indicate a need for further rationalising the provision and distribution of special care baby units.

The case for this is further strengthened by our other findings. Even in the three well-endowed regions in this study it has not proved possible to staff and equip all officially recognised units to the standard recommended by the expert group. Moreover, since the group’s report was published, increasing technological requirements together with inflation have made it a continuing struggle to maintain the standard of excellence required of the few units that provide intensive care for the illiest babies. A further argument for rationalisation is the demonstration by Blake et al of the successful results of transporting sick babies when this is well organised by the intensive care nursery that is to receive the babies.

Any replanning of nurseries must, however, take into account such factors as the density of population of child-bearing age and, particularly, local variations in incidence of low birth weight, which may be related to poor social conditions and the presence of ethnic minorities. New planning tools such as maps which indicate travelling times from place to place must be used, and the need to place the units in hospitals with specialist paediatric, maternity, and pathological facilities must be recognised. Other problems that need to be tackled include that of maintaining a high quality of neonatal care in hospitals without special care units. Medical and nursing staff should be encouraged to move between hospitals much more than they do at present so that as many staff as possible have experience in caring for sick babies.

Any future planning or rationalisation of resources must be accompanied by systematic and continuous monitoring of the results of treatment in all units that accept babies for special care. Monitoring the outcome assumes greater significance in the light of the results of treatment that have recently been published. What happens to babies of low birth weight is a highly specific indicator of the effectiveness of hospital care. Variables such as maternal age, parity, and social class are of minor relevance beside birth weight. The neonatal mortality of low birth weight infants can already be monitored through the annual returns made by districts and areas on form LHS 27/1. The national neonatal mortality of infants weighing less than 2500 g based on these returns was 99 per 1000 in 1974, and this figure could be used as a baseline for local comparison. The presence of certain handicaps, notably cerebral palsy, would be a more specific indicator than neonatal mortality in this group of infants. However, current information systems do not include such data but they would be easy to collect if properly organised by, for example, a specialist in community medicine (child health). But whatever the method, such monitoring should become a routine procedure.

We acknowledge the help given by many medical, nursing, and administrative staff in the three regions, without whom the study could not have been done. Professor J N Morris gave much constructive advice. The survey in the South-east Thames Regional Health Authority was carried out with the support of the DHSS.

References
6 Department of Health and Social Security. Notes on Form SH5 for 1976, para 56.
(Accepted 31 August 1977)

Treatment of hepatic hydatid disease with mebendazole: preliminary results in four cases

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Summary
Mebendazole was given to four patients with hepatic hydatid disease. In three patients hydatidosis had remained after surgery, and in the fourth it could not be treated surgically. Mebendazole was given orally in maximum doses of 400-600 mg three times a day during courses lasting 21 to 30 days. Ultrasonic echotomography showed a complete regression of the intrahepatic cysts after four to 13 months in all four cases. In three patients the course of treatment had to be repeated. Mebendazole also induced clinical improvement and a progressive lowering of the concentration of specific IgE of Echinococcus granulosus. During treatment circulating blood levels of specific immune complexes of antigen 5 were increased.

These observations indicate that mebendazole has a lethal effect on E granulosus cysts in primary hydatid disease in man and that the efficacy of chemotherapy can be assessed with ultrasonography and by measuring changes in the concentration of specific IgE of E granulosus and circulating immune complexes.

Introduction
Hydatid disease is one of the rare parasitic conditions that can be treated only by surgery. Despite the improvements in surgical
techniques, however, the result is often incomplete, with frequent local recurrences or accidents of secondary dissemination. Repeated interventions are often mutilating and do not always guarantee a definite cure.

Much work has been done in developing drugs for supporting chemotherapy and improving the prognosis of the disease. Certain substances possess a scolicidal action in vitro but not in vivo. Mebendazole is effective against nematodes in the digestive tract and the trachea and against cestodes; it is also active in vivo against the larvae of *Trichinella spiralis* and *Taenia taeniaformis.* Working with mice infected experimentally with *Echinococcus granulosus,* Heath *et al.* found that mebendazole had a lethal effect on the germinal membrane of the larvae. Vanparijs *et al.* came to similar conclusions and observed that in mice treated with 250 ppm or more of mebendazole either there were no intraperitoneal cysts or the cysts were sterile and smaller than in control animals. Reisin *et al.* have shown in vitro that mebendazole diffuses passively through the membrane that forms the walls of the cysts of *E. granulosus.* Electronmicroscopical studies by Kammerer and Judge have shown multiple changes in the ultrastructure of germinal cells under the influence of mebendazole.

On the basis of these results, we proposed a new therapeutic approach for patients with residual or inoperable hydatid disease. We report here the results of clinical echotomographic, and serological investigations in four cases of hepatic hydatid disease treated with mebendazole.

**Patients and methods**

The clinical and diagnostic data for the patients are shown in table I. Hydatid disease was suspected on the basis of the history

![](image)

**FIG 1**—Case 1. Cyst in suprahilar region of liver: (a) echotomographic cross-section and schematic representation (day 0); (b) dense and echo-producing zone at site of former cyst (23 months). L = Liver. C = Cyst. K = Kidney. SC = Spinal column. P = Pancreas. PV = Portal vein. Ao = Aorta.

**TABLE I**—Data on four patients with residual hydatid disease after surgery and one patient with recent hydatidosis before chemotherapy with mebendazole

<table>
<thead>
<tr>
<th>Case No</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Previous treatment</th>
<th>Duration of postoperative surveillance</th>
<th>Immunodiagnostic data</th>
<th>Echography</th>
<th>Arteriography</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(diameter)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(cm)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

|         |     |             |                    |                                        |                        |            |              |

1. M 55 | 1967 | Sphincteroplasty | 4 years | 5 | 1/5120 | 1/160 | 1/64 | 1/8 | Median cyst (4–5 cm) | Median cyst |

2. F 39 | 1968 | Y-shaped cysto- \( \text{eternal} \) \( \text{anastomosis} \) \( \text{Resection of projecting dome in left lobe} \) | 6 years | 3 | 1/1280 | 1/40 | 1/16 | 1/8 | Median cyst (4–5 cm) | Median cyst |

3. M 52 | 1971 | Cystectomy of two hepatoperitoneal cysts | 4 years | 1 | 1/160 | 1/40 | 0 | 0 | Cyst (2–2 cm) in right lobe |

4. F 22 | 1972 | Resection of projecting dome in right lobe \( \text{Exploratory laparotomy} \) | 6 years | 4 | 1/320 | 1/40 | 1/8 | 1/8 | Two cysts in right lobe | Two cysts in right lobe |
and clinical, echotomographic, and angiographic observations and was confirmed serologically. The disorder had recurred locally in three patients (cases 1, 2, and 3). The fourth patient had associated valvular heart disease, which made surgery rather hazardous.

Our study lasted from 15 January 1975 to 15 December 1976. The drug was administered in increasing doses up to a maximum of 400-600 mg three times a day* in courses lasting 21 to 30 days. The preparation was initially given by mouth in hospital to test the patients' tolerance towards the relatively large doses used. When their tolerance seemed satisfactory they were treated as outpatients with the doses fixed according to the state of the cysts and serological results.

**Echotomography** was performed with two types of apparatus: (a) a one- and two-dimensional Combison machine of Krez Technic, which was used at frequency of 2 MHz and a conduction velocity of 1550 m/s, and (b) a Siemens Vidoson.

**Computerised axial tomography (CAT)**—This could be performed only toward the end of the trial and was used partly to search for any residual hydatid disease. The apparatus was an Acta Body Scanner (CGR).

**Serological methods**—Liquid removed aseptically from hydatid cysts grown in horse or sheep liver was used as the antigen for serological tests. It was centrifuged, dialysed, and subjected to immunoelectrophoresis in the presence of a reference immune serum to determine its qualitative composition. Each patients' serum was tested simultaneously by immunoelectrophoresis, passive haemagglutination test, fluorescent antibody test, complement fixation test, and agglutination with latex particles according to a modification of the methods of Pauntrizel and Baintler, and Fischman. Total IgE concentrations were determined with a Phadebas Kit (Pharmacia, Uppsala) and were considered significant when they exceeded 500 IU/ml. The specific IgE antibodies to *E. granulosus* were measured after they had been isolated on an immunoabsorbent material prepared with the specific antigen 5 fraction of the hydatid fluid purified by the method of Bout et al. The specific IgE antibodies were eluted at an acid pH and determined by radioimmunoassay. The specific IgE concentrations were considered significant if they reached 6 IU/ml or more. The circulating immune complexes were determined by a method based on fixation with 125I-labelled Clq. A circulating immune complex level of 13% or more was considered significant.

**Results**

**Clinical progress**—After mebendazole treatment two patients (cases 1 and 3) became clinically normal and two improved. The drug was used in a total of nine courses and was always well tolerated. No allergic reactions or other side effects were observed.

**Echotomographic examinations**—The data in table II show the changes in the ultrasonic appearance of the cysts during the course of treatment. The cyst disappeared after 13 months in case 1 (fig 1b), after 11½ months in case 2 (fig 2c), after nine months in case 3, and after

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*This regimen was recommended by Janssen Pharmaceutica, Belgium, who market mebendazole.
four months in case 4. The lesions regressed more slowly when they were larger, and passed through an intermediate stage, with the contours becoming less rounded and their diameter becoming progressively smaller (fig 2b). Eventually the cavity was replaced by dense tissue, which gave an ultrasound echo and was probably scar tissue.

Specific antibodies and IgE levels—Fig 3 shows that in case 1, where the initial values were relatively high, the total and specific IgE levels rose during the treatment; they also fell sharply in the second month. The changes in the specific antibody level detected by serological methods in this patient were comparable to those in the total and specific IgE levels. Subsequent determinations showed that the total IgE and antibody levels were relatively stable in the group of patients as a whole. In contrast, the specific IgE levels showed a progressive and significant decrease in all the patients and disappeared in case 4 (fig 3).

Circulating immune complexes—Fig 4 shows the variation in these, as determined by 125I-C1q fixation before and after the use of mebendazole. The level was significantly higher in all four patients after treatment.

Discussion

The use of mebendazole for treating hepatic hydatid disease invariably led to clinical improvement. Echotomography showed that the cysts regressed to moderate lesions and then
TABLE II—Results obtained by echotomography and CAT in four patients with hepatic hydatid disease treated by mebendazole

<table>
<thead>
<tr>
<th>Case No</th>
<th>Treatment No</th>
<th>Monthly since beginning of treatment</th>
<th>Results obtained by echotomography and CAT (measurements refer to diameter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Start</td>
<td>Well-contoured 5-cm cyst giving no echo</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
<td>Same</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>5</td>
<td>Same</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>5</td>
<td>Small cyst (1.5 cm)</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>13</td>
<td>Small bounded tissue formation (1.5 cm)</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>23</td>
<td>No more echo (fibrous tissue ? intraperitoneal calcification ?)</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Start</td>
<td>Echotomographic picture unchanged; no visible cyst indicated by CAT</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2</td>
<td>4-cm cyst</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>3</td>
<td>4-cm cyst</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>Start</td>
<td>Very clearly contoured 2-cm cyst</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>9</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1</td>
<td>Very dense and echoproducing zone remaining</td>
</tr>
</tbody>
</table>

Disappeared, to be replaced by dense and probably cicatrization tissue giving an ultrasound echo. This suggests that mebendazole attacks and kills the parasites. The changes on ultrasonography accorded with the results of animal studies, in which the treated animals either had no peritoneal cysts of E. granulosus or had very few collapsed and underdeveloped cysts compared with the number present in control animals.10 11 13

A patient with immunologically very advanced hydatid disease showed an initial rise in IgE and antibody levels, which suggested that immunological stimulation was triggered off by antigens released from the cyst after lysis by mebendazole. Furthermore, after treatment for two to three months two patients (cases 1 and 4) had a more or less negative serological picture; although this was only temporary it was accompanied in case 1 by a sharp fall in the IgE level. These phenomena may have been due to the formation of circulating immune complexes in the presence of excess parasite antigens. The subsequent positive serological result appeared too quickly to be ascribed to synthesis of new antibodies and is better explained by the reappearance of serum antibodies that had participated in the formation of immune complexes. The latter were in fact detected in significant and increasing amounts in patients treated for the first, second, or third time.

All these observations suggest that mebendazole has a lethal effect on hydatid cysts in the human liver. The changes caused by the drug in the permeability, morphology, and size of the lesions suggest that mebendazole attacks the parasite’s germinal layer, which plays a major role in the homoeostasis and regulation of its metabolic exchanges with its external environment. This hypothesis is supported by the findings of Heath et al.12 who found that mebendazole almost completely destroyed the germinal membrane of cysts in mice with secondary hydatid disease when used in a daily dose of 50 mg/kg over 14 to 21 days. The changes in the ultrastructure of the germinal cells observed by Kammerer and Judge13 resemble the changes described by Borgers et al. in the intestinal cestodes of nematodes such as Ascaris suis and Syngamus trachea, and the tegumental cells of cysticeri of Taenia taeniaeformis.14 According to Dussaillant et al.,10,16 the changes in the endoplasmic reticulum lead to an accumulation of secretory products in the cytoplasm, and the resulting activation causes autolysis and death of the affected cells.

The disappearance of the cyst on ultrasonography was accompanied in all cases by a progressive fall and sometimes complete disappearance of specific IgE concentrations. IgE seems to respond to the loss of vitality of the cysts sooner than the other immunoglobulins. According to Dussaillant et al.,10 specific IgE is detected in significant amounts when the cyst is alive, and it has, as the main allergen, a major and specific antigen fraction of the Echinococcus species, called antigen 5.17

The latter has been purified by Bout et al.,19 which has enabled Yarzabal et al.20 to identify it in the innermost layer of the germinal membrane and in some parenchymatous cells of protoscoleces, where it is probably formed before being released in the peritoneal cavity. These results suggest that destruction of these germinal structures may lead to suppression of the antigenic stimulus connected with antigen 5, which may be reflected by a diminished production of the most highly specific antibodies. Owing to its shorter half life, the specific IgE of E. granulosus seems to offer a more sensitive means of detecting the loss of the vitality of hydatid cysts and thus of evaluating the efficacy of the selected chemotherapy.

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References
22. Dissaut, J., et al., Immunology, 1975, 29, 813.

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