A Study of Detoxification Mechanisms in Children with Aplastic Anemia

By Hans P. Wagner and Nathan J. Smith

Many pediatric clinics in the United States are recognizing a disturbing increase in the number of patients seen with aplastic anemia following exposure to a variety of synthetic organic compounds. These compounds, many of which are known to be bone marrow depressants, are being used extensively as drugs, pesticides, solvents, dyes, and cosmetics. Exposure to this large group of potentially dangerous chemicals is increasingly common for present-day children, and the observed increase in the incidence of chemically induced bone marrow depression might well be expected.

It is of interest that it is usually impossible to relate the degree of a toxic chemical exposure of an individual child to the degree of bone marrow damage that develops. Obviously, many children are exposed to synthetic organic compounds that are potentially dangerous without suffering any perceptible degree of damage. Such observations suggest that there might exist individual susceptibility predisposing certain persons to develop chemically induced aplastic anemia, a conclusion well supported in recent years by clinical experience with aplastic anemia following use of the drug chloramphenicol. Deficiency states, autoimmune factors and defective detoxification mechanisms have all been suggested as possibly being responsible for this individual susceptibility to bone marrow damage.

Bomford and Rhoads, using a pyridoxine loading test, noticed a disturbance in the excretion of non-fermentable reducing substances, including glucuronates, in urine of patients with refractory anemias. They also noticed a reduction in the excretion of total sulphates in two of their patients. Since their publication, no further experimental data on detoxification studies in patients with aplastic anemia have been presented.

Prompted by the hypothesis that aberrations in detoxification mechanisms might make certain children unusually susceptible to chemically induced bone marrow damage, and by results of a preliminary study, it was decided to investigate certain detoxification mechanisms in a group of normal children and in children with aplastic anemia seen at this hospital.

The present findings suggest that no defect exists in the detoxification mechanisms studied and do not confirm the results of the preliminary study. Further indirect evidence that aplastic anemia is not related to insufficient detoxification may be inferred from the recent work of Weiss, Glazko and Weston. These workers investigated the metabolic disposition of chloramphenicol in newborn infants who are known to have immature enzyme systems.

From the Department of Pediatrics, University of Wisconsin School of Medicine, Madison, Wis.

This work was supported in part by a grant from Baker Laboratories, Cleveland, Ohio.

Submitted Aug. 25, 1961; accepted for publication Feb. 12, 1962.
DETOXIFICATION IN CHILDREN WITH APLASTIC ANEMIA

involved in detoxification. It was found that doses of chloramphenicol which are well tolerated in older children and adults will produce a prolonged elevation of chloramphenicol blood levels in the newborn. Repeated administration of chloramphenicol results in unusually high blood levels and is associated with the so-called "gray syndrome." This syndrome, which at least in part is due to inefficient detoxification, has not been accompanied by characteristic pathologic changes attributable to the use of chloramphenicol in the hematopoietic tissues.

METHODS

Acetanilide and N-acetyl-paraaminophenol loading tests: Brodie and Axelrod have shown that a major fraction of acetanilide (N-phenylacetamide) ingested by humans will be oxidized to N-acetyl p-aminophenol and excreted in conjugated form (fig. 1). These authors found that in adults 1.9 to 2.0 Gm. doses of acetanilide were almost completely absorbed from the gastrointestinal tract, that absorption and metabolic turnover were rapid and that the acetanilide metabolites were excreted almost exclusively through the kidneys.

Total 24-hour urine collections were made on five consecutive days. Following collection of the control urine on day 1, 0.1 mM/Kg. of acetanilide was administered orally in divided doses on day 2. Urine was collected on days 2 and 3. An equimolecular dose of N-acetyl p-aminophenol was similarly administered on day 4 and urine was collected on days 4 and 5.

Total p-aminophenol (including free, acetylated and hydroxyconjugated derivatives), glucuronide and total glucuronic acid, total and inorganic sulphates and total nitrogen excretion were quantitatively determined in each 24-hour urine specimen.

Total p-aminophenol was estimated by a method described by Brodie and Axelrod.

Glucuronide and total glucuronic acid in the urine were determined by the method of Fishman and Green.

Total and inorganic sulphates were measured according to Håkkinen and Håkkinen. The ethereal sulphates were calculated by subtracting the inorganic from the total sulphates.

CLINICAL OBSERVATIONS

Seven patients with aplastic anemia were studied. Patient No. 1 has a congenital aplastic anemia, patient No. 2 an acquired aplastic anemia of unknown cause and the five remaining children have been exposed to unusual amounts of potentially toxic chemicals. All seven presented with peripheral pancytopenia and a hypocellular or essentially acellular bone marrow. The results

---

Fig. 1.—Acetanilid metabolism as suggested by Brodie and Axelrod.
from studies of the five patients with chemically induced aplastic anemia were used for statistical analyses.

Patient #1. R. N., a white boy, was born on August 7, 1952. During the first two years of life he was seen at another university hospital because of frequent loose stools and failure to gain weight. The presence of steatorrhea and a lack of trypsin activity in his duodenal contents suggested pancreatic insufficiency. A tentative diagnosis of cystic fibrosis was made, but questioned due to the fact that no pulmonary complications developed, that growth was normal, and that the sweat tests were normal. During the same period, a chronic otitis media developed and, at ten months of age, a left radical mastoidectomy was performed. Various antibiotics were used, but no chloramphenicol and no sulfonamide preparations.

At the age of 5½ years, the boy was referred to a specialist for evaluation of easy bruising and anemia. Pancytopenia and a markedly hypocellular marrow suggested the diagnosis of aplastic anemia. The patient was treated with Kenacort, 4.0-6.0 mg. daily, for a period of three months but his condition remained essentially unchanged.

Two years later, at the age of 7¾ years, the patient was admitted to the University of Wisconsin Children's Hospital. His height was in the 25th percentile, and his weight in the 75th percentile. There was no lymphadenopathy, no enlargement of liver or spleen, no testicular hypoplasia and no excessive pigmentation. The hemoglobin was 11.2 Gm. per cent, hematocrit 32 per cent, red cell count 2.23 million/cu. mm.; the white cell count 4900/cu. mm. with 11 per cent granulocytes, 80 per cent lymphocytes, and 9 per cent monocytes; platelet count 73,000. A bone marrow biopsy was read as hypocellular. There were some hyperplastic erythroid foci, but the white cell precursors and the megakaryocytes were markedly decreased. The serum iron level was 182.0 γ per cent, serum iron-binding capacity 150 γ per cent, free erythrocyte protoporphyrin 87 γ per cent, plasma copper 93 γ per cent; the serum protein electrophoresis was normal.

The patient was treated with 100 or 150 mg. of the cyclopentylpropionate ester of testosterone intramuscularly every four weeks and 20 mg. of prednisone daily for a four-months' period. The pancytopenia improved partially but recurred after the medication was discontinued. Three months after all medication had been stopped, an acetylilide N-acetyl p-aminophenol loading test was performed.

At the age of 8½ years, the patient was readmitted to the hospital. The height was in the 10th, the weight in the 95th percentile. On physical examination, no lymphadenopathy and no enlargement of liver or spleen were found. However, this time, an increase in skin pigmentation was found, especially on the extensor surfaces of the extremities. The hemoglobin level was 8.8 Gm. per cent, the hematocrit 25 per cent, red cell count 2.3 million/cu. mm., reticulocytes 2.5 per cent, white cell count 2,500 with 9 per cent granulocytes, 87 per cent lymphocytes, and 4 per cent monocytes. Platelet count 38,000/cu. mm. Material obtained from a bone marrow aspiration revealed a relative erythroid hyperplasia with megaloblastic changes and a reduction of granulocyte precursors and megakaryocytes. The serum iron level was 206 γ per cent, serum iron-binding capacity 50 γ per cent, free erythrocyte protoporphyrin 84 γ per cent, plasma copper 79 γ per cent; x-ray studies, including an intravenous pyelogram, did not reveal any anomalies. I131 labeled oleic acid and I131 labeled trioleic acid were absorbed normally. No increased excretion of formimino glutamic acid was observed after histidine load. A therapeutic trial with one gamma of vitamin B12 intramuscularly was unsuccessful.

It is felt that this boy has a form of congenital aplastic anemia.

Patient #2. T. B., a white girl, was born on December 22, 1956. Both parents have hay fever and food allergies; the mother has diabetes.

The patient was first seen at 1-10/12 years of age because of anemia (hemoglobin 4.0 Gm. per cent) which was refractory to intramuscular iron and required transfusion. At the age of 2 years, the patient was hospitalized and found to have pancytopenia. A bone marrow specimen obtained by surgical biopsy was read as hypoplastic. The past history did not reveal any exposure to antibiotics or toxic chemical agents. The patient was treated with prednisone (10-15 mg. daily) and 1-2 methyltestosterone linguis daily for a period of
six months. She was then seen for the first time at 2½ years of age at the University of Wisconsin Children's Hospital. Height and weight were in the 25th percentile. There was no lymphadenopathy and the liver and the spleen were not enlarged. The hemoglobin level was 10.2 Gm. per cent, the white blood count 6,000 with 25 per cent neutrophils, 16 per cent eosinophils, 54 per cent lymphocytes, and 5 per cent monocytes. The platelet count was 125,000/cu. mm., the serum iron 186 γ per cent, serum iron-binding capacity 120 γ per cent, plasma copper 151 γ per cent, red cell copper 227 γ/100 ml. red cells. Free erythrocyte protoporphyrin was 39 γ/100 ml. red cells. The normal serum was protein electrophoresis.

At 3½ years of age the hemoglobin had risen without further therapy to 12.8 Gm. per cent. The white cell count was 7,500/cu. mm. with 50 per cent neutrophils, 8 per cent eosinophils, 36 per cent lymphocytes, and 4 per cent monocytes. The platelet count was 166,000/cu. mm. At this time an acetanilide N-acetyl p-aminophenol loading test was performed.

Patient #3. S. O., a white girl, was born on August 26, 1954. She was delivered prematurely because of blood group incompatibility, which had caused the loss of two of four previous pregnancies. Her birthweight was 1,400 Gm. Two younger siblings were also delivered by Caesarean section, but died a few hours after delivery. Of the two older, unaffected siblings, only one survived and is healthy. The other died at the age of three months for unknown reasons. Relatives of the father were said to bruise and bleed easily, but none were available for study.

At 4 years of age, S. O. was admitted to a local hospital because of purpura, epistaxis, and fever. The past history revealed that the girl had been exposed on numerous occasions over a period of several months to vapors of an unknown type of volatile, organic solvent used in refinishing firearms. The hemoglobin level was 9.8 Gm. per cent, the leukocyte count was 4,700 with 13 per cent granulocytes, 80 per cent lymphocytes, and 7 per cent monocytes. The platelet count was 14,000/cu. mm. A surgical bone marrow biopsy was read as hypoplastic with reduced erythroid and myeloid elements and no megakaryocytes. In spite of 40–70 mg. of prednisone daily for a period of two months, the child’s condition remained unchanged and she had to be transfused on several occasions. At the age of 4½ years, S. O. was referred to the University of Wisconsin Children’s Hospital. Numerous petechiae and bruises were found, but no lymphadenopathy and no enlargement of liver or spleen. The patient’s height was below the third percentile and the bone age corresponded to that of a two-year old. No anomalies or pigmentation were found. The hemoglobin level was 7.0 Gm. per cent, the hematocrit 20 per cent, the red cell count 2.35 million, the reticulocytes 0.3 per cent, and the leukocyte count 4,400 with 18 per cent neutrophils and 90 per cent lymphocytes. The platelet count was 34,000/cu. mm. Bone marrow studies showed a marked hypocellularity. The serum iron level was 250 γ per cent, the serum iron-binding capacity 50 γ per cent, the plasma copper 300 γ per cent. The child had several episodes of epistaxis and within a period of two weeks nine transfusions were required to maintain the hemoglobin at about 7.0 Gm. per cent. The patient was then given prednisone, 20.0 mg. daily, and cyclopentylpropionate-testosterone intramuscularly every 3–4 weeks.

After 12 months of this therapy, the hemoglobin had risen to 14 Gm. per cent, the white cell count to 6,900/cu. mm. with 28 per cent neutrophils, 3 per cent eosinophils, 63 per cent lymphocytes and 6 per cent monocytes, and the platelet count was 32,000/cu. mm. The medication was then discontinued. After an initial drop, the hemoglobin values stabilized at a level between 11 and 12 Gm. per cent, the white cell count remained between 6,000 and 7,000 and the platelets increased to 160,000/cu. mm. An acetanilide N-acetyl p-aminophenol loading test was performed six months after all medication had been discontinued. S. O. has received no medication for 24 months without relapse.

Patient #4. S. K., a white girl, was born on August 16, 1952. The father of the child has a dust allergy and a paternal aunt has severe hay fever.

The level of hemoglobin was 4.8 Gm. per cent, the hematocrit 12 per cent, the reticulocytes 1.0 per cent, and the leukocyte count was 5,850, with 20 per cent neutrophils, 76 per cent
lymphocytes, and 4 per cent monocytes. The platelet count was 12,000. A bone marrow biopsy revealed marked hypoplasia. At the age of 8½ years, S. K. was referred to the University of Wisconsin Children’s Hospital. The past history revealed that the girl had been exposed several times each day for at least three months to vapors of an insecticide which she was using for the first time in her life in a poorly-ventilated barn. The insecticide consisted of 0.1 per cent pyrethrins, 1 per cent piporonyl butoxide and 98.9 per cent petroleum distillate.

Her height and weight were between the 75th and 90th percentile. There was no lymphadenopathy. The liver and spleen were not enlarged. There was no unusual pigmentation. The peripheral blood study showed pancytopenia with slight macrocytosis of the red cells. A surgical bone marrow biopsy revealed an almost completely aplastic marrow with the marrow spaces filled mainly with fat and occasional lymphocytes and plasma cells. The serum iron was 232 $\gamma$ per cent, the serum iron-binding capacity less than 50 $\gamma$ per cent, plasma copper 98 $\gamma$ per cent.

At 8½ years of age, therapy was begun with oral prednisone, 40.0 mg. daily, and cyclo-pentylpropionate-testosterone lipogels, 30.0 mg. daily. After 13 months of treatment, the patient still required occasional small transfusions to maintain a satisfactory hemoglobin level.

The acetalanide N-acetyl p-aminophenol loading test was performed before administration of any therapy except blood transfusions.

Patient #5. C. J., a white boy, was born on September 3, 1952. At the age of 6½ years he was admitted to a hospital for evaluation of pallor, petechiae, melena, and fever. Eight months prior to his admission he had been treated on two occasions with chloramphenicol for recurrent upper respiratory tract infections. The hemoglobin level was 7.0 Gm. per cent, the hematocrit 14 per cent, and the red cell count 1.6 million/cu. mm. The leukocyte count was 9,000/cu. mm. The bone marrow was found to be hypoplastic on surgical biopsy. The child was treated without benefit with oral prednisone, 20.0 mg. daily, and crude liver fortified with folic acid.

At the age of 6½/12 years, G. J. was referred to the University of Wisconsin Children’s Hospital. His height was between the 25th and the 50th percentile, his bone age was that of a 5½ year old. The physical examination revealed ecchymotic areas on the lower extremities. There was no lymphadenopathy and no enlargement of liver or spleen. His hemoglobin level was 9.8 Gm. per cent, hematocrit 26 per cent, red cell count 3.32 million/cu. mm., reticulocytes 0.7 per cent, white cell count 5,200/cu. mm. with 16 per cent neutrophils, 80 per cent lymphocytes, and 4 per cent monocytes. The platelet count was 15,000/cu. mm. Bone marrow specimens obtained by aspiration and surgical biopsy showed a marked reduction in cellularity. There were no megakaryocytes and only small, scattered areas of erythroid and myeloid cells in an otherwise fatty marrow. The serum iron was 305 $\gamma$ per cent, the iron-binding capacity of the serum 0 $\gamma$ per cent, the plasma copper 141 $\gamma$ per cent, red cell copper 337 $\gamma$/100 ml. red cells, the free erythrocyte protoporphyrin 64 $\gamma$/100 ml. red cells. The serum protein electrophoresis was normal.

G. J. was treated with oral prednisone, 20.0 mg. daily, and cyclo-pentylpropionate-testosterone, 50.0 mg. intramuscularly at three week intervals. In addition, two transfusions were necessary during the first two months of therapy. Treatment was continued for eight months. The hemoglobin gradually returned to 14.8 Gm. per cent and there was improvement of the granulocytopenia and thrombocytopenia. The boy has been followed for about 18 months and is free of symptoms. An acetalanide N-acetyl p-aminophenol loading test was performed four months after all medications had been discontinued.

Patient #6. L. P., a white girl, was born on September 11, 1950. She was referred to the University of Wisconsin Children’s Hospital at the age of 10-5/12 years with a history of intermittent fever for approximately one month. Four weeks prior to admission she had received a three-day course of chloramphenicol therapy (250 mg. q.i.d.). In addition, she had been exposed for several months to car exhaust gases and vapors of volatile hydrocarbons circulated through her bedroom by a defective heating system. On admission her height was between the 50th and 75th percentile, her weight between the 25th and 50th
DETOXIFICATION IN CHILDREN WITH APLASTIC ANEMIA

percentile. There was no lymphadenopathy and no enlargement of liver or spleen. Petechiae were present on both lower legs and small retinal hemorrhages were present. The hemoglobin level was 4.3 Gm. per cent, the hematocrit 12 per cent, the red cell count 1.31 million/cu. mm., the reticulocytes 1 per cent. The white cell count was 3,100/cu. mm. with 30 per cent neutrophils, 1 per cent eosinophils, 66 per cent lymphocytes, and 3 per cent monocytes. The platelet count was 5,000/cu. mm. Bone marrow specimens obtained by aspiration and surgical biopsy showed a hypocellular marrow with no megakaryocytes and a predominance of small lymphocytes. There were, however, some nucleated red cells and some members of the granulocytic series in the biopsy specimens. Serum was 244 γ per cent, the serum iron-binding capacity less than 50 γ per cent, plasma copper 110 γ per cent, The serum protein electrophoresis was normal.

She was given prednisolone, 20 mg. daily, orally and testosterone-enanthate, 100.0 mg. intramuscularly every four weeks. On three occasions a transfusion was necessary.

Following 10 months of treatment, her peripheral blood count revealed the hemoglobin to be 13.5 Gm. per cent. The erythrocyte count 4.21 million/cu. mm. with 2.5 per cent reticulocytes. The leukocyte count was 16,500/cu. mm. with 78 per cent neutrophils. The platelet count was 60,000/cu. mm. At this time, all therapy was discontinued.

The acetanilide N-acetyl p-aminophenol loading test was done prior to institution of therapy.

Patient #7. K. P., a white girl, was born on October 11, 1955. At 5½ years, she was referred to the University of Wisconsin Children's Hospital for evaluation of an anemia and easy bruising. She had been slightly anemic for the past 15 months and had received oral and intramuscular iron and vitamin B12. The past history revealed that the girl had used a deodorant spray containing petroleum naphtha several times weekly for months. These petroleum naphthas represent petroleum fractions with boiling points of approximately 60 to 175 C. and may contain unsaturated ring hydrocarbons.

On admission, bruises were noted on both lower extremities. There was no lymphadenopathy and no enlargement of liver or spleen. A dry erythematous rash was found in both antecubital fossae. Both height and weight were at the 50th percentile. The hemoglobin level was 9.4 Gm. per cent, the hematocrit 26 per cent, the red cell count 2.35 million/cu. mm. The reticulocytes 2.3 per cent, and the white cell count 5,100/cu. mm. with 38 per cent neutrophils, 1 per cent eosinophils, 57 per cent lymphocytes, and 4 per cent monocytes. The platelet count was 12,000/cu. mm. The erythrocytes appeared on the smear to be slightly macrocytic. A bone marrow sample revealed a moderately hypocellular marrow with some megaloblastic erythroid elements, no megakaryocytes. The serum iron concentration was 149 γ per cent, serum iron-binding capacity 120 γ per cent, plasma copper 94 γ per cent.

After an unsuccessful trial with oral folic acid, 15.0 mg. daily for three weeks, the patient was given prednisone and methyltestosterone linguets. After nine months of treatment, her blood values were as follows: hemoglobin level, 15.3 Gm. per cent; erythrocyte count, 4.7 million/cu. mm.; reticulocytes, 1.4 per cent; leukocyte count, 7,100/cu. mm. with 62 per cent neutrophils; platelet count, 55,000/cu. mm. Treatment has now been discontinued.

The acetanilide N-acetyl p-aminophenol loading test was performed prior to therapy. A group of 10 apparently healthy, non-hospitalized children of similar age and weight were used as normal controls.

RESULTS

Figure 2 represents the results of studies relating the excretion of total p-aminophenol to the administration of acetanilide and N-acetyl p-aminophenol. These compounds produce a marked increase of the total p-aminophenol fraction in all subjects studied. Analyses of variance show no significant difference between the increase produced by acetanilide and the increase produced by N-acetyl p-aminophenol. No significant difference in total p-aminophenol excretion between normal controls and children with aplastic anemia was found.
The average increase in total p-aminophenol excretion after administration of 0.1 mM/Kg. of acetanilide and an equimolecular dose of N-acetyl p-aminophenol was 0.087 mM/Kg. (= 0.021 mM/Kg.). This would indicate that on the average about 87 per cent of the compounds given was recovered in the urine either as free, acetylated or hydroxy-conjugated p-aminophenol. These values are similar to those reported by Brodie and Axelod.5

Figure 3 relates the excretion of conjugated glucuronic acid to the administration of acetanilide and N-acetyl p-aminophenol. Both compounds produce a similar, significant increase in conjugated glucuronic acid excretion. Analyses of variance show no significant differences between the normal controls and the patients with aplastic anemia. The average increase in conjugated glucuronic acid excretion after 0.1 mM/Kg. of acetanilide and an equimolecular dose of N-acetyl p-aminophenol was 0.013 mM/Kg.

Figure 4 relates the excretion of ethereal sulphates to the administration of acetanilide and N-acetyl p-aminophenol. In the children with aplastic anemia, as well as in the normal controls, the excretion of ethereal sulphates was found to vary considerably. Analyses of all values showed no significant differences in ethereal sulphate excretion between the two groups investigated. However, if the influence of the acetanilide and N-acetyl p-aminophenol ingestion on the excretion of ethereal sulphates was studied in each group, it was found that the ingestion of N-acetyl p-aminophenol produced a significant (p value between 0.02 and 0.01) increase in ethereal sulphates in the normal controls but not in the patients with aplastic anemia. In both groups, no correlation between the acetanilide administration and the excretion of ethereal sulphates was found.
In figure 5 it can be seen that there is no correlation between the excretion of total sulphates in the urine and the administration of either acetanilide or N-acetyl p-aminophenol. Statistical evaluation of these results shows no difference in total sulphate excretion between controls and children with aplastic anemia.
Figure 6 represents results of a study relating the total nitrogen/total sulphate ratio to the ingestion of acetanilide and N-acetyl p-aminophenol. This ratio was calculated by dividing the total nitrogen excretion in mg./hours. The ratio was not influenced by the administration of acetanilide or N-acetyl p-aminophenol and remained fairly constant in a given individual. There was
no significant difference in this ratio between controls and patients with aplastic anemia. Its average value was found to be 5.6 (s = 0.8).

**Discussion**

The elimination and excretion of naturally occurring waste products and of foreign substances accidentally ingested is of vital importance for normal function and survival of the human organism. Naturally occurring waste products are eliminated by substrate-specific mechanisms; foreign substances are transformed by enzymes which seem to be more reaction- than substrate-specific. Inhibitors were found which interfere specifically with foreign compound metabolism and which alter the biotransformations not only of one, but of many foreign substances. It might be assumed, therefore, that certain common mechanisms provide elimination of a variety of foreign compounds.11

The present study was undertaken in order to evaluate arylhydroxylation and hydroxy-conjugation with activated glucuronic acid and sulphate in children with aplastic anemia.

After oral administration of one or two Gm. of acetanilide, Brodie and Axelrod found about 80 per cent of the drug as conjugated and about 4 per cent as free N-acetyl p-aminophenol in the urine. In the present study, no differentiation was made between free, N-acetylated and hydroxy-conjugated p-aminophenol, but it was possible to recover 85 to 90 per cent of the acetanilide administered as total p-aminophenol in both children with aplastic anemia and controls. This seems to indicate normal function of the hydroxylation mechanism involved in acetanilide excretion. Brodie and Axelrod also suggested that most of the N-acetyl p-aminophenol would be conjugated with glucuronic or sulphuric acid. The increase in conjugated glucuronic acid observed in our studies accounts for only about 15 per cent of the total p-aminophenol recovered. In addition, it was not possible to demonstrate an obvious pattern in ethereal sulphate excretion after administration of acetanilide and N-acetyl p-aminophenol. This would indicate that conjugation with activated sulphate is not very significant, at least in the dose range chosen. It is difficult, however, to evaluate the ethereal sulphate excretion due to its considerable variation under normal circumstances. Random 24-hour urine specimens have been collected from 31 healthy, non-hospitalized children with body weights between 10 and 55 Kg. On the average, 0.0192 mM/Kg. of conjugated glucuronic acid, 0.0060 mM/Kg. of ethereal sulphate and 0.593 mM/Kg. of ethereal sulphate and 0.593 mM/Kg. of total sulphates were excreted daily. The respective standard deviations were 0.0055, 0.0027, and 0.156 and the corresponding coefficients of variation, 29.45 and 26 per cent. These results confirm the impression that the ethereal sulphate excretion is much more variable than the excretion of conjugated glucuronic acid. Thus it has not been possible to account for more than 15 per cent of the conjugation products of total p-aminophenol, but it was found that there is essentially no difference between the two groups of children studied. This would indicate that at least the conjugation with activated glucuronic acid occurs at a normal rate in children with aplastic anemia.
SUMMARY

The excretion of acetanilide and N-acetyl p-aminophenol in normal controls and children with aplastic anemia was found to be similar. These results suggest that arylhydroxylation and conjugation with activated glucuronic acid are not disturbed in toxic aplastic anemia. No good evidence could be obtained indicating conjugation of acetanilide metabolites with activated sulfate.

SUMMARIO IN INTERLINGUA

Esseva trovate que le excretion de acetanilido e de N-acetyl-p-aminophenol es simile in normal juveniles de controlo e in juveniles con anemia aplastic. Iste resultatos suggere que arylhydroxylation e conjugation con activate acido glucuronic non es disturbate in toxic anemia aplastic. Nulle bon indicationes poteva esser ohtenite pro justificar le these de un conjugation de metabolitos de acetanilido con sulfato activate.

REFERENCES

A Study of Detoxification Mechanisms in Children with Aplastic Anemia

HANS P. WAGNER and NATHAN J. SMITH