blood Wassermann reaction was also negative. Liver-function tests were normal. The Casoni intradermal test gave a weak and delayed positive response.

It was felt clinically that the patient had a right lateral recess space-occupying lesion, and she was referred to Mr. Wylie McKissock with a view to ventriculography and subsequent exploration of the posterior fossa. The ventriculogram, which entailed the introduction of myodil for more accurate assessment, gave the appearance of a space-occupying lesion in the medial part of the cerebellopontine-angle cistern (Special Plate, Fig. 2).

Operation.—The cerebellar tonsils were widely separated and in the space between them lay some whitish-walled amorphous-looking material associated with a series of small clear-walled cysts containing clear fluid. The amorphous material was picked out with a number of cysts adherent to it. There was a considerable amount of thickening of the arachnoid over the cisterna magna. No further operative treatment was carried out in her case. She made a satisfactory post-operative recovery.

Histology.—The tissue submitted for histological study consisted of a papilliferous membrane, part of which had undergone coagulative necrosis. The viable membrane was covered with high columnar cells with a deeper eosinophilic cytoplasm and a basal nucleus. External to this was a loose meshwork of round cells. Scolices and daughter cysts were not seen, but the appearances were highly suggestive of a hydatid cyst.

Post-operative Course.—The patient improved symptomatically and the papilloedema began to subside in each eye. The facial weakness improved, but there was no change in the facial anaesthesia. Two weeks after the operation a cystic swelling developed over the operative site. Lumbar puncture was performed and examination of the fluid showed the presence of 10 lymphocytes, 160 mg. of protein per 100 ml., and a Lange 5555544333. Culture of the fluid gave no growth. The swelling persisted and was reduced in size temporarily by lumbar puncture, indicating that it was a collection of cerebrospinal fluid which developed as a result of impaired absorption. The blood count was normal. The E.S.R. was 55 mm. in the first hour. The Casoni intradermal test gave an immediate positive response.

She was sent home to Cyprus five weeks after the operation and up to the time of writing there had been little change in her condition as compared with her immediate post-operative state. She required frequent aspiration of the swelling in the back of her neck; this brought temporary relief of her headache, dizziness, and vomiting. She was unable to walk on her own because of the severity of her ataxia.

Discussion

An accurate pre-operative diagnosis is of great importance in cerebral hydatid disease, as surgery without prior knowledge can lead to cyst rupture and wide dissemination of the daughter cysts. The diagnosis is by no means easy, and of the available tests the Casoni intradermal and hydatid complement-fixation are disappointing in cerebral cases (Robinson, 1960). In both our patients an eosinophilia was found in the blood, and it is interesting to note that some authorities claim it is the only test of value in these cases. The presence of a hydatid cyst elsewhere in the body does not necessarily prove that the lesion in the central nervous system is of the same nature (Schroeder, 1947). Ventriculography is often undertaken as a means of locating the site of the lesion more precisely. This can be a dangerous procedure on account of accidental rupture of the cyst; consequently, if this diagnosis is considered, then the ventricle on the opposite side to the suspected site of the lesion should be injected with air.

We consider that the diagnosis of cerebral hydatid disease should be entertained in any patient who comes from an area where the disease is prevalent and who presents with symptoms of increased intracranial pressure together with focal signs pointing to a lesion in the posterior part of either hemisphere or in the posterior fossa.

Summary

Two cases of hydatid disease occurring in the posterior fossa, a comparatively rare location, are presented.

Both patients came from abroad, the diagnosis in each case being established at operation and confirmed by histological study.

The importance of an accurate pre-operative diagnosis is stressed, and in this connexion the finding of an eosinophilia in the blood is thought to be of greater significance than both the Casoni intradermal and the hydatid complement-fixation tests.

The danger of accidental rupture of the cyst on ventriculography is noted.

In conclusion, the diagnosis of cerebral hydatid disease should be entertained in any patient who comes from an area where this disease is prevalent and who presents with signs of raised intracranial pressure.

Our grateful thanks are due to Dr. J. St. C. Elkington and Dr. John Marshall for allowing us to use these patients for presentation, and to Mr. Wylie McKissock for permission to use the surgical notes. We also thank Mr. Prickett, of the photographic department, for the photographs of the *x*-ray films, and the Medical Committee of the National Hospital, Queen Square, for permission to publish this paper.

REFERENCES

Barnett, L. E. (1943). *Aust. N.Z. J. Surg.*, **12**, 240.
Dévé, F. (1913). Quoted by Barnett (1943).
Maunsell, H. W. (1889). *N.Z. med. J.*, **2**, 151.
Robinson, R. G. (1960). *Ann. roy. Coll. Surg. Engl.*, **26**, 145.
Schroeder, A. (1947). *Arch. int. Hidatid.*, **7**, 195.
Valentino, V. (1959). *Radiology*, **73**, 250.

THALIDOMIDE DISASTER CONSIDERED AS AN EXPERIMENT IN MAMMALIAN TERATOLOGY

BY

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During the past ten years experimental work on laboratory animals has revealed that a large number of chemical substances have the power when administered to the pregnant female of producing congenital malformations in the young. The unfortunate experience with thalidomide parallels these observations in all but two respects—in this case man is the experimental animal, and the choice of animal was made not deliberately but accidentally. From the numerous experiments which have been carried out in the laboratory there have emerged certain general principles of mammalian teratogenesis. These principles, which are summarized below, are highly relevant not only to the understanding of the mode of action of thalidomide but also in suggesting how similar tragedies are to be avoided in the future.

Significance of Timing and of Dosage

The most important single factor that has to be considered by the experimental teratologist is when the

noxious agent should be administered. The foetus is sensitive to the effects of such agents only during a limited period in the early part of pregnancy. Moreover, within this already restricted period there is for each structure in the body a shorter critical period when it is specially vulnerable. Generally this period, which differs from structure to structure, coincides with the time of greatest mitotic activity. The time at which an agent is administered does not necessarily coincide with the time at which it exerts its deleterious effects. It may indeed be necessary for administration to begin before pregnancy in order to achieve a sufficient accumulation of teratogen by the critical period.

The production of a live deformed animal by experimental means may be regarded as a reproductive near-success, for the greater part of its tissues must be healthy and normal if it is to survive. To achieve this effect, therefore, it must be exposed to a definitely noxious but relatively slight stimulus. Within the spectrum of activity of any teratogenic agent there is a relatively narrow band of dosage which is capable of producing deformed young. If too little is given, the young are born alive and normal. If too much is given, they die *in utero* and are aborted or resorbed. Whether the requisite stimulus to abnormal development is obtainable with a drug must depend to a considerable extent on the chemical nature and behaviour of that drug. It would, for example, be very difficult to devise a system of dosage for hydrocyanic acid which would damage the foetus yet fail to kill the mother. At the other extreme it is obviously impossible to give a dose of sodium bicarbonate to the mother which is large enough to damage the foetus. The list of drugs which have a teratogenic effect is therefore bound to be rather a small one, and within this list fewer still will be of practical importance.

Factors Responsible for Variations in Effects of Teratogenic Agents

Different animal species exhibit wide variations in response to teratogenic agents. Within a single species there are smaller variations which may be attributed to the genotypes of both mother and foetus. The age and reproductive status of the dam, her standard of nutrition, and her hormonal levels are all important in determining the occurrence of malformations in the young. In addition, the effect of certain agents may be considerably modified by the simultaneous administration of other substances. The teratogenic activity of vitamin A, for example, may be aggravated by cortisone and alleviated by thyroxine.

It is worth considering why thalidomide should be the first drug clearly implicated as the cause of human malformations when a wide variety of chemical substances, ranging from drugs such as caffeine and salicylates to vitamins and hormones and their antagonists, have marked teratogenic properties in the experimental animal. To be effective as a teratogenic agent a drug must be given during the first three months of human pregnancy, the period of differentiation. The earlier in pregnancy that its administration is begun the more likely is it to have deleterious effects. Morning sickness is likely to be most troublesome just at the very time when the foetus is most at risk. It is quite possible, moreover, that morning sickness is accompanied by nutritional and hormonal disturbances in the mother which render the foetus more susceptible to the effects of a teratogenic agent. There seems to be, therefore, a certain risk in giving a drug to a woman suffering from morning sickness. Paradoxically, the peculiar danger of thalidomide probably resides in its relative lack of toxicity to the mother. If it were completely non-toxic to the adult it would probably be equally innocuous to the foetus. The occurrence of glossitis and neuropathies in the adult, however, suggests that thalidomide exerts a relatively slight but definitely deleterious effect on the foetal tissues comparable to that which has made rubella the unique viral teratogen.

It is important to consider whether any steps can be taken to prevent a similar catastrophe from occurring in the future with another new drug. The presence of species variation in the response to teratogens means that no drug can finally be shown to be safe until it has been demonstrated to be without deleterious effect on the human foetus. Experiments upon animals may, however, be valuable in determining which drugs are most likely to exhibit teratogenic activity in the human. As a general principle it seems probable that any drug which will kill the foetus will also deform it if given in a lower dose. If the dosage of a drug required to kill the foetus is close to that which is lethal to the mother, the danger of producing a malformation is obviously small. The greater the difference between the lethal dose for the foetus and that for the mother, the greater the probability that the drug will possess the ability to produce congenital malformations. It ought therefore to be relatively easy to establish in the laboratory whether a drug is likely to produce malformations in the experimental animal. The extrapolation of such findings to the human presents a problem of considerable difficulty which is unlikely to be solved until much more is known of the principles which determine the occurrence of experimentally induced malformations. In the present state of our knowledge the only safe course is to bar absolutely the use of new drugs by women who are believed to be in the early stage of pregnancy.

Medical Memoranda

Foetal Complication of Vaccination in Pregnancy

[WITH SPECIAL PLATE]

The recent outbreak of smallpox at Bradford and in Wales resulted in the vaccination of many people in England. Many pregnant women must have been among those vaccinated, despite the assumption that damage to the foetus may result if vaccination is performed in the first trimester of pregnancy (MacArthur, 1952). Very few cases of foetal involvement resulting from intra-uterine infection with vaccinia virus have been reported, and it is the purpose of this paper to record a further case of generalized vaccinia *in utero* following successful vaccination of a pregnant woman.

CASE REPORT

A 19-year-old woman attended her general practitioner early in January, 1962, for vaccination, but did not state that she was pregnant. Her last menstrual period was towards the end of October, 1961, but she was uncertain as to the exact date. She was therefore approximately 2½ months pregnant when she was vaccinated. She had not