+1	−1	+2
3	+3	Nil	+1
4	+2	−7	−1
5	+3½	−4	+1
6	+3	−2½	Nil
7	+1	−8	+1½
8	+½	−5	+3
9	+1½	−2½	+3½
10	+½	−7½	+1½
11	+3	−4½	−1½
12	+1	−½	+4
13	+1	−3	+2
14	+½	−4	+1½
15	+½	−6	+1
16	+5	−3	+2
17	+3	Nil	+3
18	+1	−6	+1
19	+2½	−1½	Nil
20	+5	−2	+3
21	+1	+4	+5

1 lb. = 454 g.

lost between ½ and 8 lb. (227 and 3,630 g.) with an average of 4 lb. (1,815 g.), two children remained stationary, and one child gained 4 lb. (1,815 g.). While receiving the dummy tablets 17 children gained from 1 to 5 lb. (454 to 2,270 g.) with an average of 2 lb. (907 g.), two remained stationary, and two lost 1 and 1½ lb. (450 and 680 g.) respectively. On studying the figures it will be seen that in every case phenmetrazine was more effective than the dummy tablet. Even the children who did not lose weight while receiving the drug gained more while they were not receiving it; while all the children who did not gain weight while on the placebo lost considerably while taking phenmetrazine.

Only four children failed to gain weight on the dummy tablets. These had gained at least 2 lb. (907 g.) during the probationary two weeks. Three of the four children happened to have the active drug first and the dummy second. These children give some indication of the way in which illicit dieting or minor ailments may have affected the outcome of the experiment.

Discussion

Phenmetrazine, in the dosage given, was a highly effective weapon againt obesity. The result of the experiment is the more remarkable when it is remembered that the children's diet was not restricted and they had been shown to be gaining weight prior to the time they received the drug. None of the children complained of any ill effects, though one child became very ill-tempered while receiving phenmetrazine, and her parents stopped giving her the drug.

Phenmetrazine is not an innocuous drug. Subacute delirium (Silverman, 1959), toxic psychosis (Bethell, 1957), and addiction (Kahan and Mullins, 1958; Evans, 1959) have all been described in adults with psychopathic personalities.

In order to discover the effect of phenmetrazine, no dieting was allowed in the experiment reported above. This does not, of course, mean that diet plays no part in the treatment of childhood obesity. On the contrary, appropriate dietetic measures should be the mainstay of treatment, and only if that fails should phenmetrazine be introduced as a useful adjuvant. No treatment apart from starvation in hospital will succeed unless the child is willing to co-operate. Indeed, as Wallgren (1959) has indicated, it may well be better in some cases for the child to remain fat than to provoke an unnecessary psychological tussle.

Summary

A double-blind controlled trial of phenmetrazine on 21 children receiving an unrestricted diet gave the following results: while receiving phenmetrazine 18 children lost weight, 2 remained stationary, and 1 gained weight. While receiving inert tablets: 17 children gained weight, 2 remained stationary, and 2 lost weight.

The potential dangers of phenmetrazine and the indications for its use are indicated.

I thank Drs. C. C. Harvey, J. Lorber, M. W. Partington, and Mr. J. Sharrard for referring cases to me; Miss C. I. Crawford, the hospital pharmacist, for her co-operation; and Professor R. S. Illingworth for referring cases and for kindly criticizing this paper.

References

Bethell, M. F. (1957). *Brit. med. J.*, **1**, 30.
Bleckmann, K. H., and Salus, D. (1955). *Med. Mschr.*, **9**, 382.
Evans, J. (1959). *Lancet*, **2**, 152.
Fazekas, J. F., Ehrmantraut, W. R., and Kleh, J. (1958). *Amer. J. med. Sci.*, **236**, 692.
Kahan, A., and Mullins, A. G. (1958). *Brit. med. J.*, **1**, 1355.
Leith, W., and Beck, J. C. (1958). *Canad. med. Ass. J.*, **79**, 897.
Patterson, M. (1959). *Antibiot. Med.*, **6**, 207.
Silverman, M. (1959). *Brit. med. J.*, **1**, 696.
Wallgren, A. (1959). *Acta paediat. (Uppsala)*, **48**, Suppl. 117, p. 83

USE OF ^{82}Br IN DIFFERENTIAL DIAGNOSIS OF LYMPHOCYTIC MENINGITIS

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The Bromide Partition Ratio

In 1929 Walter described a method for estimating bromide levels in blood and cerebrospinal fluid (C.S.F.) and showed that in the normal subject there was a blood/C.S.F. barrier. The partition of bromide between blood and C.S.F. could be expressed as a bromide ratio,

$$\frac{\text{bromide per unit volume serum}}{\text{bromide per unit volume C.S.F.,}}$$

which fell within the range 2.9 to 3.5 (mean 3.1). Walter also showed that in tuberculous meningitis and in

neurosyphilis the permeability of this barrier to bromide increased and that the ratio consequently fell.

By using a different chemical method and with slight modification of Walter's technique, Taylor *et al.* (1954) showed that in subjects "without overt disease of the nervous system" the mean bromide partition ratio was 2.6 ± S.D. 0.3 Smith *et al.* (1955). The same workers studied 66 patients with early lymphocytic meningitis. In 33 of these tuberculous meningitis was subsequently proved, and 30 of them had a bromide partition ratio of less than 1.6. Only 2 of the 33 cases of non-tuberculous lymphocytic meningitis had partition ratios of less than 1.6. The differences in the bromide ratios in the two groups were independent of any differences in the amount of protein and cells in the fluids. Other workers (Cheek, 1956; Nicol and Fawns, 1958), using this same method, have reported favourably on the differential diagnostic value of the bromide partition test in cases of non-purulent meningitis. In a series of 26 cases of early undiagnosed lymphocytic meningitis, Nicol and Fawns (1958) showed that every case subsequently confirmed as of tuberculous origin had a bromide partition ratio of less than 1.4 during the first few days of observation. There were no false-negative results.

Chemical Methods of Estimating the Bromide Partition

Serum or C.S.F. levels of bromide are normally too small to be measured accurately, and in order to estimate the bromide ratio it is necessary to administer supplementary bromide. This is usually done by the oral or intravenous routes 48 hours before the simultaneous sampling of blood and C.S.F.

Walter (1929) originally used a gold chloride method for his bromide estimations. Hunter *et al.* (1954) later showed that though the method gave reliable results for estimations of bromide in C.S.F. the figures obtained in the estimation of serum bromide were too high, substances other than bromide being present in serum and reacting with gold chloride to give the same brown colour. The iodometric titration methods originally described by van der Meulen (1931) and later modified by Hunter (1953) were found to give more reliable results. Even with such methods, however, the chemical estimation of bromide in body fluids is difficult and often laborious. Ashing, extraction, and subsequent titration of each sample is necessary. The accuracy of the estimation has been noted to vary with the concentration of bromide present and the volume of the sample available. Moreover, the method requires the standardization of a number of reagents. The procedure is time-consuming and the error of occasional single estimations is probably more than the ±1% claimed.

We have therefore investigated the possibility of using a radioactive isotope of bromine to estimate relative bromide concentrations in blood and C.S.F. The method was found to be simple, reliable, and applicable to very small samples.

Material and Methods

The radioactive isotope used is ^{82}Br, which has a half-life of 36 hours and emits β rays of maximum energy 0.4 MeV and γ rays with energies in the range 0.55–1.47 MeV.

A dose of 50 μc. of radioactive sodium bromide is administered orally in 50 ml. of water. Forty-eight hours later a lumbar puncture is performed. The first 5 ml. of C.S.F. is taken for estimation. A 5-ml. blood sample is taken at the same time.

Equal volumes (usually 1 or 2 ml.) of serum or C.S.F. are counted in a sodium iodide, thallium-activated scintillation counter, similar to the Ekco well-type scintillation counter (serial No. N557). The counts obtained on each specimen are corrected for background and dead-time, and the ratio of these corrected counts (serum/C.S.F.) gives the bromide partition ratio.

On the assumption that the ingested material is fairly uniformly distributed and that none of it is excreted during the period of the test (which is probably never the case) it was calculated that the body would receive a total dose of 200 mr. This may be compared with a maximum permissible dose of 300 mr/week for persons *habitually* working with radioactive materials in controlled areas (Code of Practice for the Protection of Persons Exposed to Ionizing Radiations, H.M.S.O., 1957).

Results in Patients without Meningitis

Diagnostic lumbar puncture on patients without clinical evidence of meningitis gave opportunities of obtaining control data.

Our patients had various neurological disorders (cerebrovascular disease, cerebral and spinal tumours, cortical atrophy, cervical or lumbar spondylosis with neurological complications, syringomyelia, and disseminated sclerosis). In most instances the lumbar puncture was part of the procedure of myelography or air encephalography.

The bromide partition ratios were estimated in 30 such patients and varied between 1.9 and 3.7 (mean 2.6, S.D. 0.4). The ratios were independent of the protein or cell content of the fluid. In no instance were readings obtained which might invalidate the hypothesis of a blood/C.S.F. barrier to bromide in patients with non-infective neurological disorders.

Our findings confirm the existence of a blood/C.S.F. barrier for bromide in patients without meningitis and show that this barrier can readily be estimated by the use of ^{82}Br.

Results in Patients with Meningitis

In the Table are recorded some investigations on patients who presented with symptoms or signs of meningeal irritation.

The serum/C.S.F. bromide barrier, as estimated with ^{82}Br, was maintained in the five cases of non-tuberculous lymphocytic meningitis and grossly affected in two cases later proved, by C.S.F. culture and guinea-pig inoculation, to be tuberculous meningitis.

Investigations in Patients with Signs or Symptoms of Meningeal Irritation

Case No.	Age	C.S.F. Protein (mg./100 ml.)	C.S.F. Cells (per c.mm.)	C.S.F. Glucose (mg./100 ml.)	Serum/C.S.F. ^{82}Br Partition Ratio	Diagnosis
1	28	120	850	50	2·0	Benign lymphocytic meningitis
2	29	150	30	71	2·4	Subdural empyema
3	27	124	90	73	2·6	Poliomyelitis
4	25	200	2,215	41	2·3	Benign lymphocytic meningitis
5	28	90	330	62	3·3	,, ,,
6	35	104	500	37	0·9	Tuberculous meningitis
7	45	260	160	37	0·9	,, ,,

The diagnostic value of the bromide partition test is illustrated by Cases 3 and 6, described in more detail below.

Case 3.—A 27-year-old haulage contractor had developed back pain and later headache, nausea, and vomiting while shovelling gravel. He was admitted to hospital with fever (102° F.; 38.9° C.) and photophobia. He was irritable and there was marked stiffness of the neck and back. The fundi were normal. The C.S.F. contained: cells, 90/c.mm. (90% lymphocytes); protein 124 mg./100 ml.; and glucose 73 mg./100 ml. The bromide partition was 2.6. It was decided to observe him for 24 hours. Two days later he developed paresis of the hip flexors and of the muscles of the back and anterior abdominal wall. Diagnosis: acute poliomyelitis.

Case 6.—A 35-year-old Nigerian student nurse was admitted after the sudden onset of severe headache and vomiting. She was pyrexial (102° F.; 38.9° C.), photophobic, and showed marked meningism. The fundi were normal. The C.S.F. contained: cells, 500/c.mm. (all lymphocytes); protein, 104 mg./100 ml.; and glucose, 37 mg./100 ml. No organisms were seen on direct smear. The bromide partition ratio was 0.9. Anti-tuberculous therapy was started. Culture of the initial sample of C.S.F. subsequently grew acid-fast bacilli. With continued treatment the patient has become symptom-free. Eight months after the onset of the illness the bromide partition ratio was still low. Diagnosis: acute tuberculous meningitis.

Comment

Tuberculous meningitis often presents as a lymphocytic meningitis, the bacterial cause of which may remain unproved until the results of culture or guinea-pig inoculation are available. Anti-tuberculous therapy is often started in such cases, the diagnosis being based on clinical suspicion and indirect laboratory evidence. This is undoubtedly justified in view of the risks that attend delay in initiating treatment in tuberculous meningitis. On the other hand, it has been claimed that injections (for instance, streptomycin injections) given during the pre-paralytic phase of acute poliomyelitis may contribute to the development of local paralysis. The bromide partition test seems to be a useful adjunct to our diagnostic armamentarium when confronted with cases of lymphocytic meningitis of as yet undetermined aetiology.

Using a radioisotope of bromine, we have demonstrated significant lowering of the bromide partition ratio in two cases of tuberculous meningitis, while in five other cases of lymphocytic meningitis and in control subjects the ratio was not significantly altered.

The chief advantage of using radioactive bromide is the speed and simplicity of estimation of the serum/C.S.F. ratio.

Summary

A technique using oral radioactive bromine to determine the serum/C.S.F. partition ratio is described. The values obtained in five cases of non-tuberculous lymphocytic meningitis, in two cases of tuberculous lymphocytic meningitis, and in 30 controls are given.

References

Cheek, D. B. (1956). *Pediatrics*, **18**, 218.
Hunter, G. (1953). *Biochem. J.*, **54**, 42.
—— Smith, H. V., and Taylor, L. M. (1954). Ibid., **56**, 588.
Meulen, J. H. van der (1931). *Chem. Weekbl.*, **28**, 82.
Nicol, V. S., and Fawns, H. T. (1958). *Arch. Dis. Childh.*, **33**, 440.
Smith, H. V., Taylor, L. M., and Hunter, G. (1955). *J. Neurol. Neurosurg. Psychiat.*, **18**, 237.
Taylor, L. M., Smith, H. V., and Hunter, G. (1954). *Lancet*, **1**, 700.
Walter, F. K. (1929). *Die Blut—Liquorschranke*. Thieme, Leipzig.

Medical Memoranda

Reduction of Fractures and Dislocations Without a General Anaesthetic

In a casualty department the administration of a general anaesthetic for the reduction of fractures or dislocations has a number of disadvantages. These include the need for an anaesthetist to be present, the need for the patient to wait for four hours if food or drink has been taken recently, and the delay in recovery from a general anaesthetic, during which time the patient cannot leave the hospital.

Because of these disadvantages we decided to study the possibility that most or all of these reductions can be carried out after giving an intravenous dose of a narcotic analgesic such as pethidine. For the purpose of this trial, we decided to use "pethilorfan," a proprietary preparation containing pethidine and levallorphan tartrate in the proportion of 80 to 1. It is claimed that the inclusion of a small dose of a narcotic antagonist (levallorphan tartrate) greatly reduces the respiratory-depressant effect of the pethidine, and we felt that this should be an advantage, particularly in young children and in the elderly.

Technique

As soon as we are ready to carry out the reduction the patient is given an intravenous injection of pethilorfan. The dose is usually 2 ml. (100 mg. of pethidine + 1.25 mg. of levallorphan tartrate) but varies with the age and size of the patient, children being given one-half to three-quarters of this dose according to age. The drug is given undiluted and is injected slowly over a period of 20 seconds. The patient is told that he will become drowsy but will not fall asleep, and that a manipulation will be carried out but that he will not feel pain. It is necessary to give this explanation carefully, as otherwise some patients expect to lose consciousness and think that the injection has failed when they do not do so. It is essential to maintain the patient's co-operation throughout the procedure. We have found that the optimal time for starting the manipulation is 10 minutes after the injection or as soon as the patient becomes drowsy. After the reduction is completed, the effects of pethilorfan wear off very rapidly, and the patient can usually go home as soon as the post-reduction *x*-ray film has been taken.

We have used this technique for the treatment of 30 fractures and 9 dislocations.

Reduction was successfully carried out in 36 of these 39 patients with the use of pethilorfan alone. We noted that, even if some pain was complained of during the actual manipulation, when seen in the fracture clinic two days later the patient had no memory of this. In children, in particular, the manipulation was often completely painless. We quote the casualty officer's

Fractures		Dislocations	
Colles's fractures in adults (aged 48–83)	11	Shoulder	3
Shaft of radius and ulna in children (aged 5–14)	10	Jaw (bilateral)	1
Tibia and fibula	6	Elbow	2
Shaft of femur	2	Metacarpo-phalangeal joint of thumb	1
First phalanx of index finger	1	"Locked knee"	2