Pediat. Res. *2:* 69–71 (1968)

Correspondence

Defect in Uric Acid Metabolism

Sir:

In connection with your interesting article 'Genetics of an X-linked disorder of uric acid metabolism and cerebral function' (Pediatric Research *1:* 5 [1967]), we would like to comment on a case of hyperuricosuric encephalopathy without hyperuricemia which we were able to observe.

Although the majority of the clinical manifestations found in the classic form of encephalopathy with hyperuricemia was present, the following clinical features were unusual: our case concerned a girl; the parents were related to the second degree; and no other members of the family were affected. The girl was 2 ½ years old when first admitted for evaluation of psychomotor retardation. She was born after a full-term and normal pregnancy; birth weight was 3500 g.

Initially, the mother noticed nothing particular, except that compared with her older brother, feeding and weight gain were more difficult in this child. Gradually, the delay in psychomotor development became obvious.

At 10 months, she could hardly sit upright and only when prompted to do so. At 14 months, she could scarcely stand when supported. From the age of 1 ½ years on, she started crying continuously and an important deterioration of the psychic condition was observed. Social contact was practically absent; the child was unmanageable and very choleric, letting out sudden loud screams and lying moaning for hours.

Extreme anorexia developed and motoric development practically ceased.

The parents were related to the second degree (their mothers were sisters). There were three other healthy children; one child died when 5 days old from congenital heart defect.

The clinical picture was nearly identical to that described in the hyperuricemia syndrome: the girl was hypotrophic, very backward, irritable and showing sudden attacks of crying as well during the day as during the night. Biting of the hands, with resulting painful crying, was also noted. After pushing it against the teeth, the inner side of the cheeks was also bitten.

She knocked her head against the edge of the bed provoking ecchymoses and abrasing. Neurologically, there was a marked hypertonicity and hyperreflexia of the extremities. Moreover, there were choreo-athetoid movements of the extremities which sometimes resulted in violent spasms and opisthotonos. She hardly uttered some distinguishable sounds but could not even pronounce the most elementary word. A pink staining of the diapers had been noted occasionally. On metabolic investigation, performed when the patient was on a purine-free diet, we found urinary uric acid values which varied from 35 to 45 mg/kg/day.

Uric acid concentration in the serum was normal.

There was a constant microscopic hematuria; large amounts of uric acid crystals were seen in the sediment.

After I.V. administration of labelled glycine, the specific activity was maximal at 120 hours with 72 CPM per mg of urinary uric acid, while the cumulative excretion after 7 days was 1.8 % of the injected doses.

Our case differs from the classic syndrome of encephalopathy with hyperuricemia by the following features: our case is a girl whereas all the other cases are boys; we found a marked hyperuricosuria with a normal uricemia; although the pattern of glycine incorporation to uric acid differs from that seen in classic cases of hyperuricemia, the cumulative excretion after 7 days was practically identical.

It is highly probable, therefore, that we are dealing with another form of encephalopathy due to a disturbance of the biosynthesis of purines. As an extensive investigation of the family history revealed no other cases, and as the parents were related to the second degree, we can be practically certain that the disease is inherited as an autosomal recessive trait.

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C. Van Nevel, M.D.
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Sir:

I appreciate the opportunity to review and comment on the letter from Drs. Hooft and Van Nevel. I am interested in this communication.

The occurrence in the female of similar syndromes to the one we described is apparent in a handful of cases—most but not all of which have so far had no abnormality of purine metabolism. This patient appears of interest in that although there is no hyperuricemia, there certainly appears to be an abnormality of purine metabolism.

The ^{14}C-labeled glycine study is critical. Were these studies performed while the patient was receiving a

purine-free diet? It would be important to know the actual values obtained. I do not know what is meant by maximal excretion of labeled uric acid on day five and six. If this is maximal specific activity, it suggests increased nucleic acid turnover. If not, it might simply reflect vagaries of diet and urine collection. These items are all simply questions of data and I would feel that their clarification would considerably increase the value of the communication.

A final point is a problem. The occurrence of a high incidence of consanguinity in a series of kindreds of a disease does indeed suggest an autosomal recessive mode of transmission. A single instance in a single family does nothing for you. This could well be a chance occurrence in an X-linked trait. The particular importance is that, if the Lyon hypothesis is true, in its presently accepted form, we should see examples in the female—not many but some. If the female is a mosaic of two populations of cells, each with a single active X, and if the proportion of cells is random, then a certain number of females heterozygous for X-linked traits should have clinical disease.

This is an important question and it deserves careful analysis. Patients with the syndrome we have described lack the activity of the enzyme, hypoxanthineguanine phosphoribosyl transferase. In a patient such as the one described by HOOFT and VAN NEVEL who is female, it would be critical to determine the activity of the enzyme. We would be happy to perform this assay for Drs. HOOFT and VAN NEVEL and will communicate with them as to details.

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Anemia in Preschool Children

Sir:

We have three criticisms of the article entitled 'Anemia in preschool children in the United States of America' (Pediatric Research *1:* 169 [1967]).

1. The authors refer several times to the 'incidence' of anemia and at other times to 'prevalence'. These two epidemiologic terms have precise and different meanings. What the authors determined, in fact, was *prevalence* or the number of cases present in their study population at a point in time, not incidence, which refers to new cases appearing in a population per unit of time.

2. The sample of children used for the study was not a random one. In order to be able to generalize to any larger population, such as all children living in poverty, one should have taken a more random population than presented by Head Start children. One of the concerns of those responsible for Head Start programs is that they are not reaching the lowest economic group. We would prefer to see a sample selection by area probability methods which, had they been used, would have gotten more representative data with a far smaller sample. The regional variation purportedly shown by this study could have been due to sampling variations.

3. The authors conclude in one place that 'the microhematocrit determination represents a valid indicator of anemia in these children'. This is probably true but the data to support this are not given. The fact that 4.5 % of the Chicago Head Start children in the study have microhematocrit values less than 31 % and 3.2 % have hemoglobin concentrations below 10.0 g % does not provide sufficient information. Are these the same children? What is the *sensitivity* of the test (the percentage of children with hemoglobin below 10.0 g % who also have hematocrits less than 31 %) and what is the *specificity* of the test (the percentage of children with hematocrits above 30 % with hemoglobin over 10.0 g %)?

To use an analogy, if 4.5 % of children were found to be mentally retarded and 3.2 % anemic, would that mean that mental retardation is a valid indicator of anemia? Obviously not, but we are not given sensitivity and specificity data to prove the relation between hematocrit and hemoglobin in this study.

Our criticism is not so much on the data presented, which is important and which has been inadequate to date in the literature, but of inadequate attention to the use of appropriate epidemiologic techniques which limit the usefulness of the study.

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Sir:

Drs. CHARNEY and HAGGERTY's three criticisms of our article 'Anemia in preschool children' merit brief response.

They are, of course, correct in pointing out the precise epidemiologic difference between the terms prevalence and incidence. However, their suggestion that we should have done a systematic inclusive study within a single community is neither valid nor germane. Granted, comprehensive studies comparing the nutritional status of affluent, poor and very poor children of specific communities are much needed, such was not the purpose or the aim of our study. Their argument on the economic status of the children accepted in Head Start programs is irrelevant. These children have come to represent a specific poverty group. The criteria for their inclusion in these programs are uniform from area to area and they represent a suitable reasonably

homogeneous group of subjects for study. In point of fact, our most novel and important finding, namely that there is a significant geographic variability in the prevalence of anemia, was only discerned by comparing data from several cities.

Their final question was not answered in the report and cannot be answered precisely. In 100 children from Gainesville, however, *both* hematocrit or hemoglobin determinations identified precisely the same individuals as being anemic. This comparison was not possible using the Chicago data. Many years of hematologic experience indicate that hematocrit and hemoglobin values bear a close and predictably parallel relation. The finding of essentially the same percent of anemic children in the large number studied in Chicago using either measure persuades us that both do in fact identify the same population. Finally, to ask ultimate precision in a screening program is unreasonable. We sought and obtained evidence that in a large-scale screening program, microhematocrit determination identified the prevalence of anemia.

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