NORMAL RENAL FUNCTION IN THE FIRST TWO DAYS OF LIFE

BY

R. A. McCANCE and E. M. WIDDOWSON

From the Medical Research Council Department of Experimental Medicine, University of Cambridge

(RECEIVED FOR PUBLICATION APRIL 26, 1954)

Our knowledge about renal function in the first two days of human life is meagre. Most of it is due to Thomson (1944, 1947, 1949), Smith, Yudkin, Young, Minkowski and Cushman (1949) and Hansen and Smith (1953). Dean and McCance (1947) measured the inulin, diodone and creatinine clearances of four children aged 2 days, and other investigators have included one or two children under 3 days old in a series which they were studying for one or more aspects of renal function (Dean and McCance, 1948; Rubin, Bruck and Rapoport, 1949; Vesterdal and Tudvad, 1949) but, except in the case of Ames' (1953) work on the excretion of water, there have never been enough of these children to make much of the findings, and our ideas about the function of the baby's kidney are almost entirely based upon studies which have been made on older age groups (Barnett, 1940; McCance and Young, 1941; Gordon, Harrison and McNamara, 1942; Barnett, Hare, McNamara and Hare, 1948; Dean and McCance, 1949; McCrory, Forman, McNamara and Barnett, 1952). Thomson (1944) gave average figures and the individual scatter for the volumes of the urines of newborn infants, their specific gravities and pH, the concentration of chloride (Cl) and urea, and later (1949) added his findings for the urea clearances. He also (1947) studied two children with 'dehydration fever'. He made no comparisons with adults.

In studying renal function, particularly clearances, it is usual to give enough fluid either by mouth or vein to promote a large diuresis. This facilitates the collection of specimens, but it would be an unphysiological thing to do to a baby less than 48 hours old who at that time normally passes through a period of undernutrition and dehydration. It would have destroyed one of the main objects of this investigation, moreover, which was to try to piece together some of the events which normally take place during those two days. The babies were investigated, therefore, under standardized but almost normal

conditions and compared with adults who had been subjected to what we know is a similar degree of starvation and hydropenia.

Subjects and Methods

Eighteen full-term baby boys and six healthy young men have been investigated. Twelve of the babies were born *per vias naturales*, all without the aid of forceps; five of these babies were first children, and seven of them second or later children. The other six babies were delivered by caesarian section. Permission to make these investigations was obtained from the mother before birth, and soon after birth the baby was fitted with an apparatus for collecting the urine quantitatively, and nursed in the usual way, except that he was not put to the breast and was given in all about 25 ml. of water, spread out over the two days at what seemed the most appropriate moments. Cord blood was obtained, the serum separated, analysed for creatinine, urea, sodium, chloride, potassium and phosphates, and its total osmolar concentration determined by freezing point. Small samples of blood were taken from the heel at the end of 24 and 48 hours and the concentration of urea determined in the serum. Sometimes enough blood was withdrawn at the forty-eighth hour by vein puncture for the more extensive assays usually carried out on cord blood. Urine was collected as it was passed spontaneously and the samples were analysed separately. Very small samples were occasionally pooled. Since babies may be assumed to empty their bladders at birth any 'carry over' of foetal urine may be neglected, but some of the urine formed in the first 24 hours may not have been passed till the second 24 hours. The infants, however, usually emptied their bladders when the samples of blood were taken. If this did not happen at the end of 24 hours, the analytical results obtained on the next specimen of urine were partitioned between the first 24 hours and the second 24 hours, according to the time over which the

urine had been collecting in the bladder. If the baby did not empty the bladder at the end of 48 hours no change in the treatment was made till he voided spontaneously, or a voiding just before the end of the 48 hours was held to terminate the urine collections, and calculations were made to correct the volume in, say, the fortieth to the forty-sixth hour, to the fortieth to the forty-eighth hour.

Six healthy young men, all sailors, were also studied. During the experiment they lived in a small room with an almost constant, comfortably warm temperature. They had nothing to eat, and only 350 ml. of water a day to drink for a period of three days. Samples of blood were taken without anticoagulant before the experiment began, and at the end of each 24 hours during the test, and the serum was separated. All urines were collected under toluol in 24-hour periods.

Total nitrogen in all the urines was determined by the ordinary micro-Kjeldahl technique and the other physical and chemical methods were the same as those used by McCance and Widdowson (1953). The body water of the infants and adults was calculated as described by McCance and Widdowson (1952).

Results

Table 1 gives the average urine volumes per litre of body water and the average osmolar concentrations of the urines passed by the infants during the first and second 24 hours of their lives and by the young men during the second and third days of their dehydration experiment. The figures for the adults on the first day of deprivation have not been given since the volumes were about twice as large and the osmolar concentrations correspondingly less than they were on the second and third days so that they clearly belonged to a transitional period between a state of full nutrition and hydration and one of established starvation and hydropenia. Ladell (1947) has described similar findings. These signs

of a transitional period were not evident just after birth and since no observations were made on the third day of life the results for the first and second days have been given. Since infants have a higher rate of metabolism per kg. of body weight and become dehydrated more rapidly than adults, it is open to argument whether they had not reached by the second 24 hours a state of starvation and hydropenia similar in severity to that reached by the adults on the third day. At any rate their average weight loss in two days was 9.3% of their original body weight compared with a loss of 6.1% in three days for the adults. The volumes of urine passed by the adults per litre of body water were slightly greater than those passed by the babies, but the osmolar concentrations were three times as high (Day 1, $t=15.8$ $p<0.001$, Day 2, $t=17.5$ $p<0.001$). In making these and other calculations of a similar nature the adult figure used for comparison was the average of days 2 and 3. The U/P ratios for the osmolar concentrations averaged no more than 1.25 and 1.53 for the first and second days of life, while they were 3.96 and 4.12 for the second and third days of the adults' hydropenia. These low U/P ratios for infants as compared with those for adults should be contrasted with the findings for hydrated and overhydrated babies only six to 18 days older (McCance, Naylor and Widdowson, 1954).

Table 2 shows the composition of the urines of the infants compared as in Table 1 with those of the adults subjected to similar degrees of starvation and hydropenia. The figures for urea, sodium, chloride and potassium have been given by expressing the molar concentration of each as a percentage of the total osmolar concentration determined by freezing

TABLE 1

VOLUMES AND TOTAL OSMOLAR CONCENTRATIONS OF URINE PASSED DURING FIRST TWO DAYS OF LIFE COMPARED WITH THOSE OF URINE OF ADULTS SUBJECTED TO SIMILAR STARVATION AND HYDROGENIA

		Babies		Adults	
		Day 1	Day 2	Day 2	Day 3
Volume (ml./l. body water)	Average	11.9	15.6	15.7	17.7
	S.D.	5.16	8.75	3.23	4.70
Total osmolar concentration (m. osmols/l.)	Average	375	465	1,186*	1,261*
	S.D.	91.5	51	96*	245*

* Average of Days 2 and 3 1,223, S.D. 152.

TABLE 2

COMPOSITION OF URINE OF INFANTS DURING FIRST TWO DAYS OF LIFE COMPARED WITH URINE OF ADULTS SUBJECTED TO SIMILAR STARVATION AND HYDROGENIA*

Constituents of Urine		Babies		Adults	
		Day 1	Day 2	Day 2	Day 3
Urea	Average	33.0	41.6	44.8	49.1
	S.D.	7.2	10.1	4.9	4.3
Chloride	Average	14.0	7.0	7.3	6.8
	S.D.	5.67	3.39	1.64	3.33
Sodium	Average	9.7	5.6	11.8	6.9
	S.D.	4.33	3.98	2.04	2.18
Potassium	Average	12.0	10.1	4.3*	4.6*
	S.D.	2.81	2.06	0.95*	0.73*
Undetermined	Average	31.3	35.7	31.8	32.6
	S.D.	11.7	13.8	4.20	5.94

* Average of Days 2 and 3 4.44, S.D. 0.77.

† All figures are expressed as a percentage of the total osmolar concentration.

point, since this facilitates comparison of the two age groups and enables the undetermined fraction to be considered as well. Considering the great differences in osmolar concentration, Table 2 shows that the contributions of the solutes were relatively alike. Urea contributed less to the total in the infants but sodium and chloride similar amounts. The sudden reduction of the quota due to these two ions immediately after birth has been described by McCance and Widdowson (1953). A significantly higher proportion of the total osmolar concentration was due to potassium in the infants' urines than in those of the adults (Day 1, $t=6.5$ $p<0.001$; Day 2, $t=6.7$ $p<0.001$); the fraction which was undetermined was about the same at the two ages. In the infants' urines the proportion due to urea rose slightly on the second day of life ($t=2.87$, $p=0.01-0.001$) whereas the proportion due to potassium fell ($t=2.23$, $p=0.05-0.02$).

It follows from the figures given in Table 1 that the amount of osmotically active material excreted by the infants per litre of body fluid per day was less than the amount excreted by the adults. The average figure was 5.6 milliosmols per litre of body water per day for the infants as against 19.9 for the adults. There was, however, a further difference between the two age groups in that the milliosmols excreted by the individual adults ranged only from 15.3 to 23.6 (S.D. 2.62) whereas the values for the babies ranged from 2.35 to 9.7 (S.D. 2.24). These individual differences among the infants were far outside any that could have arisen from incomplete collections. Among the adults the ml. of urine/milliosmol varied from 0.74 to 1.07 with a mean of 0.84 and a S.D. of 0.117. The average for the infants was 2.52 (S.D. 0.484) and the extreme values 1.87 and 3.96. If an adult is short of water it is generally agreed that the volume of the urine depends upon the quantity of osmotically active material claiming excretion per unit of time (Ambard

and Papin, 1909; Gamble, 1944; McCance, 1945; Rapoport, Brodsky, West and Mackler, 1949). Fig. 1 shows that the volume of urine excreted by

FIG. 1.—The relationship between the excretion of osmolar material and the volume of the urine.

the babies also increased with the output of osmotically active material, Fig. 2 that there was a similar relationship between the volume of the urine and the total nitrogen excreted per day, and Fig. 3 that the urea clearances also rose as the minute volume increased.

It might be surmised from the information already given that the urea and other clearances would be much lower just after birth than among adults who had been correspondingly dehydrated, and that the babies would differ more among themselves. Table 3 shows that this was so. Thomson (1949) found urea clearances of the order of 8 ml./min.

TABLE 3
UREA, SODIUM AND CHLORIDE CLEARANCES OF INFANTS DURING FIRST TWO DAYS OF LIFE
COMPARED WITH THOSE OF ADULTS SUBJECTED TO SIMILAR HYDROPENIA AND STARVATION*

				Babies		Adults	
				Day 1	Day 2	Day 2	Day 3
Urea	..	..	Average	9.1	14.6	34.4	39.9
	..	..	Range	2.7-19.7	2.4-32.3	21.7-48.7	31.5-52.2
	..	..	S.D.	4.39	8.00	8.44	7.42
Sodium	..	..	Average	0.089	0.101	0.437	0.300
	..	..	Range	0.023-0.347	0.013-0.466	0.305-0.678	0.120-0.442
	..	..	S.D.	0.074	0.123	0.133	0.114
Chloride	..	..	Average	0.175	0.160	0.384	0.433
	..	..	Range	0.032-0.627	0.024-0.450	0.290-0.525	0.229-0.985
	..	..	S.D.	0.140	0.142	0.075	0.264

* All figures are expressed as ml. 42 l. body water/min.

on the basis of a surface area of 1.73 sq. m. in babies aged 2 to 4 days who were being reared at the breast. This corresponds to 20 ml./min. per 42 litres of body water (McCance and Widdowson, 1952). There is little doubt that the glomerular filtration rates were correspondingly low for, although inulin was never given in order to determine them, the endogenous creatinine clearances were measured in six infants and found to bear the normal and expected relationship to the urea clearances. Averages (ml./42 litres body water/min.) gave for Day 1, creatinine 20.8; urea 8.8, and for day 2, creatinine 25.5; urea 13.9.

FIG. 2.—The relationship between the excretion of nitrogen and the volume of the urine.

Table 4 shows the total nitrogen, the potassium and the nitrogen : potassium ratios found in the urine of the infants on the first and second days of life and of the adults on the second and third days of dehydration. The infants excreted nearly as much K per kg. of body weight as the adults but only one-third as much N, and consequently their N/K ratios were correspondingly lower than those of the adults. Both differences were highly significant (N excreted on Day 1, $t=16.7$ $p<0.001$; Day 2, $t=5.65$ $p<0.001$. N/K ratio, Day 1, $t=11.9$ $p<0.001$; Day 2, $t=6.28$ $p<0.001$). There can be no reasonable doubt about the correctness of these ratios; they agree very well with those given by Smith *et al.* (1949) and by Hansen and Smith (1953) and, as their charts show in two individual babies, the ratios were higher, like the present ones, on the second day than on the first. The difference between the ratios on the first and second days in the present series was a significant one ($t=3.45$, $p=0.001$).

The phosphate excretions and clearances require

TABLE 4

EXCRETION OF NITROGEN AND POTASSIUM BY INFANTS DURING FIRST TWO DAYS OF LIFE AND BY ADULTS SUBJECTED TO SIMILAR STARVATION AND HYPOXEMIA

		Babies		Adults	
		Day 1	Day 2	Day 2	Day 3
Nitrogen* excreted	Average	38.0	77.7	151.0	185.0
	S.D.	13.8	35.7	30.2	18.3
Potassium* excreted	Average	13.3	19.9	17.6	22.1
	S.D.	5.78	13.1	2.19	4.08
Ratio of N/K in urine	Average	2.9	3.9	8.6	8.4
	S.D.	1.00	1.48	1.56	1.27

* Figures for nitrogen and potassium are expressed as mg. per kg. body weight per day.

separate treatment. The inorganic phosphate in cord blood was higher than in the maternal blood and even when infants were given no food there would appear to have been a small rise in the serum P during the first 48 hours of their lives. The increase in eight infants was from an average of 6.0 to one of 8.0 mg./100 ml. The concentration of P in the urines and the amounts excreted per unit of time averaged very much less in the two days after birth than they did in adult life but this statement requires considerable amplification. Before a normal birth the urine may be regarded as containing almost no phosphate (McCance and Widdowson, 1953) and in many babies the amount was found to remain very small for the first 48 hours. In others the excretion of P began to increase soon after birth and was quite considerable by the end of the second day (Fig. 4). These changes in the concentration of P in the urine and in its rate of excretion may have been mediated by the rise in the

FIG. 3.—The effect of an increase in urine volume on the urea clearance.

serum P but could not be correlated with it or with the excretion of any of the other urinary constituents.

FIG. 4.—Typical examples of the way in which the excretion of phosphorus may behave during the first two days of life.

Baby X Serum inorganic P at birth 4.45 mg./100 ml.
 " " " at end of 48 hrs. 7.15 mg./100 ml.
 Baby Y Serum inorganic P at birth 6.4 mg./100 ml.
 " " " at end of 48 hrs. 7.7 mg./100 ml.

Discussion

The Osmolarity of the Urine. Dubs (1949) considered that the low osmolarity of the urine of dehydrated infants was due to a lack of electrolytes to be excreted. This suggestion runs counter to the work which has been done on osmotic diuresis and the secretion of urine in hydropenic adults, and it seems better at present to regard the volume of the urine in dehydrated infants (as in dehydrated adults) as being fixed by the amount of osmotically active material claiming excretion per unit of time and the concentrating power of the kidney. The latter seems to be relatively constant from one baby to another over the first two days of life whereas the former is extremely variable and the two of them together account for the relationships shown in Figs. 1 and 2. Hansen and Smith (1953) did not

recognize this relationship but they gave to eight of their infants 50 ml. and to one 100 ml. of water/kg. of body weight/day and this seems to have hydrated them enough to provide 'free' water for the kidneys to excrete. It did not, however, increase the excretion of nitrogen, sodium or potassium, at any rate in full-term babies. The problem at present seems to be to explain why the osmotically active material claiming excretion per minute should vary as it does from one baby to another whereas in this respect healthy young adults exhibit greater similarity among themselves. It may be the number of nephrons which have become functionally active by the time of birth, or it may be due to the influence of renal haemodynamics upon glomerular function as a whole (McCance and Widdowson, 1954a). There is little evidence at present to indicate whether the difference between one baby and another is due to a different rate of filtration through a similar number of glomeruli or the same rate of filtration through a different number of glomeruli—or even to a little bit of both. The last is perhaps the most probable. It is interesting that the excretion of osmotically active minerals by hydrated as well as by dehydrated infants appears to be higher if they are premature and oedematous than if they are full-term and normal (Smith *et al.*, 1949; Hansen and Smith, 1953) and it is reasonable to submit that in this we may be witnessing the maturation of that function of the kidney which controls the volume of the body fluids.

Partition of Solutes and Nitrogen in Urine. There is little to discuss in the contribution of the various solutes to the total osmolar concentration except the relationships of N and K. In commenting on the N/K ratios, Smith *et al.* (1949) pointed out that Gamble (1947) had noted that dehydration lowered the N/K ratio of adults and implied that this was enough to explain the low ratios found by them in infants. (To be correct, Smith *et al.* worked and wrote in terms of K/N ratios.) This would appear not to be the case because (1) even if dehydration does lower the N/K ratio in adults the ones who were dehydrated for the present investigation had an average N/K ratio of 8.5, still more than twice as high as those of the infants; (2) Hansen and Smith (1953) did not find that hydrating newborn infants sufficiently to increase considerably the volume of the urine altered the N/K ratio found in it. It is evident that the low N/K ratios in infants found in this investigation and by Smith *et al.* (1949) represent a real difference due to age and are not merely the result of dehydration. Apart altogether from the function of the kidney, one explanation is that the

bodies of newborn infants, as of other animals at birth, have a lower N/K ratio in them than those of adults (McCance and Widdowson, 1954b). If the results set out in Table 4 are to be regarded purely from the renal point of view, there are then three questions to be asked and answered. First, Why are the ratios relatively constant in spite of great fluctuations in the total amounts of N and of K excreted from one baby to another and in the same baby from time to time? This is really one aspect of the problem of why the urine should have such a fixed composition and why the excretion of the total milliosmols, nitrogen and urea should be so closely linked with the excretion of water (Table 2 and Figs. 1, 2 and 3). A single mechanism is likely to be responsible for the variations and the only probable one is glomerular filtration (and see above), with which the excretion of both the total N and the K are linked. Second, Why do the ratios rise appreciably on the second day? This is presumably due to the small rise in serum urea and non-protein nitrogen which took place during the first 48 hours of life and led to more nitrogen being excreted with each millilitre of glomerular filtrate. Evidence derived from the study of a few babies suggests that during this time the serum K tended to fall, not to rise. Third, Why are the ratios so much lower than those of adults? Table 5 gives the potassium : urea clearance ratios in the first urine passed after

clearance ratios of the infants given in Table 5 are higher than those of the adults. The conclusion may therefore be drawn that the N/K ratios are low because the infants extract less K than the adults from, or excrete more K into, each millilitre of their glomerular filtrates. Why they do so is not yet known but there is evidence that they probably reabsorb more Na and Cl than adults after the first few days of life (McCance, 1950).

Urea Clearances and Glomerular Filtration Rates.

The low clearances have been described and they require emphasis because within a week or two of birth hydrated and overhydrated infants have been found under test to have urea clearance and glomerular filtration rates equal to those of adults on the basis of body water (McCance *et al.*, 1954). Some stimulus must initiate this rapid development soon after birth, and operate in other newborn mammals, and it must be particularly effective in those like the rat which have such immature renal function at birth. This problem is under investigation.

The Excretion of Inorganic Phosphate. The excretion of P before and after birth was discussed by McCance and Widdowson (1953), and there seems no need at the moment to withdraw the suggestion made in that paper that the increase in excretion of P after birth was due to an increase of parathyroid activity at that time. It must be admitted, however, that the rise in serum P during the first 48 hours of life may be somewhat against this explanation. The present results on P excretion indicate that if the suggestion was correct the development of these glands took place at a different rate in each baby and that it did not depend, at all events entirely, on the introduction with the food of large amounts of phosphates into the system.

Summary

In the first two days of life, on a limited intake of water and no food, infants (1) excreted volumes of urine which averaged 13·8 ml./l. of body water/day as compared with average volumes excreted by hydropenic and starving adults of 16·7 ml./l. of body water per day; (2) passed urines with an average osmolar concentration of 420 milliosmols/l. as against 1,224 for urines passed by healthy adults; (3) made up the osmolar concentration of their urines in a similar way to adults except that the fraction due to potassium was higher; (4) had a ratio of nitrogen (in mg.)/potassium (in mg.) in the urine which averaged 3·4 (healthy adults similarly dehydrated and starved had a ratio of 8·5); (5) showed a close relation among themselves between the osmotically active material or

TABLE 5

AVERAGE RATIO OF POTASSIUM TO UREA CLEARANCES OF INFANTS MEASURED IN FIRST URINE PASSED AFTER BIRTH AND IN FIRST 24 HOURS OF LIFE COMPARED WITH CORRESPONDING RATIO FOR ADULTS SUBJECTED TO SIMILAR STARVATION AND HYDROPNIA

	Average	S.D.
<i>Infants</i>		
First urine passed after birth	0·221	0·113
First 24 hours of life	0·230	0·057
<i>Adults</i>		
Second day of dehydration	0·157	0·055

birth and during the first 24 hours of the infants' lives, and also in the urine of the adults during the second day of dehydration. Urea is not one of the substances which can be used for measuring the glomerular filtration rate, and it forms a somewhat smaller percentage of the total N in the urine of infants than it does in the urine of adults (Barlow and McCance, 1948). Nevertheless, the urea clearance probably bears much the same relationship to the glomerular filtration rate in the hydropenic infants after birth and in the adults (see above for the urea/creatinine clearance ratios and Table 5 of McCance and Widdowson, 1953). The potassium : urea

the total nitrogen excreted and the volume of the urine; (6) had low urea clearances and glomerular filtration rates. The former averaged 9.1 and 14.6 ml./42 litres of body water/min. on the first and second days whereas those of healthy young adults averaged 37.2 ml./min.; (7) excreted very little phosphate just after birth relative to adults and showed a tendency to increase the rate of excretion by the end of the second day.

REFERENCES

- Ambard, L. and Papin, E. (1909). *Arch. int. Physiol.*, 8, 437.
 Ames, R. G. (1953). *Pediatrics*, 12, 272.
 Barlow, A. and McCance, R. A. (1948). *Archives of Disease in Childhood*, 23, 225.
 Barnett, H. L. (1940). *Proc. Soc. exp. Biol., N.Y.*, 44, 654.
 —, Hare, K., McNamara, H. and Hare, R. (1948). *J. clin. Invest.*, 27, 691.
 Dean, R. F. A. and McCance, R. A. (1947). *J. Physiol., Lond.*, 106, 431.
 — (1948). *Ibid.*, 107, 182.
 — (1949). *Ibid.*, 109, 81.
 Dubs, E. J. (1949). *Amer. J. Dis. Child.*, 77, 114.
 Gamble, J. L. (1944). *Proc. Amer. phil. Soc.*, 88, 151.
 — (1947). *Chemical Anatomy, Physiology and Pathology of Extracellular Fluid*. Cambridge, Mass.
 Gordon, H. H., Harrison, H. E. and McNamara, H. (1942). *J. clin. Invest.*, 21, 499.
 Hansen, J. D. L. and Smith, C. A. (1953). *Pediatrics*, 12, 99.
 Ladell, W. S. S. (1947). *Brit. med. Bull.*, 5, 9.
 McCance, R. A. (1945). *J. Physiol., Lond.*, 104, 196.
 — (1950). *Amer. J. Med.*, 9, 229.
 —, Naylor, N. J. B. and Widdowson, E. M. (1954). *Archives of Disease in Childhood*, 29, 104.
 — and Widdowson, E. M. (1952). *Lancet*, 2, 860.
 — (1953). *Proc. roy. Soc. B*, 141, 488.
 — (1954a). *Archives of Disease in Childhood*, 29, 495.
 — (1954b). *Cold Spr. Harb. Symp. quant. Biol.* To be published.
 — and Young, W. F. (1941). *J. Physiol., Lond.*, 99, 265.
 McCrory, W. W., Forman, C. W., McNamara, H. and Barnett, H. L. (1952). *J. clin. Invest.*, 31, 357.
 Rapoport, S., Brodsky, W. A., West, C. D. and Mackler, B. (1949). *Amer. J. Physiol.*, 156, 433.
 Rubin, M. I., Bruck, E. and Rapoport, M. (1949). *J. clin. Invest.*, 28, 1144.
 Smith, C. A., Yudkin, S., Young, W., Minkowski, A. and Cushman, M. (1949). *Pediatrics*, 3, 34.
 Thomson, J. (1944). *Archives of Disease in Childhood*, 19, 169.
 — (1947). *Ibid.*, 22, 226.
 — (1949). *Ibid.*, 24, 180.
 Vesterdal, J. and Tudvad, F. (1949). *Acta paediat., Uppsala*, 37, 429.