Both of the patients who exhibited a considerable ability to oxidize galactose had typical histories of the disease as infants. T.B. was the first reported case of galactosemia in the American literature (*5*), and his clinical picture in infancy served as the basis for the recognition of other such patients. L.Br. had malnutrition, hepatosplenomegaly, jaundice, ascites, and cataracts in the 6-month period after birth. Townsend *et al.* (*7*) pointed out that at age 7 T.B. could be given 200 ml of milk with each meal without subsequent galactosuria. This suggests that T.B. had the capacity to metabolize galactose in childhood as has L.Br.

It was pointed out above that the red cells of L.Br. and T.B., like those of the other six patients, are lacking in the transferase enzyme and are incapable of oxidizing galactose-1-C^{14} to $C^{14}O_2$. In these two patients, therefore, the results of the erythrocyte tests do not reflect the in vivo capacity to metabolize galactose to CO_2, although they are consistent with the presence of the galactosemic syndrome in infancy.

These results indicate that from a group of individuals with typical galactosemia in infancy a subgroup can be delineated in childhood, the members of which possess metabolic pathways for galactose metabolism in tissues other than red blood cells. The precise biochemical and genetic basis for this observation is not known (*8*).

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Dimethylacetamide: A Hitherto Unrecognized Hallucinogenic Agent

Abstract. Dimethylacetamide in large doses was found to be a potent hallucinogenic drug in the human. Characteristic electroencephalographic changes accompanied the clinical abnormalities.

Dimethylacetamide has been found to have a significant antitumor effect in the experimental animal (*1*). During the course of a preliminary clinical trial with this drug, unusual psychological phenomena reminiscent of those described in individuals receiving hallucinogenic drugs such as lysergic acid or mescaline were encountered. In view of current interest in the psychotomimetic drugs, and because of the simplicity of the chemical structure of dimethylacetamide itself, we feel it desirable to record our observations in these cases.

Fifteen patients with advanced malignancies of various types were treated with dimethylacetamide (*2*). With the exception of one patient with seizures, none exhibited clinical signs of disease of the central nervous system prior to therapy. Two patients died within a few days of the institution of treatment; their critical state precluded adequate evaluation of mental function, and they cannot be considered further here. The remaining 13 patients all developed a distinctly abnormal mental state when the dosage of the drug reached a critical level of 400 mg per kilogram of body weight per day for 3 days or more.

Several of the patients had previously received this drug in dosages of 200 to 300 mg/kg without developing consistent untoward effects; when therapy was instituted at the higher levels, abnormal mentation was noted with predictable regularity. The earliest recognizable signs, generally noted on the 2nd or 3rd day of treatment, were depression, lethargy, and occasionally confusion and disorientation. Lethargy and confusion became very severe in four patients; in these individuals it was not possible to assess more subtle psychological abnormalities, or to determine with any accuracy the presence or absence of hallucinations. In the nine others, however, the lethargy and confusion syndrome either remained relatively mild in degree or fluctuated in such a manner as to allow of more detailed, albeit intermittent, evaluation. On the last (4th or 5th) day of therapy, or within 24 hours thereafter, striking hallucinations, perceptual distortions, and at times delusions became evident in all nine. The hallucinations were predominately visual, although auditory hallucinations were also described, and were extraordinarily well formed and vivid. With but one exception the patients developed relatively little anxiety about these experiences, an appearance of detachment, unconcern, and affective blunting being common. These phenomena persisted in severe form for an additional 24 hours, after which they gradually disappeared, the patients becoming normal several days after discontinuation of the drug. With recovery, the majority of these individuals were aware that they had experienced an altered mental state, and that their experiences had been hallucinatory in nature. At no time during the course of these psychological derangements could additional abnormalities be detected with repeated neurological examinations.

Serial electroencephalographic studies were carried out in five of these patients (Fig. 1). Four of these had normal electroencephalograms prior to therapy; one demonstrated focal activity in the right frontoparietal region. Electro-

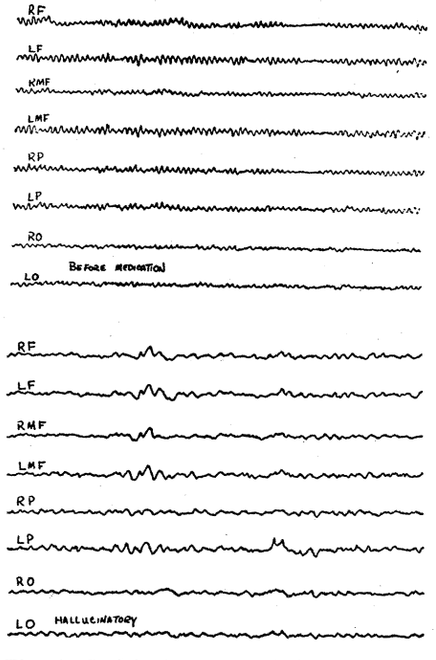

Fig. 1. Serial electroencephalograms in a patient who received dimethylacetamide. (Top) Normal tracing before therapy was begun. (Bottom) Episodic moderately high-voltage slow waves on final day of therapy during period of active hallucinations. Note absence of alpha rhythm.

encephalographic changes were noted in every patient studied, paralleling the clinical alterations. The earliest changes, generally occurring within 24 to 48 hours after the beginning of treatment, consisted of low-voltage fast activity (20 cy/sec), particularly prominent in the frontal regions; this was the sort commonly encountered with a variety of drugs, such as barbiturates. Increasing slowing in all leads was then observed, with abolition of the alpha rhythm; these changes became maximal on the day of most striking hallucinations. The degree of slowing varied from patient to patient; a frequency of 4 to 5 cy/sec was common, and occasionally waves of 1 to 2 cy/sec were encountered. The slow waves were of moderate to high voltage, and tended to occur in episodic bursts simultaneously in all leads. The focal pattern noted in one patient prior to therapy disappeared, being replaced by the typical abnormality observed in the others. With clinical recovery, the electroencephalographic abnormalities subsided, and the pattern became normal after several days.

Five patients died during or soon after the completion of therapy. In one of these it was possible to study the brain pathologically; no significant alterations were found.

The clinical and electroencephalographic observations indicate that the abnormalities are reversible, presumably drug-induced changes; the absence of meaningful morphologic changes in the one brain studied pathologically supports this contention. The fact that after institution of therapy with dimethylacetamide a period of a few days always elapsed before these abnormalities appeared suggests that these effects are not due to a direct toxic effect of the compound per se, but rather that by metabolic processes as yet undetermined a different substance, capable of adversely affecting neuronal function, is formed.

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Appearance of Radioactivity in Mouse Cells after Administration of Labeled Macromolecular RNA

Abstract. Although various induced effects have been reported to follow administration of ribonucleic acid, direct evidence of cellular uptake has been lacking. Radioautographic evidence is presented of incorporation of label from radioactive macromolecular RNA presented to normal and neoplastic mouse cells. Although most of the label appeared in cellular RNA, deoxyribonucleic acid also was occasionally labeled. This suggested that at least partial degradation of the RNA occurred prior to or after incorporation.

Various functional and morphological alterations in vertebrate systems have been observed following administration of intact ribonucleic acid (RNA). These included induced protein synthesis in the adult rat (*1*), embryonic differentiation (*2*), alterations in production of antibody (*3*), recovery following lethal irradiation (*4*), and reversal of neoplastic traits (*5, 6*).

While the induced biological effects of administered nucleic acids have been known for some time, only recently has interest turned to the demonstration of cellular uptake of these materials. Incorporation of deoxyribonucleic acid (DNA) by mammalian cells has been reported by a number of authors (*7–9*). Evidence suggesting the uptake of RNA has been published by Ficq (*10*), who found considerable radioactivity in neural tubes induced by grafting an organizer containing labeled RNA to normal amphibian gastrulae. Most recently, Amos (*11*) and Niu *et al.* (*6*), through the use of counting techniques, have reported the uptake of RNA by cells in tissue culture. Our work was designed to test and localize the incorporation of normal and neoplastic RNA by various cells of the mouse in vivo and in vitro.

Labeled, macromolecular RNA was isolated from the livers of three newborn Ajax mice by the phenol method of Kirby (*12*). Each mouse was labeled over an 11-day period with a total of 135 μc of H^3-cytidine (*13*) given in twice daily intraperitoneal injections. After isolation, the protein-free RNA was incubated with deoxyribonuclease (*14*) for 2 hours to insure removal of DNA. The digest was then dialyzed overnight against normal saline, after which the RNA was reprecipitated from a 4-percent potassium acetate solution with one volume of 2-ethoxyethanol. After resuspension in normal saline, analyses of DNA and RNA content were performed with the indole (*15*) and orcinol (*16*) methods, respectively.

The neoplastic RNA was prepared by identical chemical procedures from an isologous, ascites tumor of the Ajax mouse, Sarcoma I (Bar Harbor, Maine). During a 5-day period this mouse received three intraperitoneal injections per day of a saline mixture of H^3-cytidine (*13*), H^3-uridine (*17*), and H^3-adenine (*18*), in a ratio of 2 : 1 : 1 and totaling 200 μc of radioactivity.

The ability of both normal and malignant mouse cells to utilize RNA was investigated. Sarcoma I was employed as the neoplastic cell type, while peritoneal mononuclear cells were used as a normal population. Those experiments done in vitro were performed in a Dubnoff shaking incubator at 35°C. Culture medium was No. 199 (Microbiological Associates, Bethesda, Md.), to every milliliter of which 0.3 mg of streptomycin and 70 units of penicillin G sulfate were added.

In order to investigate the uptake of normal RNA, Ajax mice with and without Sarcoma I received an intraperitoneal injection of 680 μg of labeled liver RNA in 1.0 ml of normal saline. At the same time 680 μg of this RNA was added to 1.1×10^7 sarcoma cells in 6.0 ml of medium for in vitro culture. Radioautographs (*19*) were prepared from smears of periodic samples of the sarcoma in vivo and in vitro and of aspirates of the peritoneal cavity of normal, non-tumor-bearing animals. Prior to processing, one smear of each interval was digested with ribonuclease (*20*) for 2 hours. The enzyme-treated smears with the other experimental slides were carried together through radioautography. After exposure for 20 to 26 days the preparations were developed, dried, and stained as previously described (*19*).

The uptake of neoplastic RNA was studied in vivo by injecting 170 μg of labeled sarcoma RNA intraperitoneally

Table 1. Sequential labeling of sarcoma I after in vivo presentation of macromolecular, mouse liver RNA. Range of label: ++ (greatest) through + and ± to − (least).

Time (hr)	Degree of labeling		
	Nucleolus	Nucleus	Cytoplasm
2	++	++	±
9	+	++	+
18	−	+	+