Negative Effects of Oral Monobenzyl Ether of Hydroquinone in Malignant Melanoma in Man. (19456)

K. H. KELLY, H. R. BIERMAN, AND M. B. SHIMKIN.

From the Laboratory of Experimental Oncology, National Cancer Institute, National Institutes of Health, Public Health Service, and the Division of Medicine, University of California School of Medicine, San Francisco.

Monobenzyl ether of hydroquinone ("agerite alba") is an effective inhibitor of melanin formation both *in vitro* and *in vivo*(1,2), perhaps due to direct action on tyrosinase. The compound has been described to cause occupational leukoderma(3). Prolonged oral administration produces depigmentation of the skin in pigs(4) and in guinea pigs(5).

Although melanin formation by malignant melanoma may not be intrinsically involved in the initiation or continued growth of the neoplasm, it was considered of interest to ascertain whether monobenzyl ether of hydroquinone would affect melanoma or the course of patients with this disease.

Methods. Monobenzyl ether of hydroquinone* was administered orally, 3 times a day, in capsules containing 0.1 g or in tablets of 0.5 g. The dose of the compound ranged from 0.3 to 27 g per day, and was given for 18 to 214 days. Eight patients with metastatic melanoma, verified by at least one relevant biopsy, were treated, Table I. Their ages ranged from 27 to 63. There were 2 premenopausal and one post-menopausal women in the group. All patients were of the white-skinned races. Estimations were made at frequent intervals of the size, consistency and appearance of the metastatic lesions. Urine specimens were examined weekly for melanin by the ferric chloride method. The patients were followed by weekly determinations of hemoglobin, red and white blood cell counts, as well as repeated determinations of such chemical blood constituents as protein, non-protein nitrogen, bilirubin and electrolytes.

Results. No effect upon the growth of the neoplasms, or beneficial effects upon the patients, were observed. A definite reduction in the size of the subcutaneous mass was observed early in the course of therapy in Case 8, but within 12 weeks the mass enlarged steadily in size despite doubling the dose of the chemical. There was no depigmentation of the lesions. Five patients had melanin in the urine during the course of the disease. No consistent effect of monobenzyl ether of hydroquinone was noted upon the melaninuria.

TABLE I. Oral Monobenzyl Ether of Hydroquinone in Patients with Malignant Melanoma.

Case No.	Sex	Age	Dose/day, g	No. days treated	No. days between course	Total dose /course, g	Total No. days observed
1	♂	62	.2– .3	21	—	2.9	40
2	♂	47	.3–15	51	28	181	—
			5 –10	7	—	60	253
3	♂	63	10 –15	18	—	250	90*
4	♂	28	5 –10	36	25	240	—
			10 –27	6	—	118	142
5	♀	55	.5–10	46	23	247.5	—
			10	12	—	120	72
6	♀	27	.5–15	46	—	472.5	135
7	♀	33	.4–12.5	41	25	188.3	—
			7.5–20	40	—	592.6	120
8	♂	36	.5–12.5	151	22	385.2	—
			10 –25	63	—	1085	365

* Alive.

* Purchased from Goodrich Rubber Co.

Nausea and occasional vomiting occurred in five patients, with daily doses of over 10 g per day. No other reactions were noted, and no effects were observed clinically or biochemically upon the functions of the kidneys, liver, or hemapoietic tissues.

Seven of the 8 patients died after an expected course of the disease; Case 3 is still alive. Necropsy examination in seven cases failed to reveal histologic evidence of toxic effects or other changes attributable to the ingestion of the chemical.

Conclusion. Daily oral doses of 0.3 to 27 g of monobenzyl ether of hydroquinone, for total doses of 2.9 to 1490 g in 21 to 214 days, had no effect upon the growth of malignant melanoma in 8 patients. Ingestion of monobenzyl ether of hydroquinone produced no toxic effects other than transient nausea and vomiting when the daily dose exceeded 10 g.

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Received March 4, 1952. P.S.E.B.M., 1952, v79.

Bactericidal Action Mediated by Antibodies Specific for Heterologous Antigens Adsorbed to Bacterial Cells. (19457)

FRANK L. ADLER. (Introduced by J. Bronfenbrenner.)

From the Department of Bacteriology and Immunology Washington University School of Medicine, St. Louis, Mo.

Many gram negative bacteria are killed, and some are lysed, when they are exposed to complement and homologous antibody. It is generally believed that the antibody which mediates the killing of the bacterial cells by complement is specific for somatic antigens (1-3), though antibody specific for flagellar antigens has been held responsible for bactericidal serum activity against motile strains of *Proteus*(4).

The present communication, based on data obtained in the course of a more detailed investigation of qualitative and quantitative aspects of the bactericidal reaction,* is concerned with the site at which the antigen-antibody reaction responsible for cellular death occurs.

It is known that bacterial cells may adsorb to their surface components of the medium in which they are grown or suspended(5,6). The presence of some of these adsorbed substances can be demonstrated by the observation that such coated bacterial cells are agglutinated by antibody specific for the adsorbed substances. It appeared of particular interest to determine whether, in the presence of complement, reactions between antibody and adsorbed antigen would cause the death of susceptible bacteria. That bactericidal activity might actually occur as the result of such reactions was indicated by the work of Angerer and Hartoch(7) who demonstrated accelerated lysis of *Vibrio* cells which had first been exposed to suboptimal amounts of bactericidal horse serum and then to rabbit anti-horse serum. Bacterial antigens were chosen as the coating agents in this investigation because their use promised to throw some light on the quantitative aspects of the bactericidal reaction and also on the apparent lack of specificity in the bactericidal action of normal sera. These problems will be dealt with in subsequent papers.

Materials and methods. The antigens employed for the coating of bacteria were extracted with trichloroacetic acid as described by Boivin(8). They were precipitated by the addition of alcohol to a final concentration of

* Thesis submitted in partial fulfillment of requirements for the degree of Doctor of Philosophy at Washington University.