# Hypertension in children and adolescents 

BEN H. BROUHARD, MD

- BACKGROUND Children have lower blood pressure than adults do, and normal values for children have been established based on age and also on height and weight. Blood pressures in childhood correlate with blood pressures in adulthood, although weakly; a stronger correlation has been established between obesity in childhood and adulthood. Further, obese people are more likely to have high blood pressure than are slender people, both as children and adults. In hypertensive children, the higher the blood pressure and the earlier hypertension appears, the more likely is a secondary cause.
- KEY POINTS Physicians should measure and record children's blood pressure, just as they do their height and weight. An algorithm can help physicians decide whether a child with high blood pressure needs further workup and treatment. Nonpharmacologic therapy includes dietary sodium restriction, weight reduction (if the child is overweight), aerobic exercise, and relaxation. In some cases pharmacologic therapy may be necessary. In general, all children should be encouraged to be physically active and to eat healthy foods.

[^0]From the Department of Pediatric and Adolescent Medicine and the Department of Nephrology and Hypertension, The Cleveland Clinic Foundation.
Address reprint requests to B.H.B., Department of Pediatric and Adolescent Medicine, A120, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.

HYPERTENSION, usually viewed as a disease of middle age and the elderly, may actually begin much earlier: children at the 90 th percentile or above for blood pressure are more likely to have hypertension as adults than are other children. Obesity in children is also worrisome, as overweight children remain so as adults, and overweight people of any age are more likely to have hypertension. Pediatricians and family practitioners are beginning to measure and record the blood pressure of all their young patients at all visits-and to ponder what to do when a reading is high. This article reviews what we currently know about hypertension in children and what experts recommend to do about it.

## PREVALENCE AND SIGNIFICANCE

Hypertension in children and adolescents is not uncommon. Sinaiko et al ${ }^{1}$ found the prevalence of "significant" hypertension to be $2 \%$ in 14000 school children age 10 to 15 ; other reported frequencies range from $1.2 \%$ to $13 \% .^{2}$ Thus, the extent of hypertension in the pediatric

## TABLE 1

THRESHOLD HYPERTENSIVE BLOOD PRESSURE
VALUES IN THE YOUNG BY AGE GROUP*

| Age | High <br> normal <br> (90th percentile) | Significant <br> hypertension <br> (95th percentile) | Severe <br> hypertension <br> (> 99th percentile) |
| :--- | :---: | :---: | :---: |
| 0-7 days | - | $96 /-$ | $106 /-$ |
| 8-30 days | - | $104 /-$ | $110 /-$ |
| $\leq 2$ years | $104 / 70$ | $112 / 74$ | $118 / 82$ |
| 3-5 years | $108 / 70$ | $116 / 76$ | $124 / 84$ |
| 6-9 years | $114 / 74$ | $122 / 78$ | $130 / 86$ |
| 10-12 years | $122 / 78$ | $126 / 82$ | $134 / 90$ |
| 13-15 years | $130 / 80$ | $136 / 86$ | $144 / 92$ |
| 16-18 years | $136 / 84$ | $142 / 92$ | $150 / 98$ |

*Adapted from the Second Task Force on Blood Pressure Control in Children, reference 3; values are in mm Hg

## LONGITUDINAL STUDIES

Children with hypertension risk future cardiovascular, renal, and nervous-system complications. Further, sustained hypertension or even isolated high blood pressure readings may be associated with future risk of hypertension itself, as longitudinal studies suggest that children with high blood pressure will continue to have it as adults.

Lauer and Clarke ${ }^{5}$ observed 2445 subjects who had their blood pressures measured every 2 years between ages 7 through 18 and once between ages 20 and 30 . The longitudinal correlation coefficients for systolic blood pressure ranged from .21 to .39 , from -.01 to .50 for diastolic blood pressure, and from .45 to .74 for the Quetelet index (a measure of obesity; weight/[height squared]). In addition, the investigators used logistic regression to calculate the risk of future high blood pressure and obesity based on a single childhood observation (Figure 2).

Other studies have confirmed these findings ${ }^{6-8}$ : the correlation coefficients ranged from .2 to .5 for systolic pressure, from .2 to .3 for diastolic pressure, from .4 to .6 for cholesterol concentration, and from .6 to .8 for height and weight. Although blood pressures "track" poorly in childhood, these studies have shown that children with blood pressures less than the 50 th percentile have little risk of having pressures in the 90th percentile or higher as young adults.

Gillman et $\mathrm{al}^{9}$ found these relatively weak correlations for blood pressure could be increased with repeated testing. The investigators measured the blood pressure of 333 children ages 8 through 15 for 4 successive years, on four weekly visits in each year, with three measurements at each visit; they used the mean blood pressure for each visit to calculate the mean annual blood pressure for each child. The correlation coefficients for systolic blood pressure at the 3 -year follow-up for the first, second, third, and fourth weekly visits were $.45, .55, .64$, and .69 , respectively; for diastolic pressure the cor-


FIGURE 1. Algorithm for detecting and treating hypertension in children. Adapted from the Second Task Force on Blood Pressure Control in Children, reference 3.
responding values were $.28, .41, .47$, and .54 . In another study, Gillman et a ${ }^{10}$ measured the blood pressure of 337 children and remeasured it 8 to 12 years later in 317 (94\%). They found the correlation coefficient to be .55 for systolic pressure and .44 for diastolic pressure.

Although these correlations from childhood to early adulthood are higher than previously reported, taken together, the data cast doubt on the usefulness of routinely measuring blood pressure to identify children at high risk of developing essential hypertension as adults. Perhaps of more importance is the high longitudinal correlation of the Quetelet index; since hypertension is correlated with obesity in adults, preventing or reducing obesity in childhood may be a useful strategy for preventing hypertension in adults.

Nelson et al ${ }^{11}$ reported on 221 subjects who had


FIGURE 2. The risks of having high blood pressure or being obese (ie, at the 90 th percentile or above for systolic pressure, diastolic pressure, or Quetelet index) at ages 20 to 25 based on measurements at age 16 in 2445 subjects. From Lauer and Clarke, reference 5.
their blood pressures measured between ages 3 and 18 years, at age 30 , and at age 50 . The systolic blood pressure at age 30 was significantly and positively correlated with systolic pressures from age 5 onward in female subjects ( $r=.18$ to .46 ) and age 6 onward in male subjects ( $r=.22$ to .42 ). The correlation of blood pressure at age 50 was much lower for both sexes. The correlations for diastolic blood pressures were generally weaker than for systolic blood pressures. Height and body mass index were found to be independent predictors of adult blood pressure. The investigators concluded that juvenile blood pressure is one of several predictors of adult blood pressure.

## ETIOLOGY

The cause of childhood hypertension is often suggested by the age of the child and by the level of blood pressure-the older the child and the lower the blood pressure, the more likely it is that the hypertension is idiopathic; the younger the child and the higher the blood pressure, the more likely is

TABLE 2
COMMON CAUȘES OF HYPERTENSION IN CHILDHOOD

Age 1 to 6<br>Renal parenchymal disease<br>Renovascular disease<br>Coarctation of the aorta<br>Endocrine causes ${ }^{\dagger}$<br>latrogenic ${ }^{\dagger}$<br>Essential hypertension<br>Age 6 to 12<br>Renal parenchymal disease<br>Renovascular disease<br>Essential hypertension<br>Coarctation of the aorta<br>Endocrine causes ${ }^{\dagger}$<br>latrogenic ${ }^{\dagger}$<br>Age 12 to 18<br>Essential hypertension<br>latrogenic<br>Renal parenchymal disease<br>Renovascular disease<br>Endocrine causes ${ }^{\dagger}$<br>Coarctation of the aorta<br>*From Ingelfinger, reference 15<br>${ }^{\dagger}$ 'Substantially less common

a secondary cause for the hypertension (Tables 2 and 3$).{ }^{12}$ Of the secondary causes, a renal origin is the most common. It is beyond the scope of this article to explore all of these possibilities. However several recent articles ${ }^{13,14}$ and chapters ${ }^{2,15,16}$ provide excellent reviews of these secondary causes of hypertension.

## Genetic factors

Idiopathic hypertension in children is multifactorial. Since hypertension tends to run in families, genetic factors have been implicated. Studies in populations and in twins point to important genetic influences on blood pressure in childhood and adolescence. In studies in twins, it has been estimated that genetic influences account for as much as $82 \%$ of the variability in systolic blood pressure, but only $64 \%$ of the variability in diastolic blood pressure. ${ }^{17}$ Investigation of polygenic pathways led to the study of factors such as ion transport, kallikrein excretion, plasma haptoglobin, and sympathetic reactivity, all of which correlate with blood pressure. Such pathways appear to be under strong genetic influence. ${ }^{18,19}$

Univariate analysis shows that a significant proportion of the variability of systolic and diastolic blood pressure is under genetic control. ${ }^{20}$ Multivariate analysis demonstrates that in adolescents, genetic paths shared with body mass index appear to

TABLE 3
SECONDARY CAUSES OF HYPERTENSION

```
Renal
    Acute glomerulonephritis
    Hemolytic uremic syndrome
    Obstructive uropathy
    Congenital abnormalities (polycystic kidneys, multicystic
        kidneys, Ask-Upmark kidney)
    Renal arterial disease
    Renal parenchymal disease
    Perirenal masses
    Anaphylactoid purpura
    Renal transplantation
    Acute renal failure
    Renal tumors
    Collagen vascular disease
Endocrine
    Pheochromocytoma
    Congenital adrenal hyperplasia
    Hyperthyroidism (systolic only)
    17-Hydroxylase deficiency
    Aldosteronism (primary)
    Neuroblastoma
    Cushing's disease
    Hyperparathyroidism
Vascular system
    Polycythemia
    Anemia (systolic only)
    Takayasu's arteritis
    Patent ductus arteriosus (systolic only)
    Coarctation of the aorta
Metabolic
    Diabetes mellitus (renal involvement)
    Acute intermittent porphyria
    Hypercalcemia
Neurologic
    Dysautonomia (Riley-Day syndrome)
    Neurofibromatosis
    Increased intracranial pressure
    Guillain-Barré syndrome
    Anxiety
Drug-related
    Steroid administration
    Heavy metals
    Amphetamine overdose
    Following sympathomimetic drugs
    Birth control pills
Miscellaneous
    Essential hypertension
    Burns
    Stevens-Johnson syndrome
    Cyclic vomiting with dehydration
```

influence systolic but not diastolic blood pressures. ${ }^{17}$ More direct evidence of the involvement of specific genes have been provided by Caulfield et $\mathrm{al}^{12}$ and Jeunemaite et $\mathrm{al},{ }^{22}$ who reported linkage between the angiotensinogen-gene locus on chromosome 1 and essential hypertension. However, these studies found linkages only-they did not identify a causative gene.

## Obesity

Obesity is a modifiable risk factor strongly associated with hypertension. Many studies of children and adolescents have demonstrated the association of body size (measured by body mass indices or skinfold thickness) with blood pressure. ${ }^{18}$ As in adults, the distribution of fat also may be important. Shear et al ${ }^{23}$ reported that central deposition of body fat may be more strongly related to hypertension than is peripheral body fat. Additional evidence of the role of obesity comes from longitudinal studies, which demonstrate that children who have an increase in relative body size may also have more of an increase in blood pressure than do their peers. Conversely, those who have a decrease in body size rank also have a decrease in blood pressure rank. ${ }^{24}$ These data, and the correlation of blood pressure in childhood and adulthood, suggest that any discussion of blood pressure control in children should emphasize avoiding obesity.

## Cation intake

Excessive sodium intake may contribute to the development of hypertension. ${ }^{25,26}$ In populations that consume little sodium, blood pressure does not rise with age, and hypertension is essentially absent. ${ }^{27}$ Of note, people in these populations consume extremely little sodium from birth on-

TABLE 4
HINTS TO CAUSE OF HYPERTENSION*

| Finding | Possible cause |
| :---: | :---: |
| Habitus |  |
| Thinness | Pheochromocytoma, hyperthyroidism (with proptosis), renal disease (growth failure) |
| Obesity | Cushing's disease |
| Virilization | Congenital adrenal hyperplasia |
| Rickets | Chronic renal disease |
| Skin |  |
| Café au lait spots | Neurofibromatosis |
| Tubers | Tuberous sclerosis (also "ash-leaf" spots) |
| Neurofibromas | Neurofibromatosis |
| Bruises | Cushing's disease, trauma |
| Rashes | Butterfly, systemic lupus erythematosus; vasculitis, collagen vascular disease; impetigo, acute nephritis; striae, Cushing's syndrome |
| Head and face |  |
| Bruit | Arteriovenous malformation |
| Unusual shape | Arteriovenous malformation, mass lesion |
| Round (moon) facies | Cushing's syndrome |
| Elfin facies | William's syndrome |
| Eyes |  |
| Extraocular muscle palsy | Nonspecific |
| Fundal changes | Nonspecific |
| Proptosis | Hyperthyroidism |
| Neck |  |
| Goiter | Possible hyperthyroid goiter |
| Lungs |  |
| Rales, rhonchi | Nonspecific, related to acute cardiac decompensation |
| Heart |  |
| Enlarged | Possible longstanding hypertension, possibly related to acute overload |
| Failure | Same as for enlarged heart |
| Rub | Possible chronic renal disease with hypertension |
| Abdomen |  |
| Masses | Wilms' tumor, neuroblastoma, hydronephrosis, polycystic disease |
| Hepatomegaly | Heart failure |
| Hepatosplenomegaly | Infantile polycystic disease |
| Scars | Genitourinary surgery, possible obstruction |
| Bruit | Renovascular disease |
| Back and flank |  |
| Bruit | Renovascular disease |
| Flank tenderness | Pyelonephritis, obstruction, acute nephritis |
| Scoliosis | Possible hypertension related to procedures |
| Pelvis |  |
| Mass | Obstructive uropathy |
| Genitalia |  |
| Ambiguous, virilized | Congenital adrenal hyperplasia |
| Extremities |  |
| Blood pressure disparity, pulse disparity, delayed capillary filling in legs | Coarctation |
| Neurologic |  |
| Seizures, Bell's palsy, irritable | Nonspecific |

*Adapted from Ingelfinger J. Evaluation of secondary hypertension. In: Holliday MA, Baratt TM, Avner ED, editors. Pediatric nephrology. 3rd ed. Baltimore: Williams and Wilkins, 1993:1148-1164.

TABLE 5
TREATMENT OF CHILDHOOD HYPERTENSION*

| Nonpharmacologic treatment |  |  |  |
| :--- | :--- | :--- | :--- |
| Weight reduction (if appropriate) <br> Salt restriction (2 g sodium) <br> Aerobic exercise (30 minutes, 2 to 3 times per week) <br> Stress reduction via relaxation techniques or biofeedback |  |  |  |
| Pharmacologic treatment | Adult dose range |  |  |
| (total mg/day) |  |  |  |$\quad$ Frequency $\quad$| Pediatric dose |
| :---: |
| (mg/kg/day) |

*Adapted from the Task Force on Blood Pressure Control in Children, reference 3, and the 1993 report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure, reference 12
${ }^{\dagger}$ This table lists only the drugs for which pediatric doses have been established; all antihypertensive drugs have been used in children; pediatric dosages should not exceed adult dosage
vention trials in adults have demonstrated a small lowering of blood pressure with calcium supplementation. ${ }^{30}$ There have been few studies in children, except for the report of Gillman et al, ${ }^{31}$ which showed a strong inverse association between dietary calcium and systolic blood pressure in a group of 3 - to 5 -year-old children.

PHYSICAL FINDINGS AND LABORATORY DATA

Once the diagnosis of hypertension has been made, a pertinent physical examination should be undertaken (Table 4). If a secondary cause is suspected, the laboratory evaluation should be directed toward that cause; if not, it may be useful to obtain a urinalysis, a hemoglobin and hematocrit, and serum concentrations of electrolytes, urea nitrogen, and creatinine. A fasting lipid profile should be obtained to help evaluate cardiovascular risk, and an echocardiogram or electrocardiogram should be obtained to evaluate possible end-organ damage.

## TREATMENT

## Nonpharmacologic treatment

Nonpharmacologic therapy includes dietary so-
dium restriction, weight reduction (if indicated), aerobic exercise, and relaxation.

Blood pressure may be particularly sensitive to
salt restriction, which has been said to be of benefit in $25 \%$ of hypertensive adolescents. ${ }^{32}$ Sodium intake should be reduced to no more than 2 g per day. Patients can achieve this goal by avoiding salty food
$\qquad$
ward. Dahl and colleagues ${ }^{28}$ bred a strain of rat in which even brief exposure to a high-sodium diet very early in life led to permanent increases in blood pressure, even if the high-sodium diet was removed. In a study in humans, Hofman et al ${ }^{29}$ found that infants exposed to a lower sodium intake from birth had lower blood pressures at 5 to 6 months than did infants exposed to a higher sodium intake.

Although studies in animals have suggested that high potassium intake tends to lower blood pressure, studies in humans have been inconclusive, especially in children. ${ }^{18}$

Recently, interest has risen in the relationship between dietary calcium and blood pressure. Inter-
and not adding salt in cooking or at the table. If this is unpalatable, potassium chloride or low-sodium spices can be used as seasoning. If sodium restriction fails to lower the blood pressure, one should prescribe a diuretic (paying appropriate attention to hypokalemia).

Aerobic exercise can also be effective for adolescents, who should participate in aerobic exercise for at least 30 minutes three to four times a week. Isometric or static exercise to improve strength is not recommended to reduce blood pressure and in fact may increase it. As long as their blood pressure is under control, there is no reason children should not participate in athletic activities. Weight reduction is an important component of blood pressure control in obese adolescents. A weight loss of just $5 \%$ has been shown to decrease blood pressure into the normal range. ${ }^{32}$

In addition, home monitoring of blood pressure is critical. Since blood pressure is the end point of therapeutic intervention, patients must know what their blood pressure is and measure it daily.

## Pharmacologic treatment

Table 5 lists antihypertensive agents for which pediatric doses have been established. Many of them have specific indications, such as angiotensin-con-

## REFERENCES

1. Sinaiko AR, Gomez-Marin O, Prineas RJ. Prevalence of significant hypertension in junior high school-aged children: the children and adolescent blood pressure program. J Pediatr 1989; 114:664-669.
2. Yetman RJ, Bonella-Felix MA, Portman RJ. Primary hypertension in children and adolescents. In: Holliday MA, Barrett TM, Avner ED, editors. Pediatric nephrology. 3rd ed. Baltimore: Williams \& Wilkins, 1994:117.
3. Task Force on Blood Pressure Control in Children. Report of the second task force on blood pressure control in children1987. Pediatrics 1987; 79:1-25.
4. Rosner B, Prineas RJ, Loggie JMH, Daniels SR. Blood pressure nomograms for children and adolescents, by height, sex and age in the United States. J Pediatr 1993; 123:871-886.
5. Lauer RM, Clarke WR. Childhood risk factors for high adult blood pressure: the Muscatine study. Pediatrics 1989; 84:633-641.
6. Hofman A, Valkenburg HA, Mass J, Groustra FA. The natural history of blood pressure in childhood. Int J Epidemiol 1985; 14:19-96.
7. Michels VV, Bergstralk EJ, Hoverman VR, et al. Tracking and prediction of blood pressure in children. Mayo Clin Proc 1987; 62:875-881.
8. Clarke WR, Schrott HG, Leaverton PE, et al. Tracking of blood lipids and blood pressure in school age children: the Muscatine study. Circulation 1978; 58:626-634.
9. Gillman MW, Rosner B, Evans DA, et al. Use of multiple visits to increase blood pressure tracking correlations in childhood. Pediatrics 1991; 87:708-711.
verting enzyme (ACE) inhibitors in renovascular hypertension. Others may be more useful because they are taken once a day (eg, some new ACE inhibitors) as opposed to three to four times a day (eg, hydralazine). As recommended by the fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, ${ }^{12}$ all antihypertensive drugs lower blood pressure equally well, but diuretics and beta blockers are more well studied. In general, starting with one drug, increasing the dose if necessary, and then adding another drug would seem a wise policy to follow.

## SUMMARY

Childhood hypertension is not uncommon. Children's blood pressure should be monitored routinely at physician visits and compared with normal values. When elevated blood pressures are documented, home blood pressure monitoring is indicated. If therapy is indicated, nonpharmacologic therapies such as weight reduction, aerobic exercise, and salt restriction should be encouraged. If pharmacologic therapy is needed, a single agent with which the physician is familiar should be tried and then other drugs added if necessary, while home blood pressure monitoring continues.
10. Gillman MW, Cook NR, Rosner B, et al. Identifying children at high risk for the development of essential hypertension. J Pediatr 1993; 122:837-846.
11. Nelson MJ, Ragland DR, Syme SL. Longitudinal predictions of adult blood pressure from juvenile blood pressure levels. Am J Epidemiol 1992; 136:633-645.
12. Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. Fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1993; 153:154 196183.
13. Daniels SR, Loggie JH. Essential hypertension. State of the art reviews. Adolescent Medicine 1991; 2:551-566.
14. Gredanus DE, Rowlett JD. Hypertension in adolescence. Adolescent Health Update 1993; 6:1-5.
15. Ingelfinger JR. Hypertension. In Edelman CM Jr, editor. Pediatric kidney disease. Boston: Little, Brown \& Co, 1992:1889-1908.
16. Rocchini AP, editor. Childhood hypertension. Pediatr Clin North Am 1993; 40:1-213.
17. Schieken RM. Genetic factors that predispose the child to develop hypertension. Pediatr Clin North Am 1993; 40:1-11.
18. Williams RR, Hunt SC, Harstedt SJ, et al. Definition of genetic factors in hypertension: a search for major genes, polygenes and homogeneous subtypes. J Cardiovasc Pharmacol 1988; 12(Suppl 3):S7-S10.
19. Schieken RM, Eaves LJ, Hewitt JK, et al. The univariate genetic analysis of blood pressure in children: The MCV Twin Study. Am J Cardiol 1989; 64:1333-1337.
20. Gillman MW, Ellerson RC. Childhood prevention of essential hypertension. Pediatr Clin North Am 1993; 40:179-194.
21. Caulfield M, Lavender P, Farrall M, et al. Linkage of the angiotensinogen gene to essential hypertension. N Engl J Med 1994; 330:1629-1633.
22. Jeunemaite X, Soubrien F, Kotelevtsev YV, et al. Molecular basis of human hypertension role of angiotensinogen. Cell 1992; 71:169-180.
23. Shear CL, Freedman DS, Buike GL, et al. Body fat patterning and blood pressure in children and young adults. The Bogalusa Heart Study. Hypertension 1987; 9:236-240.
24. Labarthe DR, Mueller WH, Eissa M. Blood pressure and obesity in childhood and adolescence. Epidemiologic aspects. Ann Epidemiol 1991; 1:337-341.
25. Cutler JA, Follman D, Elliott P, Suh I. An overview of randomized trials of sodium reduction and blood pressure. Hypertension 1991; 17(Suppl I):I27-I33.
26. Langford HG, Davis BR, Blaufox MD, et al. Effect of drug and diet treatment of mild hypertension on diastolic blood pressure. Hypertension 1991; 17:210-217.
27. Stamler J, Rose G, Elliott P, et al. Findings of the international cooperative INTERSALT Study. Hypertension 1991; 17:1-9.
28. Dahl LK, Krudsen KD, Heene MA, et al. Effects of chronic excess salt ingestion. Circ Res 1968; 22:11-19.
29. Hofman A, Hacebrock A, Valkenburg HA. A randomized trial of sodium intake and blood pressure in newborn infants. JAMA 1983; 250:370-374.
30. McCarron DA, Morris CD, Young E, et al. Dietary calcium and blood pressure: modifying factors in specific populations. Am J Clin Nutr 1991; 54:215S-220S.
31. Gillman MW, Oliveria SA, Moore LL, et al. Inverse association of dietary calcium with systolic blood pressure in young children. JAMA 1992; 267:2340-2342.
32. Gruskin SB, Dabaugh S. Hypertension. In: McArnarny ER, Kreipe RE, Orr DP, Comerci GD, editors. Textbook of adolescent medicine. Philadelphia: WB Saunders, 1992:360-364.



HIGHLIGHTS FROM MEDICAL GRAND ROUNDS

## Concise, current, critical information on the medical problems you encounter in your practice

IN THIS ISSUE Page 6


[^0]:    ■ INDEX TERMS: HYPERTENSION; CHILD; ADOLESCENT
    ■CLEVE CLIN J MED 1995; 62:21-28

