fetal blood levels are significantly higher than maternal ones, a situation also found for most amino acids (13). These differences between mother and fetus and between species may be related to placental function. In the rat, radioactive carnitine injected into the mother rapidly accumulates in the placenta (10) but reaches the fetus only slowly.

Even though it is doubtful whether there is a direct correlation between the rate of fatty acid utilization and the blood level of carnitine, it is nevertheless tempting to suggest that the higher levels in human fetuses are related to their relatively greater capacity to oxidize fatty acids (10). However, increased fatty acid utilization is also a feature of pregnancy. Yet, blood levels of carnitine in pregnant women are significantly lower than in nonpregnant ones.

There is a gradual fall in the free carnitine content of amniotic fluid as gestation proceeds. The origin of this carnitine is not clear. Assuming that carnitine in AF is of renal origin, it is possible that more carnitine is retained by the fetus as it approaches term and less is excreted. The lower level in the amniotic fluid of IDM may be related to the larger volume of amniotic fluid.

CONCLUSION

A highly significant negative correlation was found between amniotic fluid levels of free L-carnitine and gestational age in both normal fetuses and infants of diabetic mothers. However, at any age, levels were lower in IDM. Maternal blood levels (17 ± 3 nmol/ml) were lower than levels in nonpregnant women and in cord blood. Usually, arterial umbilical blood also showed higher values than venous umbilical blood. In a pregnant ewe, L-carnitine blood levels were more than twice as high than in her 130-day-old fetus. Injection of L-carnitine into the carotid artery of the ewe did not result in any changes in carnitine levels in fetal blood.

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Bilirubin	glucaric acid
creatinine	newborns
feedback control	nikethamide
	phenobarbital

Negative Feedback Control of Neonatal Serum Creatine and Increased Urinary Creatinine Excretion after Enzyme-inducing Drugs

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Summary

Creatinine, creatine, and glucaric acid were determined in 24-hr urine samples collected from three groups of newborns on the first, fourth, and seventh day of life. Simultaneously creatine, creatinine, and bilirubin were estimated in serum of cord blood and of venous blood on the fourth and seventh day. Urinary creatinine excretion increased from the low values on the first

day to the fourth day levels. In the control infants there was no further increase on the seventh day, on average. In both groups treated with oral nikethamide in addition to simultaneous intramuscularly applied phenobarbital in one group, and to oral sodium phenobarbital solution in the other one, further increase from the fourth to the seventh day was observed so that on the seventh day the creatinine excretion was significantly higher in both treated groups when compared with the seventh day values

in the control group. Serum creatine levels were highest on the fourth day; on the seventh day they dropped, but were higher in both treated groups. Urinary creatine excretion showed almost the same tendency as serum creatine levels. Creatinine clearance was not higher in the treated groups. The increases in glucaric acid and creatinine excretion in the treated groups were in good correlation. The pronounced serum bilirubin decrease also confirmed the inductive effect of these drugs.

Speculation

Serum creatine levels and creatinine excretion fluctuated during the first week of life, which may be a result of feedback inhibition by rapidly increasing formation during the first days. Thus, it is confirmed that urinary creatinine excretion is an insuitable reference in neonates. Enzyme-inducing drugs may increase creatinine excretion, probably by increasing creatine input into the circulation.

During our study on urinary D-glucaric acid excretion in newborns we have also determined urinary creatinine as a reference (13). It was observed that in the group of newborns treated with phenobarbital creatinine excretion increased when compared with the control group.

In the present report urinary creatinine and creatine excretion was studied together with their serum levels and their changes were followed after application of the known enzyme-inducing combination of phenobarbital with nikethamide (6). In the same series of newborns simultaneous determinations of urinary glucaric acid excretion and of serum bilirubin levels were carried out.

PATIENTS AND METHODS

Three groups of full term newborn boys with negative Coombs' test were examined. On the 1st, fourth, and seventh

days of life 24-hr urine samples were collected in plastic bags for chemical investigation. Creatinine and creatine were determined according to the method of Lieb and Zacherl (11), glucaric acid was estimated according to the method of Ishidate *et al.* (8) without previous borohydride reduction. In cord blood serum and in the serum from venous blood collected on the fourth and seventh day creatine was determined by the method of Drabikowski (3), creatinine was assayed according to the method of Yatzidis (19), and bilirubin was determined according to the method of Jendrassik and Grof (9). Endogenous creatinine clearance was calculated according to the method of Kampmann *et al.* (10).

The boys were divided into groups: group A comprised the controls (14 cases). In group B (13 cases) phenobarbital (20) (10 mg/kg/day) was applied intramuscularly together with oral nikethamide (20) (Eucoran, 25 mg/kg/day) to counteract the depressive action of phenobarbital and to potentiate its inductive effect. Both drugs were divided into three daily doses, 8 hr apart. The total number of doses was 10, the first dose being administered within 8 hr after birth and the last one on the fourth day. In group C (10 cases) the boys were treated orally with a solution of sodium salt of phenobarbital (always freshly prepared and made palatable with saccharin) and with nikethamide (Eucoran), both in dosage corresponding to the same amount and schedule as in group B. All infants studied tolerated the procedure well. The data obtained were evaluated using Student's *t*-test and the *t*-test for paired values according to the previous results of Snedecor's *F*-test.

RESULTS

The results of the determination of urinary creatinine and creatine excretion are given in Table 1. For comparison there are also presented the changes in urinary glucaric acid excretion and in serum creatine, creatinine, and bilirubin levels under the influence of the applied enzyme-inducing agents. It is evident

Table 1. Urinary creatinine, creatine, and glucaric acid excretion, serum creatinine, creatine, and bilirubin levels in neonates in first week¹

	Group	n	1st day	n	4th day	n	7th day
Urinary creatinine excretion ($\mu\text{mol/kg/day}$)	A	14	40.7 $\pm$ 4.9	14	69.0 $\pm$ 8.8	14	55.0 $\pm$ 5.0
	B	12	36.2 $\pm$ 7.0	13	62.0 $\pm$ 7.1	13	73.5 $\pm$ 6.5 ²
	C	9	32.8 $\pm$ 10.1	10	63.7 $\pm$ 9.8	10	83.2 $\pm$ 9.6 ²
Urinary creatine excretion ($\mu\text{mol/kg/day}$)	A	14	4.2 $\pm$ 0.5	13	22.1 $\pm$ 4.1	12	10.0 $\pm$ 1.8
	B	12	5.9 $\pm$ 1.7	13	24.4 $\pm$ 4.1	13	20.0 $\pm$ 4.2 ²
	C	9	3.2 $\pm$ 0.9	10	16.0 $\pm$ 4.3	9	13.7 $\pm$ 2.7
Serum creatinine ($\mu\text{mol/liter}$)	A	14	73.5 $\pm$ 4.0	13	43.3 $\pm$ 10.5	12	30.1 $\pm$ 7.5
	B	12	67.2 $\pm$ 3.0	9	52.2 $\pm$ 11.5	8	53.0 $\pm$ 3.9
	C	9	73.5 $\pm$ 8.2	10	58.3 $\pm$ 8.5	8	52.2 $\pm$ 10.9
Serum creatine ($\mu\text{mol/liter}$)	A	14	84.0 $\pm$ 6.2	14	137.5 $\pm$ 10.1	14	91.5 $\pm$ 6.4
	B	12	76.5 $\pm$ 7.6	10	160.0 $\pm$ 12.4	13	130.0 $\pm$ 7.7 ²
	C	10	84.0 $\pm$ 4.4	10	137.5 $\pm$ 8.0	10	115.0 $\pm$ 15.1
Urinary glucaric acid excretion ($\mu\text{mol/kg/day}$)	A	13	1.57 $\pm$ 0.51	13	2.14 $\pm$ 0.59	12	2.27 $\pm$ 0.43
	B	12	0.57 $\pm$ 0.06	13	2.14 $\pm$ 0.35	13	4.28 $\pm$ 0.64 ^{2,3}
	C	8	1.05 $\pm$ 0.60	10	1.90 $\pm$ 0.41	10	4.52 $\pm$ 1.0 ^{2,4}
Serum bilirubin ($\mu\text{mol/liter}$)	A	14	36.0 $\pm$ 2.1	14	203.2 $\pm$ 19.2	14	164.0 $\pm$ 25.7
	B	13	33.0 $\pm$ 3.7	13	94.2 $\pm$ 20.8 ⁵	13	51.5 $\pm$ 16.0 ⁵
	C	10	30.8 $\pm$ 2.5	10	104.5 $\pm$ 27.0 ⁵	10	65.2 $\pm$ 20.5 ⁵

¹ Group A: control newborns; group B: newborns after intramuscular phenobarbital (10 mg/kg/day) with simultaneous oral nikethamide (25 mg/kg/day) application for 3 days; group C: after oral sodium phenobarbital solution with nikethamide in the same dosage schedule as in group B. All values given as mean $\pm$ SEM; n: number of cases.

² $P < 0.05$ (significant difference between values in the respective treated group and the control group).

³ $P < 0.01$ (significance levels of increases on the seventh day when compared with the original level on the first day (pair test)).

⁴ $P < 0.05$ (significance levels of increases on the seventh day when compared with the original level on the first day (pair test)).

⁵ $P < 0.01$ (significant difference between values in the respective treated group and the control group).

that urinary creatinine excretion increased from low values on the first day to the fourth day levels. In the control subjects there was no further increase on the seventh day; on average. However, in both treated groups further increase from the fourth to the seventh day was observed so that on the seventh day the creatinine excretion was significantly higher ($P < 0.05$) in both groups receiving the enzyme inducers (*B* and *C*) when compared with the seventh day values in the control group (*A*). Serum creatine levels were highest on the fourth day. On the seventh day the levels dropped, but they were higher in both phenobarbital-nikethamide-treated groups than in the control group. This seventh day serum level of creatine was significantly higher ($P < 0.05$ only in the group receiving phenobarbital intramuscularly (*B*). Urinary creatine excretion showed almost the same tendency as serum creatine levels. Serum creatinine, in most cases, showed a decreasing trend. Creatinine clearance (milliliters per min per $1.73 \text{ m}^2 \pm \text{SEM}$) was not higher in the sum of both treated groups (11.2 ± 1.75 , 38.1 ± 8.8 , and 40.2 ± 9) when compared with the controls (11.2 ± 1.3 , 49.5 ± 11.1 , and 56.7 ± 7.4), on the first, fourth, and seventh days respectively.

Higher urinary glucuric acid elimination ($P < 0.05$) and a very pronounced decrease of serum bilirubin levels in comparison with controls ($P < 0.01$) were the signs that the liver microsomal induction of the glucuronic acid system had occurred. The correlation in the increases from the first to the seventh day values between urinary glucuric acid and creatinine excretion in the sum of both treated groups (*B* + *C*, 20 cases) was significant ($r = 0.649$, $P < 0.01$).

DISCUSSION

Our results confirm the findings that creatinine excretion (4) and endogenous creatinine clearance levels (12) are low in newborns, especially on their first day of life. In the following days they increase, but even at the end of the first week of life creatinine excretion and clearance still remain much lower than the adult values. This fact is of importance in explaining the unsuitability of creatinine excretion (1) as a basis for assessing the excretion of other metabolites in infants (1) (2) in clinical considerations regarding fluid and electrolyte homeostasis, and (3) in calculating the dosage and elimination of drugs (12).

In our study the increase in creatinine excretion in newborn boys was observed especially up to the fourth day. The serum levels and the excretion of creatine were highest on the fourth day of life. Creatinuria followed the serum creatine levels in analogous patterns. The decrease in creatine values from the fourth to the seventh day can be satisfactorily explained only by negative feedback regulation by rapidly increasing creatine formation and is in accord with the observations of Hoberman *et al.* (7), Walker and Walker (18), Walker (14, 15), Walker and Wang (17), Walker and Hannan (16), and recently by Bernhardt (2). All of these authors have found a retardation of creatine synthesis after its application. Bernhardt (2) suggested that serum creatine levels over $1.5 \text{ mg}/100 \text{ ml}$ are able to cause a repression of L-arginine:glycine amidinotransferase (EC: 2.1.4.1). The serum concentration changes of creatine were then probably followed by alterations in the course of urinary excretion of creatine and creatinine.

After phenobarbital and nikethamide application there occurred a statistically significant increase in urinary creatinine excretion from the fourth to the seventh day. The endogenous creatinine clearance, however, was not higher in both treated groups when compared with the control group. From these findings it could be concluded that the increased creatinine elimination after phenobarbital and nikethamide was not caused by the increase in glomerular filtration rate.

Increased creatine input into the circulation after an enzyme-inducing combination must not come about only because of increased formation by enzyme induction. It may be also possible to consider the higher serum levels of creatine and the

enhanced creatinine excretion under the influence of these xenobiotics as a result of the higher release of creatine from the tissues into circulation. Our findings also could be corroborated by the observation by Flint and Richardson (5), who have shown urinary nitrogen excretion and a negative nitrogen balance after phenobarbital administration to rats.

CONCLUSION

Urinary creatinine excretion increased from the first to the fourth day of life. In the neonates treated for 3 days after birth with a combination of phenobarbital and nikethamide the further increase up to the seventh day levels was significantly greater than the seventh day values in the control group. Serum creatine levels were highest on the fourth day and on the seventh day they slightly declined but were a little higher in the treated infants. Since creatinine clearance was not increased after the treatment it is suggested that phenobarbital with nikethamide causes increased creatine input into the circulation either by its higher level of production or by its release from the tissues. Increased glucuric acid excretion and the bilirubin decrease confirmed the inductive effect of these drugs.

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Adolescence scoliosis
plasma somatomedin

Plasma Somatomedin Activity in Normal and Scoliotic Children

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Summary

In a study of plasma somatomedin activity in childhood scoliosis a group of five patients with congenital scoliosis was found to have significantly lower plasma somatomedin levels compared with a group of 20 normal children. A group of 52 patients with "idiopathic" scoliosis had normal plasma somatomedin levels. There is no apparent difference in the plasma somatomedin activity between the sexes, and no change in plasma somatomedin activity with chronologic age in these children, suggesting that normal adult somatomedin levels had been reached.

Speculation

In the rapid growth period of adolescence, plasma somatomedin activity is not raised. In scoliotic children many abnormal aspects of growth and metabolism have been reported, but somatomedin activity is normal. Presumably, therefore, either very small changes in somatomedin activity will produce a stimulation of growth and metabolism or the responsiveness of the target tissues is altered during periods of growth and, perhaps, in scoliosis. Children with congenital scoliosis have low plasma somatomedin activity, which is in keeping with the general impression that they are smaller than normal children of a similar age. Further endocrinologic and biochemical studies in scoliotic children may help elucidate the cause of "idiopathic" scoliosis.

Scoliosis is a condition which is closely associated with growth, and it is, therefore, interesting that it was not until 1972 that a study was made of the serum growth hormone levels in scoliotic patients (7). It is now known that the growth hormone molecule does not directly affect growth and metabolism of cells, and its action at the cellular level is mediated by somatomedin (1). (The generic name somatomedin is used throughout this paper rather than referring to specific somatomedins.)

One of the major actions of somatomedin is to stimulate the synthesis of chondroitin sulfate (11). It also stimulates the rate of cartilage cell proliferation in growth plates (4).

It has been suggested that "uncoiled" height (13) is greater in scoliotic children than in normal children, and that there is also a relative lengthening of the anterior components of the spine

(vertebral bodies and discs) compared with the posterior components (neural arches and interspinous ligaments) (10). It has been postulated that this is the cause of the vertebral rotation associated with the rapid rate of trunk growth during the adolescent growth spurt in scoliosis.

During the adolescent growth spurt, the rate of spinal and pelvic growth is increased, as in the interstitial cartilage growth in the vertebral plates and iliac crest cartilage. The galactosamine concentration of the iliac crest cartilage is also increased (9), and is higher in scoliotic iliac crests than in normal children (8).

All these dissimilarities between scoliotic and normal children suggest that there may be increased growth hormone and plasma somatomedin activity levels in the plasma of scoliotic children. It has been reported that "idiopathic" scoliotic children (those with spinal curvature of unknown origin) have normal growth hormone levels (7). This paper reports our findings on plasma somatomedin activity in scoliosis.

MATERIALS AND METHODS

Plasma somatomedin activity was estimated in 20 normal English children, 25 French scoliotic children, and 32 English scoliotic children, from whom or from whose parents informed consent was received. The normal children were all healthy, nonhospitalized volunteers within the age range of 10-19 years. One of the French children had congenital scoliosis whereas all the others had idiopathic scoliosis. The group of English scoliotic children comprised: 4 with infantile idiopathic scoliosis (0-3 years of age when first diagnosed), 6 with juvenile idiopathic scoliosis (4-9 years), 15 with adolescent idiopathic scoliosis (10-16 years), 4 with congenital scoliosis, and 3 others. All of the scoliotic children were within the age range of 9-18 years.

Blood was taken from each of these subjects before 9:30 in the morning after an overnight fast, and before any strenuous exercise. The blood was collected by a standardized procedure to reduce variations due to diet, sleep and exercise (all of which have been shown to alter growth hormone levels), as well as diurnal variation in plasma somatomedin activity levels. The blood was collected in heparinized tubes and the plasma separated, frozen in Cardice, and kept at -30° until assayed. All plasma samples were frozen within 2 hr of venipuncture. To negate the possibility of any alteration in growth hormone levels