be found not to be markedly handicapped. It is also possible that other portions of the body may be relatively highly affected by neutrons. For instance, the Evans experiments suggest, in mice, a selective sensitivity of the gonads as well as of the lens.

It is perhaps worth while to list a few of the areas of ignorance which have been highlighted by this unfortunate episode:

1. The exact causative agent is not definitely known;
2. The dose is imperfectly known;
3. Almost no systematic neutron research has yet been performed on organisms larger than a mouse;
4. There is little knowledge extant of what other organs of the animal may be especially susceptible to damage under special circumstances;
5. The concept of the rem (roentgen equivalent man) for neutrons and indeed for other new types of radiation is probably of limited value, since the conversion factor varies with tissue.

The National Research Council has appointed a Committee on Radiation Cataracts which is collecting additional information regarding others who have been exposed to neutrons. The committee will also conduct follow-up studies of those already known to be injured. Communications should be addressed to Philip S. Owen, M.D., Executive Secretary, Committee on Radiation Cataracts, National Research Council, 2101 Constitution Avenue, N. W., Washington 25, D. C.

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Sodium 2-Methyl-4-Dimethylaminophenylphosphinite, a Probable Methyl Donor[1, 2]

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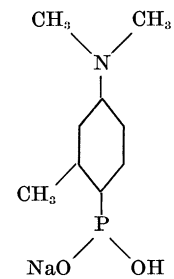
Previous investigations on biological methyl donors have shown evidence of a rather limited number of substances exhibiting donating properties, most of them being N-methyl compounds like choline. It is interesting to note that such N-methyl compounds, having the ability of giving methyl groups intact, show a similar basic structure—namely, they have their labile methyl groups bound with a quaternary or positive nitrogen (choline, betaine, dimethylethyl-β-hydroxyethylammonium chloride [6], tetramethylammonium formiate, methyltriethanolammonium iodide [2], etc. These observations fit in with the theory described by Du Vigneaud (3) based on the different ability of transmethylation shown by partially methylated aminoethanols and choline.

The relationship existing between structure and methylation capacity, described in the N-compounds cited, appears worthy of being generalized (2). Ciusa claims also that methyl compounds of arsenic, selenium, oxygen, and sulphur (2) may act as methyl donors when methyl groups are bound with electropositive atoms. A confirmation of this is obtained by experimental investigations on sodium cacodylate, and particularly in recent studies by Du Vigneaud on dimethylpropiothetin (4) and dimethylthetin (5).

A few recent observations from this laboratory concerning sodium 2-methyl-4-dimethylaminophenylphosphinite, which is used largely in therapy, are not in agreement with these assumptions.



The administration of this substance to human subjects, in normal conditions, causes a remarkable rise in urine elimination of N_1-methylnicotinamide, a product of the irreversible methylation of nicotinamide, introduced with diet and chosen as a test of the methylation activity (2).

We do not intend to take into consideration here details of technique, which are to be published later; we are reporting, instead, a few data obtained in this investigation, pointing out that the experiments have been performed on ourselves and on laboratory personnel, fed a rigorously standard diet, under normal conditions.

The values of N-methylnicotinamide reported herein refer to 24-hr urines. The administration of sodium 2-methyl-4-dimethylaminophenylphosphinite in a single therapeutic dose (30 mg), causes an immediate urinary increase in N_1-methylnicotinamide as seen in results in Fig. 1. The increase, in this case, is approximately 60%, while in other human subjects it has reached even higher values.

When the administration of the substance under observation is continued for several days in even small doses (15 mg), the elimination of N_1 is maintained constantly elevated above the normal, returning to the initial values as soon as the treatment is terminated. We do not believe the action of sodium 2-methyl-4-dimethylaminophenylphosphinite is attributable to a simple activation of methylation processes. The increased elimination, in fact, remains even when the subject is preventively treated and also treated during the experiment

[1] We are greatly indebted to Mr. Cesare Barbieri and to the American Committee, University of Bologna, New York, for donation of the Beckman DU Spectrophotometer used in this investigation.

[2] The experiments have been performed with sodium 2-methyl-4-dimethylaminophenylphosphinite supplied by Consorzio Neoterapico Nazionale, Roma.

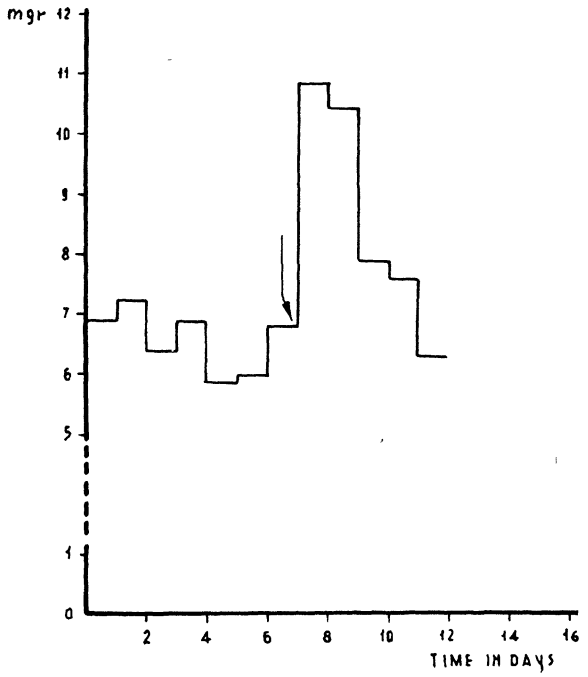


FIG. 1. Elimination of N_1 with urine. Arrow indicates the administration of 30 mg of sodium 2-methyl-4-dimethylaminophenylphosphinite.

with B_1, which regulates the elimination of urinary N_1, due to a probable catalytic action, carrying it to an almost constant level. These observations lead us, therefore, to believe that sodium 2-methyl-4-dimethylaminophenylphosphinite acts as a methyl donor.

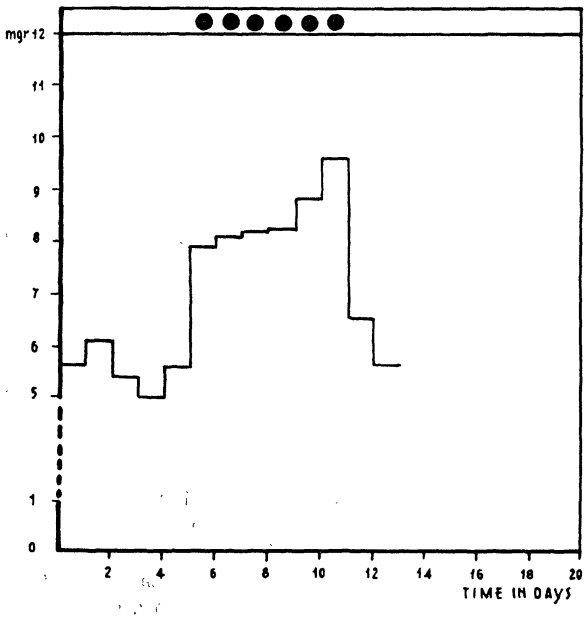
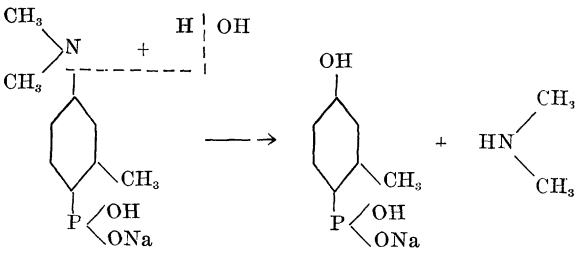
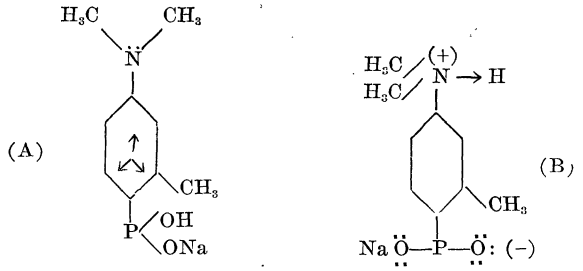


FIG. 2. Elimination of N_1 with urine after continuous treatment with sodium 2-methyl-4-dimethyl aminophenylphosphinite. Each ● indicates the administration of 15 mg.

The interpretation of the mechanism which might explain this action is hypothetical. Analogously, along with *p*-nitrous dimethylaniline, we assume that also sodium 2-methyl-4-dimethylaminophenylphosphinite may yield dimethylamine as shown in the following:



The reaction may be enhanced by the presence of a methyl group in position 2 of the benzene ring which, being similarly oriented with other substitutes according to the Bonino (*1*) symbolism, (A) affords more mobility to the substitute in position 4. We do not believe, however, that dimethylamine is a methyl donor, noting that dimethylaminoethanol is a methyl acceptor rather than a methyl donor. It appears, instead, more probable that the methylation action of sodium 2-methyl-4-dimethylaminophenylphosphinite is attributable to a dipolar form (B):



in which is shown a positive nitrogen of N_1-methylated compounds acting as a methyl donor.

Our observations are in accord with the hypothesis cited (*2*, *3*), and make evident a probably new methylating agent, the importance of which lies in its wide therapeutic use. These observations show also the interest which may derive from a structural study of substances of this type.

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