# **JCI** The Journal of Clinical Investigation

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J Clin Invest. 1948;27(6):691-699. https://doi.org/10.1172/JCI102017.

Research Article



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### MEASUREMENT OF GLOMERULAR FILTRATION RATE IN PREMATURE INFANTS <sup>1, 2</sup>

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(Received for publication June 3, 1948)

#### INTRODUCTION

Our present knowledge of water and electrolyte metabolism in young infants is derived almost wholly from balance studies. The high degree of regulation described by such studies is effected by renal mechanisms which we are attempting to define. In any study of kidney function it is necessary to select certain criteria for evaluating the observed data. In young premature infants, this problem of selection is made difficult by the possibility that the substances commonly followed in adult studies may be handled differently either by the immature kidney as such or by the immature organism as a whole. The urea clearance is probably the criterion most often employed in clinical studies of the adult subject. Its use and significance in the infant are less well established. Some studies (1,2) have suggested that the urea clearance in infants, as in adults, is dependent on urine flow; others (3, 4) have claimed that the two values are independent in infants, and that this represents a functional difference between the immature and the mature kidney.

Another, and perhaps more useful criterion in adult studies has been the clearance of inulin, now well established as a measure of glomerular filtration. There is little information about the clearance of inulin in the infant; it has been suggested that in infants this clearance, although independent of the plasma level of inulin, as in the adult, differs in that it is dependent on rate of urine flow (1, 5).

We considered that simultaneous clearances of inulin and urea at various rates of urine flow would serve not only to establish a criterion of kidney function in the infants, but might help in the interpretation of previous work where only urea was studied. If inulin clearances measure glomerular filtration rate in the young infant, such studies would in addition yield information on the renal mechanism for water excretion.

#### METHODS

Clearances were measured in 21 well, female, premature infants, aged three to 28 days, whose birth weights ranged from 1740 to 2480 Gm. and whose weights at the times of observation were 2060 to 2400 Gm. Their surface areas, calculated by the formula  $5.188 \times Wt$ .<sup>75</sup> (6), were 0.163 to 0.178 sq. M. A minimum of four and a maximum of 21 clearance periods were measured in any one infant. All observations were made in the air-conditioned metabolism unit in which the temperature and humidity were maintained at 26° C. and 60 per cent respectively.

Low rates of urine flow were produced by withholding feedings and water for varying periods of time up to 12 hours, and by using single injections of inulin rather than a continuous infusion. High urine flows were produced by giving water and feedings by mouth or by the intravenous infusion of 25 per cent mannitol, 0.9 per cent NaCl, 5 or 10 per cent dextrose, singly or in combination. Tables I and Ia show the protocols and data for clearances done on falling plasma levels after single or repeated injections. Table Ib includes similar data for clearances done using the usual priming and sustaining technic (7).

Urine was collected through an indwelling catheter, and the bladder was completely emptied by blowing out with air. The largest multi-holed soft rubber catheter that could be introduced with very slight pressure, usually a size 10 or 12 French catheter, was used and no leakage was observed even during periods of marked straining. Twenty thousand units of penicillin were given intramuscularly immediately and 12 hours after each clearance study. There was never any evidence of local tissue reaction or bladder infection from the catheterization.

In the earlier observations, the urine was collected in 10- or 25-ml. graduated cylinders calibrated in 0.1 or 0.2 ml., and the volumes read directly. Later, the urine was

<sup>&</sup>lt;sup>1</sup> Aided by a grant from the U. S. Public Health Service. Mannitol and para-aminohippurate were supplied by Sharp & Dohme. Inc.

<sup>&</sup>lt;sup>2</sup> Presented in part before the American Physiological Society, Atlantic City, N. J., March 19, 1948 (Fed. Proc., 1948, 7, 5), and before the Society for Pediatric Research, Atlantic City, N. J., May 4, 1948.

|   |  |   | T                           | NULIN                            | UREA N  |   | ENGLIN          |   |   |   | INGUIN  |   | UREA H   |  | DRILLIN   |
|---|--|---|-----------------------------|----------------------------------|---|---|-----------------|---|---|---|---|---|--|--|---|
| Subject   | Total<br>time  | Urine<br>Vol.   | Plasma<br>conc.             | Clearance                        | Plasma<br>conc.   | Clearance   | <sup>0</sup> /p | Subject   | Total<br>time   | Urine<br>Vol.   | Plasma<br>conc.   | Clearance   | Plasma<br>conc.  | Clearance  | U/p   |
| RE*<br>Age 4 days<br>Wt. 2208 Gm.<br>Ht<br>S.A167M <sup>2</sup>         | 0-90<br>90-124<br>131<br>124-153<br>153-209<br>209-263<br>294<br>263-335<br>335-390<br>390-448 | .013<br>.103<br>.103<br>.224<br>.218<br>.289<br>.33<br>.264<br>.102<br>.345 | etion of a                  | Mannitol in<br>Dextrose in       | .100<br>.107<br>travenou<br>.111<br>.112<br>.110<br>travenou<br>.116<br>.122<br>.122    | 0.12<br>1.01<br>sly<br>1.33<br>1.59<br>1.99<br>sly<br>2.09<br>0.87<br>1.68  |                 | ML<br>Age 8 days<br>Wt. 2250 Cm.<br>Ht<br>S.A170M <sup>2</sup>              | 0-42<br>42-57<br>71<br>57-105<br>105-145<br>145-177<br>177-213<br>213-276<br>283<br>276-312   | .086<br>•355<br>Inje<br>.069<br>.108<br>.153<br>•089<br>•033<br>Injec                                 | ction of<br>.552<br>.422<br>.351<br>.278<br>tion of I   | Inulin intr<br>6.27<br>4.15<br>3.22<br>3.92<br>nulin intro  | .168<br>.168<br>.168<br>.168<br>.168<br>.168<br>.168<br>.168                       | 2.29<br>3.26<br>1.37<br>3.10<br>2.61<br>1.66<br>0.97<br>1.62                                       | 58.0<br>27.1<br>36.2<br>118.8   |
| FA<br>Age 4 days<br>Wt. 2226 Cm.<br>Ht. 46 cm.<br>S.A1698 <sup>2</sup>  | 0-60<br>60-121<br>162<br>121-186<br>186-242<br>278<br>242-296<br>296-343<br>343-404<br>404-460 | .047<br>.246<br>Inje<br>.172<br>.093<br>.23<br>.089<br>.245<br>.082<br>.214 | iction of<br>1<br>1. of 10% | Mannitol im<br> <br>  Dextrose 1 | .133<br>.150<br>htravenou<br>.148<br>.147<br>intravenou<br>.145<br>.136<br>.130<br>.127 | 2.37<br>3.16<br>sly<br>2.13<br>1.98<br>wsly<br>2.12<br>3.42<br>1.92<br>2.87 | <br> <br>       |   | 312-327<br>327-365<br>365-422<br>422-481<br>528<br>481-555<br>555-594<br>594-608<br>608-622<br>622-635<br>635-668<br>668-693<br>693-723                   | .086<br>.046<br>.046<br>.032<br>Inje<br>.136<br>.162<br>.743<br>1.030<br>.831<br>.158<br>.076<br>.088 | .507<br>.422<br>.322<br>.237<br>oction of<br>.408<br>.316<br>.289<br>.266<br>.216<br>.203<br>.180 | 7.32<br>4.48<br>4.01<br>4.09<br>Wannitol au<br>5.15<br>5.95<br>5.95<br>5.93<br>4.77<br>2.92<br>4.88<br>5.33 | .168<br>.168<br>.168<br>.168<br>.168<br>.168<br>.168<br>.168                       | 2.97<br>1.38<br>1.05<br>intravenou<br>2.18<br>3.22<br>3.98<br>3.54<br>2.91<br>1.16<br>1.81<br>2.56 | 85,1<br>67,9<br>67,1<br>127,9<br>sly<br>31.8<br>6.0<br>5.2<br>5.8<br>18,5<br>64,2<br>60,6 |
| CU+<br>Age 4 days<br>Wt. 2340 Gm.<br>Ht. 46 cm.<br>S.A174M <sup>2</sup> | 0-45<br>45-81<br>0-49<br>49-94<br>94-148<br>148-284<br>284-337                                 | .049<br>-986<br>.114<br>.093<br>.081<br>.054<br>.059                        | iction of                   | VañnItöl <sup>-</sup> iř         | .085<br>.085<br>.095<br>.097<br>.097<br>.096<br>.095<br>.093                            | 0.63<br>1.92 -<br>1.96<br>2.03<br>1.65<br>0.95<br>0.91                      | <u> </u>        | MR<br>Age 10 days<br>Wt. 2200 Gm.<br>Ht. 46 cm.<br>S.A 16711 <sup>2</sup>   | 0-58<br>58-114<br>124<br>114-172<br>172-236<br>236-298<br>298-344<br>368  | .038<br>.041<br>Inje<br>.043<br>.042<br>.035<br>.046<br>Inje  | ection of   | Inulin int:<br>Kannitol an  | .207<br>.207<br>revenousl;<br>.208<br>.212<br>.217<br>.215<br>nd Inulin            | 0.81<br>0.95<br>0.87<br>0.92<br>0.67<br>0.87<br>intravenou   | <br> <br>   |
| ST<br>Age 5 days<br>Wt. 2280 Gm.<br>Ht. 44 cm.<br>S.A171M <sup>2</sup>  | 0-85<br><u>85-114</u><br>0-41<br>41-96<br>96-162<br>162-208<br>216<br>208-280                  | .034<br>-145<br>.173<br>.211<br>.082<br>.074<br>.228                        | 1. of 0.9                   | Mañnītō1-ir<br>% NaCl inti       | .181<br>.181<br>.245<br>.246<br>.247<br>.252<br>ravenousl                               | 0.57<br>2.08<br>1.45<br>2.26<br>0.97<br>1.12                                | <br>            |   | 418-452<br>452-472<br>472-485<br>485-497<br>497-510<br>510-541<br>541-572<br>572-596  | .104<br>.208<br>.715<br>.800<br>.723<br>.165<br>.284<br>.233  |   |   | .211<br>.209<br>.209<br>.208<br>.208<br>.208<br>.207<br>.206<br>.205               | 1.75<br>4.03<br>4.24<br>3.35<br>4.05<br>1.49<br>2.66<br>2.24                                       |   |
|   | 280-329  | • Neg<br>• Twi<br>•• Cor  | ro<br>n<br>strol peri       | ods on pred                      | .280<br>ceding de   | <b>3</b> .15  | <u> </u>        | BG "A"<br>Age 11 days<br>Wt. 2400 Gm.<br>Ht. 45 cm.<br>S.A176M <sup>2</sup> | $\begin{array}{r} - \underbrace{0-60}{0-47} \\ 47-107 \\ 147 \\ 157 \\ 107-227 \\ 234 \\ 227-284 \\ 284-315 \\ 315-349 \\ 349-408 \\ 408-457 \end{array}$ | - 143<br>- 160<br>- 208<br>Imj<br>- 48<br>- 311<br>- 24<br>- 274<br>- 400<br>- 170<br>- 229<br>- 531  |   | Mannitol i<br>Macl sub<br>NaCl sub  | 2217<br>-225<br>-222<br>ntravenous<br>-218<br>-218<br>-206<br>-205<br>-212<br>-225 | 2.59<br>2.50<br>2.96<br>sly<br>1<br>3.75<br>1<br>3.01<br>3.26<br>2.69<br>3.52                      |   |

TABLE I ' Protocols and data on urea and inulin clearances in premature infants

3.0 ml. of 10 per cent inulin or 2.0 ml. of 25 per cent mannitol per kilogram body weight were injected the first time either substance was given. Subsequent injections of inulin consisted of 1.5 ml. of a 10 per cent solution per kilogram body weight.

allowed to drain into 50-ml. volumetric flasks, diluted to the mark from a 50-ml. burette and the urine volume calculated by difference. The latter method is more accurate and the immediate dilution of the sample prevents precipitation of inulin or mannitol.

The large scalp veins were found most convenient for drawing blood samples for analysis, since the desired 2 ml. could be obtained without interfering with the infusion. The plasma was separated and the proteins precipitated within two hours.

The dosage of inulin, mannitol and para-aminohippurate (PAH) for individual infants was calculated on the basis of weight and expected clearance. When low urine flows were desired, single injections were used, and the clearances measured during the fall in plasma concentration. When a constant infusion was given, the concentration of the substances in the infusion fluid was varied; the total volume and rate of infusion were the same. The infusion was given through a 22-gauge needle into an ankle, foot or hand vein. The rate was controlled by a Shannon-Bradley clamp<sup>3</sup> and measured by a pipette-manometer

<sup>3</sup> Available from The Harvard Apparatus Co., Inc., Dover, Mass. arrangement suggested by White and Findley (8). Figure 1 shows that when the rubber tubing is clamped at B, the rate of fall of the fluid in A, a graduated 5-ml. pipette, may be timed and the rate of infusion regulated by adjustment of the tunnel clamp at F. After calibration with the manometer, the rate of infusion may be estimated in the usual manner by counting drops per unit time at the drip-bulb, C, which also permits observation of the course of the infusion. The T-tube at E allows rapid drainage for replacement of the infusion solution. A filter is inserted at D.

Chemical methods. Mannitol was determined in plasma and urine by the method of Corcoran and Page (9); inulin by a modification <sup>4</sup> of the method of Hubbard and Loomis (11); and para-aminohippurate by the method of Marshall as described by Goldring and Chasis (7). Urea was determined by the micro-diffusion method of Conway (12), and clearances of NH<sub>3</sub> plus urea were calculated. In some cases, urea was also determined by the method of Archibald (13), and the clearances calculated from

<sup>4</sup> The acid mixture used by Harrison (10) for the hydrolysis of inulin was substituted for the acid-alcohol mixture employed by Hubbard and Loomis.

|   | ľ   |  |  | INULIN   | σ  | REA N   | INDLIN  |  | 1   |  |  | INULIN  | 07   | BA H   | DULTH  |
|---|---|--|--|--|--|---|---|--|---|--|--|---|--|--|--|
| Subject   | Total<br>time<br>(min.)   | Urine<br>vol.<br>sl./sin.  | Plasma<br>conc.<br>mg./ml.   | Clearance<br>ml./min.  | Plasma<br>conc.<br>mg./ml.   | Clearance<br>ml./min.   | U/ p.   | Subject  | Total<br>time<br>(min.)   | Urine<br>vol.<br>ml./min.  | Plasma<br>conc.<br>mg./ml.   | Clearance<br>ml./min.   | Plasma<br>conc.<br>mg./ml.   | Clearance<br>ml./min.  | U/p  |
| SW<br>Age 13 days<br>Wt. 2320 Ga.<br>Ht<br>S.A173M <sup>2</sup>         | 0-48<br>48-7]-<br>11<br>0-35<br>52-96<br>143<br>96-156<br>156-216<br>216-262  | .050<br>-066<br>Inje<br>.143<br>.209<br>42<br>.143<br>.128<br>.248                                   | ction of<br>1. of 0.9  | WannItōl Ir<br>K NaCl subc   | .221<br>.221<br>.234<br>.233<br>.232<br>.236<br>.236<br>.241   | 1.56<br>2.27<br>31y<br>1.32<br>2.46<br>1y<br>1.45<br>2.46<br>2.77                                   | <br> <br>   | MA<br>Age 21 days<br>Wt. 2140 Gm.<br>Ht. 45 cm.<br>S.A163M <sup>2</sup>        | <b>8-</b> 57<br>57-92<br>15<br>0-35<br>35-83<br>83-145<br>145-209<br>209-268<br>268-325   | .337<br>- 1544<br>.203<br>.131<br>.144<br>.117<br>.082<br>.105   | ētīon ōr   | Mannîi€oI an  | .210<br>.210<br>J NaSCH<br>.211<br>.211<br>.215<br>.206<br>.199<br>.206                                  | 2.84<br>2.98<br>1.78************************************   | ••••<br>17   |
| ST<br>Age 13 days<br>Wt. 2380 Gm.<br>Ht<br>S.A177m <sup>2</sup>         | 0-59<br>59-94_<br>16<br>0-39<br>39-89<br>89-152<br>152-209<br>209-260<br>260-308  | .051<br>   | ction of   | iannītō1 <sup>-</sup> 1r   | .238<br>.238<br>.238<br>.236<br>.227<br>.215<br>.220<br>.225<br>.214                                 | 1.53<br>1.46<br>51y<br>0.63<br>0.89<br>2.70<br>3.86<br>2.66<br>2.66                                 |   | EE<br>Age 21 days<br>Wf. 2240 Gm.<br>Ht. 47 cm.<br>SA169M <sup>2</sup>         | 0-19<br>30<br>19-82<br>82-108<br>108-138<br>138-162<br>162-209<br>209-246<br>252<br>246-302   | .059<br>103<br>.103<br>.132<br>.210<br>.063<br>.088<br>.142<br>Inje<br>.064  | ction of<br>.470<br>.350<br>.300<br>.260<br>.228<br>ction of   | Inulin intr<br>6.02<br>5.20<br>4.10<br>6.15<br>4.43<br>Inulin intr  | .256<br>avenous)<br>.253<br>.248<br>.245<br>.245<br>.242<br>.238<br>.234<br>avenous)<br>.230             | 1.54<br>2.26<br>2.89<br>2.95<br>1.24<br>2.38<br>2.55<br>1.62   | 45.5<br>24.9<br>66.7<br>70.0<br>31.1   |
| GR<br>Age 18 days<br>We. 2370 Gm.<br>Ht. 48 cm.<br>3.A176M <sup>2</sup> | 0-42<br>42-84<br>84-126<br>126-168<br>168-210<br>0-33<br>38-71<br>71-104<br>104-132<br>141<br>132-189<br>189-249<br>249-309<br>249-309  | 28 29 29 20 20 20 20 20 20 20 20 20 20 20 20 20  | ction of<br>. 368<br>. 254   | Inulin intr<br>3.99<br>4.25<br>3.49  | .243<br>.243<br>.243<br>.243<br>.239<br>.239<br>.239<br>.239<br>.239<br>.239<br>.239<br>.23          | 3.52<br>0.85<br>1.26<br>1.78<br>-0.94<br>2.84<br>2.10<br>2.73<br>1.80<br>1.72<br>2.02               | •••<br>   |  | 302-338<br>338-405<br>405-450<br>450-494<br>494-527<br>539<br>527-578<br>572-598<br>598-612<br>625-645<br>645-671<br>671-714<br>714-741 | 578<br>051<br>052<br>044<br>051<br>103<br>208<br>500<br>500<br>500<br>500<br>500<br>500<br>500<br>500<br>500<br>5  | .420<br>.310<br>.237<br>.195<br>.165<br>ction of<br>.320<br>.326<br>.320<br>.292<br>.254<br>.230<br>.190<br>.158 | 5.12<br>4.06<br>3.97<br>3.85<br>5.27<br>Mannitol an<br>4.92<br>5.84<br>4.83<br>4.70<br>5.00<br>4.68<br>4.30 | .227<br>.223<br>.219<br>.212<br>.208<br>d Inulin<br>.201<br>.199<br>.198<br>.195<br>.195<br>.195<br>.192 | 2.04<br>1.41<br>1.59<br>1.43<br>2.07<br>intrevence<br>3.22<br>3.00<br>4.12<br>3.59<br>3.08<br>3.22<br>2.96<br>2.54 | 65.7<br>776.2<br>817<br>23.6<br>11.8<br>23.6<br>21.0<br>21.0<br>21.0<br>21.0<br>22.5<br>32.5<br>32.3 |
|   | 5077426<br>426-507<br>507-535<br>507-535<br>507-535<br>507-535<br>507-535<br>505-601  | Inje<br>.100<br>.135<br>.121<br>.121<br>.175<br>.090<br>.219   | .321<br>.240<br>.190<br>.154<br>.122   | Mannitol an<br>4.02<br>4.21<br>4.11<br>3.25<br>4.76  | id Inulin<br>.216<br>.215<br>.218<br>.221<br>.224<br>.228  | intravenous<br>2.30<br>2.93<br>2.91<br>3.35<br>1.91<br>3.03   | 1y<br>76.5<br>29.5<br>34.4<br>23.2<br>35.3<br>21.3                | BO "B" **<br>Age 23 days<br>Wt. 2060 Gm.<br>Ht. 46 cm.<br>S.A159M <sup>2</sup> | 36<br>0-57<br>57-115<br>115-173<br>173-230<br>230-287   | Inje<br>.109<br>.066<br>.278<br>.305<br>.151   | ction of   | Mannitol in   | travenou<br>.238<br>.242<br>.229<br>.214<br>.215   | 2.15<br>0.78<br>2.79<br>3.07<br>1.67   |  |
| čo<br>Ago 19 days<br>Wt. 2260 Gm.<br>Ht. 45 Gm.<br>S.A17082             | 0-36<br>52<br>98-158<br>158-228<br>98-158<br>158-280<br>20-352<br>20-352<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-355<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-40<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475<br>20-475 | .042<br>Inje<br>.058<br>.040<br>.040<br>Inje<br>.089<br>.040<br>.085<br>.117<br>.300<br>.505<br>.200 | ction of<br>.582<br>.420<br>.343<br>ction of 1<br>.546<br>.446<br>.389<br>.350<br>.312 | Inulin intr<br>3.73<br>3.37<br>3.34<br>Mannitol an<br>2.93<br>5.17<br>4.30<br>4.31<br>3.94 | .221<br>.219<br>.216<br>.216<br>.216<br>.216<br>.216<br>.211<br>.241<br>.241<br>.241<br>.241<br>.241 | 0.77<br>1.93<br>1.73<br>1.35<br>1.58<br>intravenous<br>1.88<br>1.48<br>1.48<br>3.71<br>3.18<br>2.44 | 64.3<br>84.3<br>83.4<br>1y<br>34.4<br>44.2<br>16.3<br>8.5<br>19.7 | KE<br>Age 28 days<br>Wt. 2300 Cm.<br>Ht<br>S.A177m <sup>2</sup>                | 0-30<br>60<br>30-64<br>64-115<br>155-150<br>150-181<br>181-209<br>209-241<br>241-271<br>271-285<br>285-300                              | .044<br>1.53<br>2339<br>.671<br>2555<br>.3255<br>.116<br>.2555<br>.3255<br>.116<br>.2555<br>.2255<br>.116<br>.2555<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2255<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.2355<br>.23555<br>.23555<br>.23555<br>.23555<br>.23555<br>.23555<br>.23555<br>.235555<br>.235555<br>.23555<br>.235555<br>.2355555<br>.2355555555<br>.235555555555 | ction of<br>.456<br>.343<br>.282<br>.232<br>.196<br>.173<br>.160   | Mannitol an<br>4.84<br>6.52<br>5.38<br>3.59<br>6.33<br>6.33<br>6.20<br>5.45                                 | .168<br>d Inulin<br>.167<br>.163<br>.160<br>.157<br>.156<br>.154<br>.151<br>.151                         | 1.20<br>intrevence<br>3.73<br>4.03<br>2.67<br>4.39<br>3.19<br>2.39<br>3.69<br>3.69<br>3.69<br>3.69<br>3.70         | ely<br>23.5<br>18.4<br>23.9<br>31.0<br>23.7<br>23.7  |
|   | 472-491   | .153   | 280  | 3.85   | .241   | 2.45  | 25.2  |  | ••  | Twin<br>Control  | periods  | on precedin   | g day  |  |  |

TABLE IA

these values agreed well with those of the Conway method. No preservatives were used in the urine. In the few instances in which determinations were not done on the day of collection, the sterile catheterized samples were stored in the refrigerator in sterile flasks. Determinations on samples stored in this way showed no change from the original value within 24 hours.

All determinations were done in duplicate, and usually required a total of 1 ml. of plasma. When colorimetric methods were used, a calibration curve was run with each group of unknowns and reagent blanks were used for center settings.

Pre-injection samples of plasma and urine were used for blank determinations in all clearances; the urine blanks were calculated and subtracted as milligrams per minute to allow for variations in the rate of urine flow. The values for plasma concentrations of all substances were plotted on the logarithmic scale against time on the linear scale of semi-logarithm paper. The plasma concentrations interpolated at the mid-points of the periods were used in the calculation of the clearances. All clearances were calculated as UV/P. Since the relation of the clearances in young infants to surface area, body weight, metabolic rate, age or other standards of reference has not been fully established, we have presented only the uncorrected values.

#### RESULTS

Values for 229 urea clearances and 110 inulin clearances with rates of urine flow in 23 series of observations on 21 subjects are given in Table I. Graphic analyses of these data are shown in Figures 2, 3, 4 and 5. In Figure 2, the influence of urine flow on urea and inulin clearances is shown. At urine flows below 0.1 ml. per minute the urea clearances were less than 3.0 ml. per minute and were markedly below the inulin clearances so that the symbols representing the two separate completely. At urine flows above 0.4 ml. per minute, on the other hand, there was considerable overlapping. Analysis of the data from only those periods when simultaneous inulin and urea clearances were measured is shown in Figure 3. Here, a slight increase in inulin clearance with increasing

| Subject                              | Potel              |               | Places         | NULIW               | UR                | SA N                | INULIN      |                                      |                    | min           | I         | NULIN               | UR                | BA N                | INULIN        |
|--------------------------------------|--------------------|---------------|----------------|---------------------|-------------------|---------------------|-------------|--------------------------------------|--------------------|---------------|-----------|---------------------|-------------------|---------------------|---------------|
|                                      | time (min.)        | vol.          | conc.          | m1./m1n.            | cone.             | ml./min.            | •′′P        | Subject                              | time               | vol.          | cone.     |                     | conc.             | -1 /-t-             | "P            |
|                                      | 0 (0               |               |                |                     |                   |                     |             |                                      |                    |               |           |                     |                   |                     |               |
| BA A                                 | 64                 | Print         | i<br>.ng and s | ustaining i         | nfusion           | of N-In-PAH         | 1           |                                      | 39                 | -U54<br>Prist | Ing and s | ustaining i         | .216<br>Infusion  | of M-In-PAN         | (             |
| Wt. 2130 Gm.                         | 60-90<br>90-110    | .082          |                | 1                   | .139              | 1.56                | í –         | Age 12 days<br>Wt. 2320 Gm.          | 37-70              | .167          | .506      | 5.87                | .209              | 1 3.41              | 17.3          |
| Ht. 46 cm.<br>8.A163M <sup>2</sup>   | 110-130            | .050<br>.076  | . 190          | 2.77                | .128              | 0.92                | 36.4        | Ht. 47 cm.<br>S.A. 173M <sup>2</sup> | 84-98<br>98-112    | 1.086         | 488       | 2.11                | .201              | 5.15                | 1 11.1        |
|                                      | 150-170            | .213          | 408            | 3.68                | .120              | 2.35                | 17.3        |                                      | 116                | Tn P1         | ining an  | d sustainin         | infusi            | on of PAR           | 11 C          |
|                                      | 203                | Ta Pr         | ining an       | d sustainin         | e infusi          | on of PAH a         | dded        | 1                                    | 144-158            | .412          | .459      | 6.97                | .180              | 4.48                | 16.9          |
|                                      | 220-240            | -355          | .521           | 3.45                | .110              | 2.47                | 2.7         |                                      | 172-186            | .695          | .443      | 7.04                | 1:171             | 3:12                | 10:1          |
|                                      | 260-270            | .276          | .538           | 4.96                | .107              | 1.72                | 18.0        |                                      |                    |               |           |                     |                   | <u> </u>            |               |
| _                                    |                    |               |                |                     |                   |                     |             |                                      | 68                 | Prisi         | ing and s | ustaining 1         | infusion          | of N-In-PAL         | ľ             |
| 00                                   | 31                 | .014<br>Prisi | ing and s      | ustaining i         | nfusion (         | of M-In-PAH         |             | Wt. 2190 Cm.                         | 30-00<br>88-108    | .305          | .687      | 4.35                | .266              | 3.37                | 14.3          |
| Mt. 2276 Gm.                         | 28-60<br>60-74     | .139<br>.179  | .469           | 4.03                | 1                 |                     | 4.0         | Ht. 46 cm.<br>8.A166M <sup>2</sup>   | 108-125 125-140    | .616<br>.570  | .640      | 4.14                | .260<br>.254      | 3.2                 | 9:7           |
| Et. 46 cm.<br>8.A17182               | 74-88<br>88-102    | .244          | .453           | 6.34<br>5.83        |                   |                     | 5.8         |                                      | 150<br>140-170     | .311          | iming an  | d sustainir<br>3.94 | g infusi          | on of PAN (<br>2.87 | 14ded<br>12.7 |
|                                      | 114                | Ta Pr         | ising an       | d sustainin<br>4.91 | g infusi          | on of PAH a         | dded 4.9    |                                      | 170-184            | .311          | .581      | 3.32                | .242              | 2.67                | 10.7          |
|                                      | 148-162            | .546          | .424           | 5.66                |                   |                     | 2.7         |                                      | 198-212            | .648          | . 588     | 4.35                | .242              | 3.91                | 6.7           |
|                                      | 176-190            | 1.130         | .424           | 5.54                |                   |                     | 5.5         | 80                                   | 0-67               | 195           |           |                     | 224               | 1.44                |               |
|                                      | 0.11               | 100           |                |                     | 200               | 2.82                |             |                                      | 104                | Primi         | ing and s | ustaining i         | infusion          | of H-In-PAI         | t i           |
|                                      | 78                 | Print         | ing and s      | ustaining i         | nfusion           | of M-In-PAH         |             | Wt. 2164 Cm.                         | 133-153            | .290          | .476      | 4.28                | .212              | 3.05                | 14.8          |
| Wt. 2380 0m.                         | 31-100<br>100-116  | .080          | .637           | 4.73                | 194               | 1.60                | 19.4        | S.A165M <sup>2</sup>                 | 153-167<br>167-185 | .010          | .400      | 4.70                | .200              | 2.28                | 12.3          |
| Ht. 47.5 cm.<br>8.A177M <sup>2</sup> | 116-130<br>130-140 | .463<br>.538  | .605           | 5.11                | .186              | 4.19                | 11.0        |                                      | 185-201 201-213    | .400<br>.500  | .430      | 5.20<br>4.18        | .195              | 3.66                | 13.0<br>8,4   |
|                                      | 140-149<br>156     | •433<br>7m Pi | .564           | 3.99<br>d sustainin | .183<br>g infusio | 3.07<br>on of PAE a | 9.2<br>dded |                                      |                    |               |           |                     |                   |                     |               |
| 1                                    | 149-177            | .243          | .530           | 3.77                | .178              | 2,50                | 15.5        | PA                                   | 0-20<br>42         | .130<br>Primi | ining and | sustaining          | .216<br>1 infusio | 2.02<br>n of In-PA  |               |
|                                      | 194-205            | .391          | .488           | 2.33                | .166              | 4.23                | 13.6        | Age 13 days                          | 20-60              | .103          | .629      | 2.26                | .214              | 1.41                | 24.5          |
|                                      |                    |               |                |                     |                   |                     |             | Ht                                   | 80-100             | .153          | .626      | 3.69                | .208              | 2.46                | 24.1          |
| 61 mBa ee                            | 0-46               | .116          |                |                     | .194              | 1.98                | ļ           |                                      | 126                | Prim:         | ing and s | ustaining i         | infusion          | of M                | 18.1          |
| Age 9 days                           | 46-86              | - 296         |                | 1 <u>4</u> 1 1      | .194              | 3.21                |             |                                      | 150-172            | .194          | .607      | 3.38                | .195              | 2.40                | 17.4          |
| It. 47 cm.                           | 100-114            | .218          | .410           | 5.95                | :131              | 3.48                | 27.3        |                                      | 184-196            | .355          | .629      | 3.74                | 168               | 3.13                | 10.6          |
| 9.4TOOM.                             | 139                | TE PI         | iming an       | d sustainin         | g infusi          | on of PAH a         | dded        |                                      |                    |               |           |                     |                   | <b>.</b>            |               |
|                                      | 126-160            | .401          | .431           | 3.55                | 189               | 3.66                | 11.9        |                                      |                    |               | •• Twin   |                     |                   |                     |               |
|                                      | 174-188 188-202    | -432<br>-507  | .414           | 5.15                | 186               | 3.68<br>3.64        | 11.9        | 1                                    |                    |               |           |                     |                   |                     |               |
| 1                                    |                    |               |                | 1                   | 1                 | -                   |             | I .                                  |                    |               |           |                     |                   |                     |               |

TABLE 1b Protocols and data on urea and insulin clearances in premature infants

Priming injections consisted of 2.0 ml. of 10 per cent inulin, 1.0 ml. of 25 per cent mannitol, and 0.025 ml. of 20 per cent para-aminohippurate per kilogram body weight. Sustaining infusions were given at the rate of 0.5 ml. per minute and the concentrations of the substances varied on the basis of expected plasma levels and clearances.

rate of urine flow becomes apparent; but for a given increase in urine flow, particularly at low rates, the urea clearances increased much more than the inulin clearances.

In most instances the course of a diuresis was followed until the urine flow returned to the original rate; four examples are shown in Figure 4. In one, the urea clearance was higher during periods of increasing urine flow than during periods of decreasing flow when the rates were the same. This is the effect found by Shannon (14) in the dog and by Chasis and Smith (15), in man. The other three examples, which are more representative, showed no such relationship.

The foregoing analyses have considered only the excretion of water and urea. Figure 5 shows the relationship of urea reabsorption expressed by the urea/inulin clearance ratio to water reabsorption expressed by the inulin U/P ratio (14). That there is a high degree of correlation between the

reabsorption of these substances is obvious, as was the correlation between their excretions shown in Figure 4. A similar relationship between the tubular reabsorption of urea and of water has been described in normal adult human subjects and in patients with glomerulonephritis and with hypertensive disease (15). The relationships in the various groups of subjects, while similar, are not identical; in fact, the data from the premature infants are more comparable to those from patients with glomerulonephritis or hypertensive disease, and are decidedly different from those from normal adults. A possible interpretation is that there is a back-diffusion or reabsorption of inulin in premature infants. This explanation seems unlikely because a constant clearance of inulin may be maintained in the presence of wide variations in water reabsorption. Furthermore, the mannitol/inulin clearance ratio is the same as in adult subjects in whom inulin is certainly a measure of glomerular





A, a 5-ml. Mohr pipette; B, rubber tubing from reservoir; C, drip-bulb; D, filter; E, side-arm for draining reservoir; F, Shannon-Bradley tunnel clamp.

filtration. Berger, *et al.* (16), have found that the infusion of mannitol depresses the clearance of inulin in adults; Table II shows that in our observations on infants no such effect was observed. There are two factors, however, which may account for the difference in the two series: the difference in age of the subjects and the fact that the plasma levels of mannitol in the infants were around 50 mg. per 100 ml., whereas in the adults they were usually between 125 and 150 mg. per 100 ml. (17).

#### TABLE II

Inulin clearances before and after administration of mannitol

|                           | INULIN CLEARANCES*            |                             |  |  |  |  |  |  |  |
|---------------------------|-------------------------------|-----------------------------|--|--|--|--|--|--|--|
|                           | PRIOR TO MANNITOL<br>INFUSION | DURING MANNITOL<br>INFUSION |  |  |  |  |  |  |  |
| MEAN VALUE<br>ML./MIN.    | 4.33                          | 4.47                        |  |  |  |  |  |  |  |
| NUMBER OF<br>OBSERVATIONS | 27                            | 28                          |  |  |  |  |  |  |  |
| NUMBER OF<br>SUBJECTS     | 5                             | 5                           |  |  |  |  |  |  |  |

\* AGE 8-21 Days Wt. 2164-2400 Gm. S.A. 0.165-0.178 M<sup>2</sup>



FIG. 2. Absolute Values for Urea and Inulin Clearances in Premature Infants Plotted against Rates of Urine Flow

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The clearance of any substance excreted solely by glomerular filtration should be (a) independent of plasma concentration: (b) independent of urine flow: (c) not influenced by the excretion of any known substance: (d) identical with that of other substances known to measure glomerular filtration. The clearance of inulin in these premature infants satisfies the first three of these criteria: it is independent of plasma concentrations from 12 to 68 mg. per 100 ml.; it is independent of rates of urine flow from .032 to 1.13 ml. per minute; it is not influenced by any substance used in these studies, i.e., glucose, mannitol or PAH. The direct comparison of inulin clearance with any established measure of glomerular filtration in the infant is impossible, since no substance has been proved to measure glomerular filtration in the infant. However, the average mannitol/inulin clearance ratio in these infants is 0.883 which is almost identical with that of 0.902 found by Corcoran and Page for adults, in whom inulin is a proved measure of glomerular filtration. Inulin is, therefore, probably excreted solely by the glomerulus in infants.

The inulin clearance in premature infants is low compared to that of adults, not only as an absolute value but when expressed in terms of surface area. The average clearance for this group of premature infants corrected for surface area is less than 50 ml. per 1.73 sq. M, whereas the average value is 117 ml. (7) for the adult female. This low rate of glomerular filtration in young infants has been observed previously (1, 4, 5, 18–20)

It is obvious from the preceding data that the clearance of inulin is a valuable aid in studying the kidney function of premature infants. On the other hand, urea clearance alone is without meaning; it can be interpreted only when glomerular filtration is known. This is because it is de-



FIG. 3. CHANGES IN INULIN AND UREA CLEARANCES WITH CHANGES IN RATE OF URINE FLOW IN PREMATURE INFANTS

These data were calculated from 100 periods during which inulin and urea clearances were measured simultaneously. Each point represents an average of ten periods. The clearances are expressed as per cent of the average clearance at the highest average rate of urine flow observed (0.6 ml. per minute).



FIG. 4. RELATION OF UREA CLEARANCE TO RATE OF URINE FLOW IN INDIVIDUAL SUBJECTS The arrows indicate sequence of observations.

pendent upon several different independent variables: glomerular filtration, tubular transfer of water and rate of change of urine flow. Urea clearance is, therefore, dependent upon both glomerular and tubular activity, and measures no specific renal function. If urine flow changes at a rapid rate, the relation of urea clearance to urine flow is occasionally disturbed. Shannon (14) has described abrupt increases in urea clearance during the onset of a diuresis ("exaltation"), and we find marked depressions in the urea clearance with rapid decreases in urine flow in several instances; the two points at a U/P ratio of 20 and a urea/ inulin clearance ratio of 0.3 to 0.4 in Figure 5 were examples of this. In general, it is true that urea clearances vary directly with rate of urine flow, but the quantitative change in clearance is unpredictable : in Figure 5, at an inulin U/P ratio of 20, the urea clearance varied from 35 to 80 per cent of the inulin clearance. The variation in an individual experiment is shown in Figure 4. It has been reported that infants showed no consistent change in urea clearance with urine flow (3, 4),

but the range of observations in those studies was narrow, and if their data are plotted on our graphs, the points fall on our curves.

If inulin does measure glomerular filtration, then the inulin U/P ratio measures the tubular reabsorption of water. After moderate water deprivation inulin U/P ratios as high as 227 were found in premature infants. This indicates that, in the immature kidney, water is conserved when dehydration occurs without electrolyte loss, chiefly by increased tubular reabsorption of water rather than by decreased glomerular filtration. This mechanism of water conservation is comparable to that of the adult. Measurements of osmotic pressure and of specific gravity have not given a true evaluation of water conservation in infants (21-23). This may be explained by the fact that these values are determined not only by the tubular reabsorption of water, but by the reabsorption of solutes as well.

Tubular reabsorption of water is believed to be under the control of the anti-diuretic hormone of the posterior pituitary. Finding a high capacity



FIG. 5. RELATION OF TUBULAR REABSORPTION OF UREA TO TUBULAR REABSORPTION OF WATER

Inulin U/P ratios are plotted on a logarithmic scale and clearance ratios on a linear scale. The dots represent periods of constant or decreasing urine flow, the circles periods of increasing urine flow.

for water reabsorption by the tubules of the premature infant's kidney conflicts with the finding of Heller (24) that the tubules are relatively insensitive to pitressin. We have, in a preliminary way, put this to the test by more crucial observations than those employed by Heller. A representative observation in a six-day-old, 2200-Gm. premature infant is shown in Figure 6. High inulin U/P ratios were found, as expected, following 16 hours of water deprivation. The infant was then given enough fluid to produce a water diuresis during which the U/P ratios fell as indicated. Pitressin was then infused at the rate of 1 milliunit per minute and an immediate rise in the U/P ratio followed. These observations indicate a good response of the tubules of the premature infant to anti-diuretic hormone. We cannot, at the present time, explain the finding of higher inulin U/P ratios following water deprivation than during pitressin infusion. This discrepancy apparently does not represent a peculiarity on the part of premature infants, however, since Taylor, *et al.* (25), measuring urine specific gravity, found the same difference in response in adults.

#### CONCLUSIONS

1. The renal clearance of inulin in premature infants apparently measures glomerular filtration.

2. The inulin clearances of premature infants are low compared to those of adults on a basis of surface area.

3. Urea clearances of premature infants are also low, but cannot be used in estimating glomerular filtration since they have a variable relationship to inulin clearances. The ratio of urea clearance to inulin clearance is markedly influenced by urine flow.

4. The renal tubules of the premature infant are capable of reabsorbing more than 99 per cent of the water in the glomerular filtrate.

5. The renal tubules of the premature infant are responsive to the pituitary anti-diuretic hormone.



FIG. 6. RENAL RESPONSE AS MEASURED BY INULIN U/P RATIOS OF A PREMATURE INFANT TO WATER DEP-RIVATION, TO WATER ADMINISTRATION, AND TO PITRES-SIN INFUSION

6. In premature infants, dehydration produced by withholding fluids does not diminish glomerular filtration but results in increased tubular reabsorption of water.

#### ACKNOWLEDGMENTS

We are indebted to Flora Hurwitz, R.N., for nursing and technical assistance, and to Miss Helen Siragusa for technical assistance.

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