seem to be uncommon both in our own experience and according to the literature, where we have been unable to find any reports of similar cases. A total of 450 patients with the diagnosis of aseptic meningitis were treated during 1952–62 at Aurora Hospital (formerly the Hospital for Infectious Diseases in Helsinki), which admits the majority of children and adults taken ill with meningitis in Helsinki. Three of the 450 patients suffered from aseptic meningitis on two or more occasions during this period. This incidence, 0.7%, can naturally be regarded as a minimum.

The occurrence of two attacks of aseptic meningitis is not in itself extraordinary. But an explanation is required when, as with two of our patients, there are still further attacks. When this happens it is necessary to try very carefully to exclude all other possible diseases of the C.N.S. as well as bacterial parameningeal infections. Nothing indicative of such diseases was found in our cases. It is, of course, regrettable that no carotid-angiography or pneumo-encephalography was performed on these patients. On the other hand, these procedures are not very readily undertaken when the disease is cured rapidly without sequelae. The histories indicated that these patients had no predisposition to infectious diseases. Electrophoresis showed normal amounts of gamma-globulins. Anyway, the patients with repeated attacks of aseptic meningitis in their history must have a special tendency toward such infections. However, we were unable to find any local or general reason for lowered resistance in these patients. A local congenital or acquired anatomical anomaly must nevertheless be seriously considered. Nor can the possibility be excluded that these individuals have some defect in their cell-bound defence mechanisms. A third possible explanation may be the development of hypersensitive (allergic) reactivity of the meningeal tissue to certain viral antigens.

Summary

Multiple attacks of typical aseptic meningitis were established in four patients: in two adults, one three times and the other four times, and in two children, twice in each. The follow-up periods were 18 months to 11 years. The intervals between the individual attacks were from four months to eight years.

An enterovirus isolation from the stools succeeded in 5 attacks out of 11: Coxsackie B5 three times, Coxsackie B2 once, and an untyped virus (E.C.H.O. 9?) once. Antibody responses indicated that the attacks may have been caused by the viruses isolated. In addition to the virus isolations, serological evidence of infection with E.C.H.O. 7 was obtained in one attack. In two patients different viruses appeared to be responsible for the successive attacks of meningitis.

No general or local cause was found for the predisposition towards aseptic meningitis in these patients.

This investigation indicates that different viruses may be responsible for successive attacks of aseptic meningitis in the same individual.

We express our gratitude to the following microbiologists who co-operated with us in clarifying the aetiology of meningitis: Dr. O. Wager and Dr. E. Jansson, Microbiological Laboratory, Aurora Hospital; Professor N. Oker-Blom, Professor P. Halonen, and Dr. A. Salminen, Department of Virology, University of Helsinki; and Dr. Kari Penttinen, M.D., State Serum Institute. We also thank Professor N. Hallman, who placed at our disposal the hospital records of patients with meningitis treated at the Children's Hospital, University of Helsinki.

REFERENCES

- Meyer, H. M., Johnson, R. T., Crawford, I. P., Dascomb, H. E., and Rogers, N. G. (1960). *Amer. J. Med.*, **29**, 334.
Wallgren, A. (1925). *Acta. paediat. (Uppsala)*, **4**, 158.

Preliminary Communications

Observations on Progeny of Thalidomide-treated Male Rabbits

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In earlier work (Lutwak-Mann and Hay, 1962) we found that maternally administered thalidomide produces peculiar changes in the configuration of the embryonic disk of pre-implantation rabbit blastocysts. The study of the action of maternally transmitted thalidomide upon pregnancy in the rabbit was continued and extended by Hay (1964). It was next decided to examine also the effect of thalidomide administered to *males* upon the breeding performance, to see if paternal treatment with this drug could affect progeny.

Experimental Animals.—Male rabbits (6) were chosen for consistently high fertility during 14 months of repeated matings; they were again mated twice before the start of the thalidomide treatment to make certain that they were capable of producing good-quality litters. The females (40) were picked for their excellent fertility as well as maternity records, each having raised without loss at least two litters of not fewer than 8 and up to 11 young prior to the experimental matings with the thalidomide-treated bucks. It may be added that the conception rate in our colony is 97%, and the average number of young at birth is nine.

Thalidomide was fed to males in capsules, in divided doses; the courses of treatment are stated in the Table. Body weights were recorded throughout the experimental period, but no significant changes were noted and the animals appeared to be in good health during the whole time. The bucks were mated to does after thalidomide-free intervals extending from 2 to 10 weeks. The progress of pregnancy was checked by palpation from day 8 *post coitum*. The offspring were counted at birth, weighed, and inspected for abnormalities. They were maintained for up to 14 days, when the survivors were again counted and weighed as well as sexed, before the termination of the experiment. No appreciable alteration of the sex ratio was observed.

RESULTS

Experiment 1 (see Table) records observations made with two males, A and B. It can be seen that total loss of litters fathered by these two thalidomide-fed rabbits occurred in each case—for male A at 4 weeks and for male B at 10 weeks from the end of their treatment with thalidomide. These two males were retained without further treatment for another four and a half months; during that period each was twice mated, with the following results: for A, one failure to induce conception (confirmed at necropsy of the doe on day 10 *p.c.*) and one viable litter; for B, one pseudopregnancy (confirmed at necropsy of the doe on day 10 *p.c.*) and one viable litter. These findings are not recorded in the Table, but will be taken into account in assessing the results.

Effect of Paternal Thalidomide Treatment on Litter Size and Viability of Offspring. Results are Expressed as (I) Number of Young at Birth, and (II) Number of Offspring Surviving for up to 14 Days of Life. The Time Intervals Between the End of Paternal Thalidomide Ingestion and Matings are Given in Weeks

Male Rabbit	Paternal Thalidomide Treatment		2 Weeks		3 Weeks		4 Weeks		7 Weeks		10 Weeks	
	Dose/Animal (g.)	Duration (Days)	I	II	I	II	I	II	I	II	I	II
<i>Experiment 1</i>												
A	2.5	21	8	7	14	8	7	0			8	6
B	0.75	21	9	9	9	9	10	6			5	0
<i>Experiment 2</i>												
A	0.9	16			9*	9	3†	3	0‡	0	10	8
B	0.9	16			7	7	8	6	8	2	11	11
C	1.3	12	5	5	7	6	12	0	11	11	5	5
D	1.3	12	8	6	6	5	8	1	11	0	9	4
E	1.2	10	5	5	8	8	9	9	4	2	7	7
F	1.2	10	8	3	12	0	11	0	8	5	11	5

* Spina bifida, one male offspring.

† Taillessness, one male offspring.

‡ No pregnancy was detectable by palpation at any stage from day 8 p.c. on.

Experiment 2 (see Table) included the males A and B (after a five-months thalidomide-free period) and in addition another four males (C, D, E, and F); all six animals received a course of thalidomide as indicated in the Table and were mated to normal does at intervals ranging from 2 to 10 weeks from the cessation of thalidomide administration. Based on the data in the Table, the outcome of Experiment 2 can be evaluated as follows, the respective week-intervals for matings being given in parentheses.

A: Failure of pregnancy to ensue (7 weeks), reduction of number of young at birth (4 weeks), gross malformation in one male offspring (3 and 4 weeks).

B: Marked loss of young during 14-day post-natal period (7 weeks).

C: Total loss of young during 14-day post-natal period (4 weeks), some reduction in number of young born (2 and 10 weeks).

D: Total loss of young during 14-day post-natal period (7 weeks), reduction in number born (3 weeks).

E: Marked loss of young during 14-day post-natal period (7 weeks), reduction in number born (2 and 7 weeks).

F: Total loss of young during 14-day post-natal period (3 and 4 weeks), marked losses in young (2 and 10 weeks), smaller loss (7 weeks).

It would be difficult, for the time being, to attempt an overall classification of the effects produced by each male upon his progeny, but the individual variability as regards both magnitude, temporal incidence, and type of response induced as a result of the thalidomide treatment stands out as a striking feature of the experimental findings.

The causes of neonatal loss were not explored in detail. The young appeared to be dying because of inability to feed properly. It was noticed by the chief animal technician, a keen observer who was asked to keep daily records, that the young were succumbing not simultaneously, as might have been expected—for example, in major maternal failure of lactation—but were

dying on successive days, the stronger ones presumably carrying on longer. Concerning the abnormalities, the incidence in our colony of gross congenital malformations arising spontaneously is low (1%), but was substantially raised in response to maternally administered thalidomide (10%) (Hay, 1964). For that reason the finding of two malformed young (one seriously deformed with spina bifida) in two different litters fathered by the same thalidomide-treated male is noteworthy but would acquire significance only after further experimental documentation. It was not possible to decide whether or not the losses in neonates were due to visceral malformations or to inborn errors of metabolism.

The mechanism whereby thalidomide ingested by the male rabbits exerted an effect upon progeny fathered by them is not known. The testicular tissue of the six males involved in the above experiments is being investigated by histological methods (Dr. M. F. Hay).

This numerically restricted study is published merely to draw attention to the possibility of thalidomide having an untoward influence upon progeny after paternal administration. It is fully recognized that the results of experiments limited to one species of laboratory animals must not be taken as necessarily carrying a great weight and validity for humans; nevertheless, they serve as a useful monitoring device, and in that capacity may alert the medical profession to the "procreative" risk inherent in medication of the male with thalidomide.

SUMMARY

Male rabbits (6) of proved fertility were treated with thalidomide and subsequently mated to untreated does (40) of high fertility, at intervals of 2 to 10 weeks from the end of thalidomide administration.

The criteria used to assess the influence of paternal thalidomide ingestion on the breeding performance of these animals were the number of young at birth and the number surviving for up to 14 days of life.

It was found that the 40 experimental matings resulted in three failures of pregnancy to ensue; six litters of five or fewer offspring; gross malformations in one male offspring each, of two different litters fathered by the same male; eight litters showing total loss of young and another eight litters with smaller but still marked losses of young by day 14 of the post-natal period. Thus, in rabbits of a cross-bred colony of high fertility, in 27 matings (out of 40) there appeared to be some deleterious effect on progeny ascribable to paternal treatment with thalidomide.

CECILIA LUTWAK-MANN, M.D., PH.D.,
Agricultural Research Council Unit of Reproductive Physiology
and Biochemistry, University of Cambridge.

REFERENCES

- Hay, M. F. (1964). *J. Reprod. Fertil.* In press.
Lutwak-Mann, C., and Hay, M. F. (1962). *Brit. med. J.*, 2, 944.