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CC/NUMBER 9
FEBRUARY 27, 1984

Kay H E M, Knapton P J, O'Sullivan J P, Wells D G, Harris R F, Innes E M, Stuart J, Schwartz F C M & Thompson E N. Encephalopathy in acute leukaemia associated with methotrexate therapy. *Arch. Dis. Child.* 47:344-54, 1972.

[Royal Marsden Hosp. and Inst. Cancer Res., Sutton; Queen Mary's Hosp. for Sick Children, Carshalton; Royal Hosp. for Sick Children, Edinburgh; Children's Hosp., Birmingham; and Welsh Natl. Sch. Med., Cardiff, UK]

Seven patients are described in whom dementia developed during treatment with methotrexate for meningeal leukaemia. The patients presented with confusion, tremor, ataxia, irritability, and somnolence and in one case there was progression to coma and death. Circumstantial evidence pointed to methotrexate as the cause. [The *SCI*® indicates that this paper has been cited in over 165 publications since 1972.]

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January 16, 1984

"Around 1970 it seemed that acute lymphoblastic leukaemia (ALL) might be cured by more intensive therapy and that even meningeal leukaemia could be eradicated with the aid of enough methotrexate and/or radiotherapy. Indeed it can be—but in only a small proportion of cases and with a serious incidence of cerebral damage.

"At the time, the notions that methotrexate was active solely against cells during DNA-synthesis, and that the cells of the cerebral cortex were mitotically inert, made it difficult to believe that there could be a direct and selective toxicity of methotrexate on the brain. The first case at the Royal Marsden Hospital which suggested this possibility, a young man of 22 who went rapidly through a state of dementia to coma and death, was treated in collaboration with the late Gordon Hamilton Fairley (who was later tragically killed by an IRA bomb). He argued fiercely that we must just be observing an unusual manifestation of cerebral leukaemia. There was then another similar but less severe case which convinced me we were dealing with something new. When I mentioned this to members of the Medical Research Council's (MRC) Working Party, I got an immediate response. As I commented later in giving a Leukaemia Research Fund guest lecture, 'One of the criticisms levelled against clinical trials is that they do not initiate new treatments or make original contributions to knowledge of the disease. This is true only in a limited sense. A clinical trial forms an admirable seed-bed in which new ideas and observations can flourish and yield a rich harvest of information.'[1]

"In this instance other cases were at once recalled by members of the Working Party from Birmingham, Cardiff, and Edinburgh, and in a very short time it was possible to put together detailed clinical descriptions of seven similar cases. Their clinical symptoms and signs, the EEG changes, and the absence of leukaemia infiltration or virus disease pointed to a toxic cause, and the circumstantial evidence against methotrexate seemed overwhelmingly strong. So here was a new syndrome, fully described, and with a familiar but hitherto unsuspected agent as its cause. If confirmed, it was bound to be cited by those in the field.

"Subsequent evidence, notably from the St. Jude trial, Total VIII,[2] in which some histological studies were possible, amply confirmed the association. Our observations also led directly to the first major study by Eiser[3] on the effect of treatment for ALL on intellectual development, a topic which is still not fully resolved.

"Paradoxically, it was, I think, also one of the factors which led us to take a step backward in our MRC trials of ALL treatment. The avoidance of toxicity both to the central nervous system and to the immune system became a major objective in our protocols with a consequent lowering of their anti-leukaemia efficacy. Others, such as Riehm,[4] more perceptive perhaps and less influenced by our firsthand experience, pushed ahead with more intensive antileukaemic treatments and found greater success."

1. **Galton D A G & Kay H E M.** *UK leukaemia clinical trials for children and adults.* Leukaemia Research Fund Annual Guest Lecture, November 1977.
2. **Price R A & Jamieson P A.** The central nervous system in childhood leukemia. II. Subacute leukoencephalopathy. *Cancer* 35:306-18, 1975. (Cited 235 times.)
3. **Eiser C & Lansdown R.** Retrospective study of intellectual development in children treated for acute lymphoblastic leukaemia. *Arch. Dis. Child.* 52:525-9, 1977.
4. **Riehm H, Gadner H, Henze G, Langermann H J & Odenwald E.** The Berlin childhood acute lymphoblastic leukemia therapy study, 1970-1976. *Amer. J. Pediat. Hematol. Oncol.* 2:299-306, 1980.