

PHENOLPHTHALEIN STUDIES.

A THOUSAND DOSES OF PHENOLPHTHALEIN: URINALYSES.*

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(AUTHORS' ABSTRACT.)

While various authorities (Sollmann (1), Bastedo (2) and others) on the subject find phenolphthalein harmless to the kidneys, there are a few reports extant that would suggest an opposite possibility.

To put this question to a crucial test, the study of a thousand medicinal doses of phenolphthalein was undertaken with special scrutiny of the effect upon the urine.

PHENOLPHTHALEIN RING TEST IN URINE.

When we perform Heller's test with an aqueous solution of phenolphthalein sodium we obtain a rather dispersed ring of turbidity through the upper layer of fluid, in dilutions down to 5:10,000.

Robert's reagent, being more sensitive, gives a turbidity in solutions of phenolphthalein sodium down to 2.5:10,000.

"Colloidal" phenolphthalein (3), which is much more soluble than the crystalline form, when added to urine to the point of saturation, gives a very definite trace of turbidity with Heller's test and a strong ring test with Robert's reagent. This is absent when crystalline phenolphthalein is used.

For differentiation between true albuminuria and this ring test due to phenolphthalein, advantage may be taken of the fact that phenolphthalein solution when heated does not become turbid even when acetic acid is added. On cooling, a turbidity may result which disappears again on heating.

We did not encounter a single instance of a false albumin test due to phenolphthalein because the total amount of phenolphthalein in the urine, both free and conjugated, never approaches the quantity necessary for the production of the phenolphthalein ring when its solution is layered over an acid reagent.

METHOD OF STUDY.

The standard methods described in textbooks were employed for the various albumin tests and in testing for sugar in the urine. The following additional tests were also employed: determination of free phenolphthalein in urine; determination of conjugated phenolphthalein in urine; determination of urine acidity by the Folin method.

VARIETIES OF PHENOLPHTHALEIN EMPLOYED.

By "white phenolphthalein" we mean the crystalline phenolphthalein described in the U. S. P. "Yellow phenolphthalein" contains about 2% of as yet unidentified colored bodies, some of which are strongly cathartic. Colloidal phenolphthalein (3) is considerably more soluble than the white phenolphthalein.

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OBSERVATIONS UPON NORMAL INDIVIDUALS.

The coöperation of male medical students, ranging in age from 20 to 26 years was obtained. In each a preliminary specimen of urine was secured and then the young man was given a capsule containing a medicinal dose of phenolphthalein with the direction to take it at bedtime and secure all the urine passed during the succeeding 24 hours, to mix the various specimens, to measure the total quantity, and to furnish a sample of the mixed urine for testing. Xylol was added to the specimen to prevent decomposition.

Six hundred and fifty observations of this kind were consistently negative on chemical as well as microscopic examination of the urinary specimens both before and after taking of phenolphthalein. It required over 10,000 tests of various kinds. In any one individual at least a week was permitted to elapse between succeeding observations.

In one case albuminuria was present in the morning specimen as well as in the 24-hour specimen, before as well as after the taking of the phenolphthalein. This is obviously an individual with a somewhat pathologic kidney and there is no evidence that the phenolphthalein increased the damage.

In two cases we found albuminuria in the 24-hour specimen, before as well as after the taking of phenolphthalein. As these men had no albuminuria in the morning specimen, we have here evidently cases of "orthostatic albuminuria." It will be noted that the albuminuria was inconstant and that it had no relation to the taking of phenolphthalein.

An occasional and very inconstant reaction to Robert's reagent was encountered in 5 cases. This was very irregular and generally occurred only once in all the various observations made in a particular individual. The fact that the other protein tests were negative, stamps these reactions as due to proteose rather than phenolphthalein.

In not one of these instances could the albuminuria or proteosuria be ascribed to the taking of the phenolphthalein.

HOSPITAL CASES.

To determine the reaction of sick individuals and especially of persons somewhat advanced in years, the kidneys of some of whom might presumably be more sensitive to injury, we studied a series of patients in the Nose and Throat service, including the Head Cancer Clinic at the Cook County Hospital, as well as of some patients in medical wards. We may summarize our findings by saying that *in all of the 150 of these patients who had no albuminuria before the administration of phenolphthalein in doses of 0.10 Gm. to 0.50 Gm. there was not a single case of albuminuria.* It required about 4500 tests to develop this conclusion.

A series of 44 patients who had albuminuria before administration of phenolphthalein was also studied and it was found that in no instance was there any evidence of increase in the albuminuria or microscopic evidence of change in the urinary sediment excepting in one patient who was under treatment for kidney stone and whose urine contained a trace of albumin before the giving of phenolphthalein. Another attack of renal colic occurred with blood and albumin in the urine. A case similar to this one has been reported in the literature and uncritically ascribed to a phenolphthalein reaction by Dr. B. Holz (4).

Interesting in connection with this study are those cases that had albuminuria before the taking of phenolphthalein and whose urinary condition improved after the dose as indicated by the reduction in the amount of albumin in the urine and the disappearance of the albumin reaction in a number of cases.

ELIMINATION OF PHENOLPHTHALEIN IN THE URINE.

Free phenolphthalein was found in only 8.5% of the medical students' urines and it was found in 21.5% of the urines of the Cook County Hospital patients. This is probably due to the following two facts:

1. The larger the dose the more frequently does free phenolphthalein appear in the urine.
2. Bacterial decomposition of the urine liberates phenolphthalein from its conjugated form.

Conjugated phenolphthalein was found in every urine specimen examined. In other words, *one can tell, by the presence or absence of conjugated phenolphthalein in the urine, whether a person has taken phenolphthalein or not.* The quantity of conjugated phenolphthalein when free phenolphthalein was also present, was always greater (with a few exceptions) than that of free phenolphthalein. *The larger the dose of phenolphthalein the greater the average amount of conjugated phenolphthalein eliminated.*

EVIDENCE FROM THE LITERATURE.

Zoltan von Vamossy (5), who discovered the cathartic action of phenolphthalein concentrated his attention on other possible effects of phenolphthalein upon the human body and was unable to discover any. Tunnicliffe (6), Mendelsohn (7), Blum (8) and Fleig (9) and many others paid a great deal of attention to the effect of the substance upon the kidney and they arrived at the conclusion that it is not only absolutely harmless to the healthy kidney but also to patients with nephritis of various kinds; and the contrast was pointed out between it and the unfavorable effect upon the kidney of a number of vegetable purgatives, such as colocynth, aloe and anthrapurpurin.

While then there is a host of witnesses corroborating the correctness of our findings, the question may be raised how it happens that some textbook writers report that phenolphthalein has produced albuminuria. A survey of the literature shows that this assertion rests upon a few sporadic case reports, Blumenthal (10), v. Jaksch (11), Fürbringer (12), all of them dating from the early days of the use of phenolphthalein, when its action was not yet understood and anything that happened after its administration was ascribed to it, and upon a report by J. L. Hydrick.

When a drug has a real tendency to produce a certain untoward manifestation the frequent use of this drug will invariably cause recurrences of the phenomenon and, the more extensively the drug is used, the more common will be the manifestation. This is illustrated by the phenolphthalein eruption of which, though it is, in point of fact, comparatively rare, we now have a definite number of cases on record.

J. L. Hydrick in 1914 (13) while a medical student, reports an unbroken series of twenty different individuals in each of whom the subject's urine showed no trace of albumin before the taking of the phenolphthalein, and in each and every one of whom positive tests for albumin were secured in the 24-hour specimen of urine ("a 24-hour specimen is important"), collected after the administration of 1- or 2-

grain doses of phenolphthalein. The finding of Hydrick's was never published excepting in abstract, because he had written in the report to the American Society of Biological Chemistry that what he had done was not for publication, but to call the attention to the fact that this was a subject which should be investigated thoroughly.

Dr. John L. Hydrick, in a personal communication of November 8, 1936, graciously states:

"It is, of course, impossible for me to say what possible errors of technique, or what special circumstances produced the results in my experiments that were interpreted by me and by several others who saw some of my experiments, as evidence of albuminuria after taking of phenolphthalein. . . It is possible that the phenolphthalein of 1914 was not so pure as that of 1936."

CONCLUSION.

1. Medicinal doses of phenolphthalein do not produce albuminuria.
2. While free phenolphthalein is generally absent in the urine of individuals who take a small medicinal dose of phenolphthalein, conjugated phenolphthalein is always present.
3. The larger the dose, the greater the percentage of individuals passing free phenolphthalein in the urine, and the greater the amount of conjugated phenolphthalein eliminated.

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