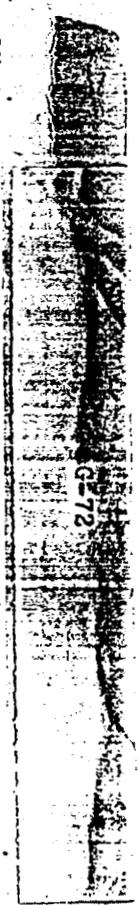


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C O P Y

Massachusetts General Hosp.,
Boston, Mass.
Jan. 1, 1943

Dr. Kenneth S. Cole
University of Chicago
Chicago Ill.

Dear Dr. Cole:

After the experiments mentioned below are carried out, Dr. Aub and I will send you a complete report, but I feel that the results thus far obtained are of sufficient interest to warrant a brief presentation at this time. I had a brief talk with Dr. Friedel yesterday and he felt that this should be done.

In the past two weeks, I have had two conferences with Mr. Cammann and Dr. Williams at MIT and two with Dr. Alexander and Mrs. Stirling at Beverly. I found all of these people very cooperative and was able to work with them quite easily. I have observed their methods and interpretations, and have gone over these in some detail (as much as permissible) with my colleagues and in most of the standard literature. In the laboratory I have made a large number of tests on twelve urine specimens, these all being the most "positive" specimens so far obtainable from the above sources, all of which have been controlled by similar tests on "normal" specimens obtained from people in this laboratory, including myself. The results of these talks and these tests have been discussed with Dr. Aub, with the following tentative conclusions.

All twelve specimens, reported as "positive" to a greater or lesser degree by one or the other of those mentioned above, have been positive in my hands. None has given a test exceeding in positivity that given by urine containing 1% glucose, with most appearing to contain 0.5% or less of glucose (about 0.2% is necessary to give any test at all). These urines, while positive, contain practically no glucose because (a) no gas is evolved on yeast fermentation (controlled), and (b) the test is just as positive after fermentation.

The character of the substance causing the copper reduction has not been ascertained, but there are several reasons for our belief that it is a normal constituent or constituents of urine, and present in normal amount. Uric acid, creatinine, and other normally-occurring compounds give the reducing test if present in sufficient concentration. In many normals, these appear in amounts simulating the presence of 0.2% glucose, and in concentrated urines they can go as high as 0.4%. These urines are almost invariably concentrated, as is shown in several ways. Furthermore, they (as well as glucose itself) are present in higher amounts in active individuals and during the active part of the day in a given individual, both of which conditions are met by the specimens considered. I have also discovered that the increased incidence of reducing substance is, to a large extent, observational; many of the traces reported would be reported as negative in a clinical laboratory.

With regard to the albumin part of the story, the following can be said. Both the incidence and the amounts are low. Small amounts occur in "normal" populations to the extent of about 1 in 14 in resting, and 1 in 7 in active individuals. This latter incidence has not been exceeded, to my knowledge, in the active group in which we are interested. Furthermore, the occurrence of a slight albuminuria during the active part of the day is not at all unusual, nor is albuminuria, of itself, indicative of disease. We therefore feel that no medical problem or procedure is indicated by the albuminurias in the incidence and amounts observed.

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Examination of the urines (six) for the metal show, in a rough way, that less than 0.02 mg of it could be present per cc of urine. The amounts necessary to give a reducing test are at least ten times this. Four examined for arsenic show around 0.1 to 0.3 mg per liter, amounts which are not alarming or surprising, and which are about 100 times less than the amounts needed for a reducing test. Irvine (at MIT) and I are working out a method to determine as little as 0.01 mg of the metal per liter of urine.

The things which Dr. Aub and I feel should be done, and which we are starting to do, in order to wind up this investigation are as follows. We will obtain urine specimens from the most positive cases in the resting as well as the active state and compare them. Quantitative uric acid determinations will be done on these, for this may well be the reducing substance; furthermore, any extensive tissue damage would be reflected in the uric acid excretion. Some of the "normals" will produce some concentrated urine for examination by me. (Incidentally, the ability of the kidney to concentrate to the degrees observed is in itself a reassuring sign). If further examinations are suggested, we will ask for 24-hour collections, the only way to arrive at any sort of quantitative figures.

There are a number of other points which I should like to discuss with you, but they are not yet worked out in my mind and are not essential at the moment. I think that I have indicated why we are now of the opinion that there is as yet no medical problem raised by these "positives".

We will report to you more formally in the near future. If the results then are the same as they are now, and wind up the problem satisfactorily to you, I presume you will then have me move to Chicago.

Yours very truly,

Waldo E. Cohn (Signed)

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