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AN ADOPTION STUDY OF HUMAN OBESITY

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Abstract We examined the contributions of genetic factors and the family environment to human fatness in a sample of 540 adult Danish adoptees who were selected from a population of 3580 and divided into four weight classes: thin, median weight, overweight, and obese. There was a strong relation between the weight class of the adoptees and the body-mass index of their biologic parents — for the mothers, $P < 0.0001$; for the fathers, $P < 0.02$. There was no relation between the weight class of the adoptees and the body-mass index of their adoptive parents. Cumulative distributions of the body-mass index

of parents showed similar results; there was a strong relation between the body-mass index of biologic parents and adoptee weight class and no relation between the index of adoptive parents and adoptee weight class. Furthermore, the relation between biologic parents and adoptees was not confined to the obesity weight class, but was present across the whole range of body fatness — from very thin to very fat. We conclude that genetic influences have an important role in determining human fatness in adults, whereas the family environment alone has no apparent effect. (N Engl J Med 1986; 314:193-8.)

RECENT studies of twins suggest that human obesity and fatness are highly heritable.¹⁻⁵ This suggestion would be greatly strengthened if it were confirmed by adoption studies, another method of assessing genetic influence in humans. Unfortunately, only four studies⁶⁻⁹ have used this method, and all were handicapped by the lack of information on biologic parents and by the failure to explore the entire range of body weight. Three were further limited by being confined to children. Moreover, the results of these studies are in serious disagreement. Hartz et al. reported that family environment was far more important than heredity in determining the percentage overweight in adults.⁶ In studies of children, Garn et al. reached the same conclusion for relative weight and skinfold thickness.⁷ Precisely the opposite conclusion was drawn in studies of children by Annett et al.⁸ in regard to weight, and by Withers⁹ in regard to percentage overweight. We performed a large adoption study of human fatness across a range from thinness to severe obesity; the study included information on both the biologic and the adoptive parents.¹⁰

METHODS

The study used the Danish Adoption Register, which has been described in detail in earlier reports.^{11,12} This register contains the

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official records of every nonfamilial adoption granted in Denmark between 1924 and 1947. Adoptions in which one or both parents were biologic relatives of the child are excluded. The register contains the name, date of birth, address, occupation, and income of the adoptive parents, as well as the date of transfer of the adoptee to the adoptive home. A unique strength of the register is that it also contains comparable information about the biologic parents; 94 percent of the mothers and 77 percent of the fathers are identified. Among the identified biologic fathers, paternity was established with considerable accuracy, usually by acknowledgment on the part of the biologic father but, in some cases, by anthropometric and blood group evaluations, as required by Danish law.

Information about 5455 adoptees whose adoption was granted in Copenhagen was obtained from Danish Folk Registers, which contain the names of every person in Denmark and the addresses at which they have lived from birth to death or emigration. A general health questionnaire that included items on height and weight was mailed to the 4643 adoptees who were still alive and living in Denmark; 3651 were returned — a response rate of 79 percent.

As a measure of fatness, we determined the body-mass index (weight in kilograms divided by the square of the height in meters)¹³ for the 3580 adoptees who provided complete responses to the health questionnaire. In this population, body-mass index was independent of height; the correlation coefficients between these two variables were less than 0.09 for all age-sex groups. The mean age of the adoptees (\pm SD) was 42.2 ± 8.1 years; 56 percent were women.

We examined four weight classes that represented the entire range of fatness — thin, median weight, overweight, and obese. These four classes were constructed to minimize the influence of sex and age, which are correlated with fatness. To this end, adoptees were divided into five birth-year intervals for each sex. Within each of these 10 age-sex sets, adoptees were rank-ordered according to body-mass index. Selection of the four weight classes (thin, median, overweight, and obese) was carried out within each of these 10 sets so that each weight class would contribute a number of adoptees that was proportional to the total size of the set. Thus, the definitions of the four weight classes referred to the rank order within age-sex sets: The thin class included the adoptees with the smallest body-mass indexes (those in the lowest fourth percentile). The median class consisted of the adoptees with body-mass indexes closest

Table 1. Range of Body-Mass Indexes among the Four Weight Classes of the Adoptees.*

ADOPTEE WEIGHT CLASS	MEN		WOMEN		TOTAL ADOPTEEES
	NO.	BODY-MASS INDEX	NO.	BODY-MASS INDEX	
Thin	60†	16.0–20.1	76	12.8–18.2	136
Median	61	24.0–24.9	76	21.2–23.3	137
Overweight	61	29.4–31.4	77	26.8–32.5	138
Obese	57‡	30.3–38.8	72‡	29.1–47.6	129

*Body-mass index is the weight in kilograms divided by the square of the height in meters. The small overlap between the ranges of body-mass index for overweight and obese classes is due to the slightly varying ranges for subgroups of different ages.

†The response of one adoptee was later found to be inaccurate.

‡Four men and three women originally classified as obese were excluded because it was found that they had reported their weight in Danish pounds (0.5 kg) and their corrected body-mass indexes lay outside the ranges of the four proband groups. However, the body-mass index of one woman who was originally classified as obese fell within the range of the overweight group after correction of this error, and she was therefore transferred to that group.

to the median. Overweight adoptees had body-mass indexes closest to those of the obese group, constituting the 92nd to 96th percentiles. The obese class consisted of the adoptees with the largest body-mass indexes — those above the 96th percentile.

This selection procedure ensured the same age–sex distribution in each of the four weight classes of 137 adoptees. Each weight class constituted 4 percent of the 3580 adoptees. Table 1 shows the range of the body-mass index for the four adoptee weight classes for both men and women. As noted above, the overweight and obese classes are contiguous within each age–sex set of the adoptee population.

After the adoptees were selected and divided into weight classes, information was sought about the heights and weights of both their biologic and their adoptive parents. The Danish Folk Registers were used to obtain the addresses of the adoptive parents, the biologic parents, and the biologic siblings and half-siblings of each adoptee. A second questionnaire was then sent to all adoptees, parents, and biologic siblings who were alive and living in Denmark. The questionnaire that was sent to the parents asked for their own height and weight, whereas those sent to the adoptees and the siblings asked for their parents', as well as their own, heights and weights. For our data analysis, we used the parents' reports of their own heights and weights when they were available. Some parents, however, were either deceased or were otherwise unable to provide reliable information. In such cases, information about the parents was obtained from the responses of the offspring (i.e., adoptees' reports of adoptive parents and the biologic siblings' reports of biologic parents).

This second questionnaire revealed a high degree of reliability in the adoptees' reports of their own heights and weights and the need for no more than minor changes from the initial assignments to weight classes (Table 1). The rate of response to this set of questionnaires was high — 80 percent of the parents and 73 percent of the adoptees and the other offspring of the biologic parents. Information about the parents was available for 74 percent (398) of the adoptive mothers, 66 percent (355) of the adoptive fathers, 64 percent (344) of the biologic mothers, and 50 percent (269) of the biologic fathers. The sources of this information are listed in Table 2.

Self-reported heights and weights were used in this study because direct measurements of the adoptees and their parents were not available and it was not feasible to obtain them. Anticipating the lack of direct measurements, we had earlier conducted two studies of the accuracy of reported heights and weights. The first investigation, which involved five sites in the United States and one (which included 750 persons) in Copenhagen,¹⁴ revealed that self-reported heights and weights corresponded closely to measured heights and weights. Similar results have been found in five other studies.^{15–19}

The second study assessed the accuracy of reports by offspring about their parents. For this purpose, we compared the heights and weights of persons examined in the Tecumseh Community Health

Study with estimates of those measures made by their offspring several years later.²⁰ Although less accurate than self-reports, the accuracy of reports by offspring seemed sufficient to warrant their use when self-reports were not available.

To determine the significance of the differences between mean parental body-mass index in relation to adoptee weight class, separate one-way analyses of variance, including tests for linear trends in means, were conducted for the body-mass indexes of the biologic mothers, the biologic fathers, the adoptive mothers, and the adoptive fathers. In each case, the independent variable was the adoptee weight class.

Separate cumulative distributions of body-mass index were plotted for the biologic mothers, the biologic fathers, the adoptive mothers, and the adoptive fathers of adoptees in the different weight classes. In addition, tests for trend were conducted on the proportion of parents who were overweight (body-mass index greater than 25) and obese (body-mass index greater than 30), proceeding from the thinnest to the fattest adoptee class.²¹

RESULTS

There was a clear relation between adoptee weight class and the body-mass index of the biologic parents; there was no apparent relation between adoptee weight class and the body-mass index of the adoptive parents. These results were consistent in all analytic tests.

Figure 1 shows the mean body-mass index of the parents of the four weight classes of adoptees. The mean body-mass index of the biologic parents increased with the increase in weight class of the adoptees. For biologic mothers, this relation was statistically significant ($F[df\ 3,340] = 7.84; P < 0.0001$). The relation between biologic mothers and daughters was also significant ($F[df\ 3,179] = 7.41; P < 0.0001$), but that between biologic mothers and sons was not, nor was the difference in association between sons and daughters.

The relation between the mean body-mass index of biologic fathers and the weight class of the adoptees was also statistically significant ($F[df\ 3,265] = 2.72; P < 0.02$), but the relation between biologic fathers and sons and biologic fathers and daughters was not, nor was the difference in association between sons and daughters.

A test for the trend of mean values revealed a very strong linear component (for biologic mothers, $F[df\ 1,340] = 20.86; P < 0.0001$; for biologic fathers, $F[df\ 1,265] = 7.78; P < 0.006$). In contrast, there

Table 2. Sources of Information about Parents.

SOURCE	ADOPTIVE MOTHERS	ADOPTIVE FATHERS	BIOLOGIC MOTHERS	BIOLOGIC FATHERS
	number (percent)			
Self-report	219 (40.6)	144 (26.7)	241 (44.6)	164 (30.4)
Adoptee/off- spring report	179 (33.1)	211 (39.1)	103 (19.1)	105 (19.4)
No response*	129 (23.9)	166 (30.7)	162 (30.0)	149 (27.6)
Untraceable	13 (2.6)	19 (3.5)	34 (6.3)	122 (22.6)
Total	540 (100)	540 (100)	540 (100)	540 (100)

*In addition to nonresponders, this category includes cases in which the parent was dead or unable to respond and there were no siblings or siblings were unable to respond. Reasons for inability to respond included mental incapacity and emigration.

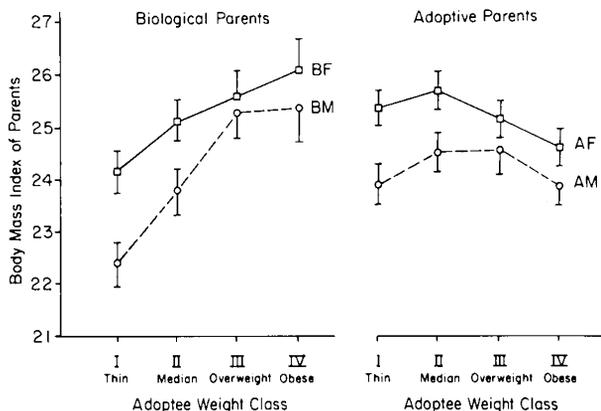


Figure 1. Mean Body-Mass Index of Parents of Four Weight Classes of Adoptees.

Note the increase in mean body-mass index of biologic parents with the increase in weight class of the adoptees. No such increase was found with adoptive parents. Bars represent 1 SEM. BF denotes biologic fathers, BM biologic mothers, AF adoptive fathers, and AM adoptive mothers.

was no apparent relation between the body-mass index of the adoptive parents and the weight class of the adoptees.

The cumulative distributions of the body-mass indexes of the biologic parents, according to adoptee weight class, are shown in Figure 2. There was little difference in the cumulative distributions of the body-mass indexes of biologic parents of adoptees in the adjacent weight classes “overweight” and “obese,” which, as noted earlier, constituted the 92nd to 96th and the 96th to 100th percentiles, respectively, of body-mass indexes of all adoptees. Therefore, the distributions of the body-mass indexes of biologic parents of overweight and obese adoptees were combined. Figure 2A shows the striking difference in the

cumulative distributions of the biologic mothers of adoptees of the different weight classes. Figure 2B shows the difference for the biologic fathers. In each case, there was a stepwise shift toward increased fatness of the parents of adoptees in the different weight classes. This pattern was clear with both biologic parents, although it was less striking among the fathers than among the mothers.

Figure 3 shows the cumulative distributions of the body-mass index of the adoptive mothers (Fig. 3A) and the adoptive fathers (Fig. 3B) among the different weight classes. There are no apparent differences among those distributions.

A test for trend in the proportion of overweight and obese parents showed a strong relation between adoptee weight class and biologic parents and no relation between adoptee weight class and adoptive parents. Table 3 shows that the proportion of overweight and obese parents increased with the increase in adoptee weight class. This trend was consistent both for biologic mothers ($P < 0.001$) and for biologic fathers ($P < 0.04$). No such trend was observed among the adoptive mothers. Among the adoptive fathers, the trend was in the opposite direction: the percentage of overweight fathers decreased with the increase in weight class of the adoptees ($P < 0.04$).

DISCUSSION

The two major findings of this study were that there was a clear relation between the body-mass index of biologic parents and the weight class of adoptees, suggesting that genetic influences are important determinants of body fatness; and that there was no relation between the body-mass index of adoptive parents and the weight class of adoptees, suggesting that childhood family environment alone has little or no effect.

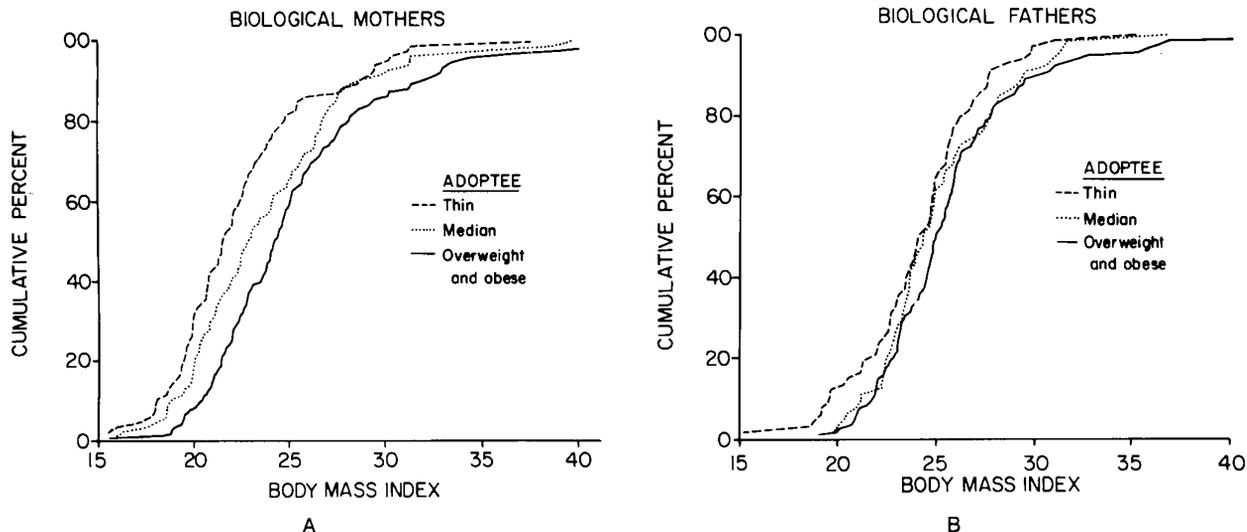


Figure 2. Cumulative Distribution of Body-Mass Index of Biologic Parents According to Adoptee Weight Class.

The body-mass indexes of parents of overweight and obese adoptees have been combined. Note the marked difference in the distributions of the biologic mothers (Panel A) and the somewhat smaller difference in the distributions of the biologic fathers (Panel B).

These results resolve the conflict between earlier adoption studies and support the results of twin analyses that have shown that obesity has a strong genetic component. The genetic influences found in the present study, however, are not confined to obese persons, but exert their effect across the whole range of body fatness — from very thin to very fat. These distributions are consistent with a polygenic inheritance of fatness, but they do not exclude the possibility of a contribution by a major gene or genes. Detection of such an effect would depend on its magnitude and on the frequency with which the gene appears in the population.

The finding that childhood family environment alone, as indexed by adoptive parental fatness, has no apparent influence on fatness in adults, is a result that varies from popular views. However, a similar surprising lack of influence of childhood family environment has been reported for a variety of personality characteristics.²²

These findings do not mean that fatness, including obesity, is determined at conception and that, as is the case with determination of eye color, the environment has no effect. The demonstration of a genetic influence tells us little about possible correlations and interactions between heredity and the environment. We do not know, for example, how a genetic predisposition to fatness may be affected by environmental factors.²³ A different level of genetic influence might have been realized under other circumstances. For instance, famine could prevent the expression of any genetic tendency toward fatness. However, the availability of amounts of food only slightly above the famine level might permit expression of only the strongest genetic tendency; in that situation, fatness might appear to be very heritable. Our findings from Denmark describe

the outcome of gene–environment interactions in an advanced Western society with an abundance of palatable food — an environment that favors the development of obesity.²⁴

Even within such a society, however, the nature of gene–environment interactions can change substantially over time. A study of obesity in a Copenhagen population that was the same age as that of the younger adoptees in our study provides a striking example of such a change.^{25,26} In the population in that study, there was a sevenfold increase (from 1 to 7 per 1000) in the prevalence of severe obesity during a 16-year period in which there was no change in median body-mass index.

The Validity of the Data

The assurance with which the findings of this study can be accepted is enhanced by the validity of its data. A key feature of these data is that they were derived from a very large sample of an adoption register that lists all adoptees for the period under study. This register made possible an adoption study of fatness that included both biologic as well as adoptive parents. Furthermore, since the register was constructed without reference to obesity and the first health questionnaire we circulated made no mention of obesity, two potential sources of bias were absent. There was also no evidence of other potential sources of bias — non-response, selective or late placement of adoptees,^{23,27} and contact between adoptees and their biologic parents.

Nonresponse rates were low, as noted above, and an earlier study of nonresponders had revealed that they differed little from responders.²⁸ Selective placement, had it occurred, should have been manifested by a relation between the body-mass index of biologic and

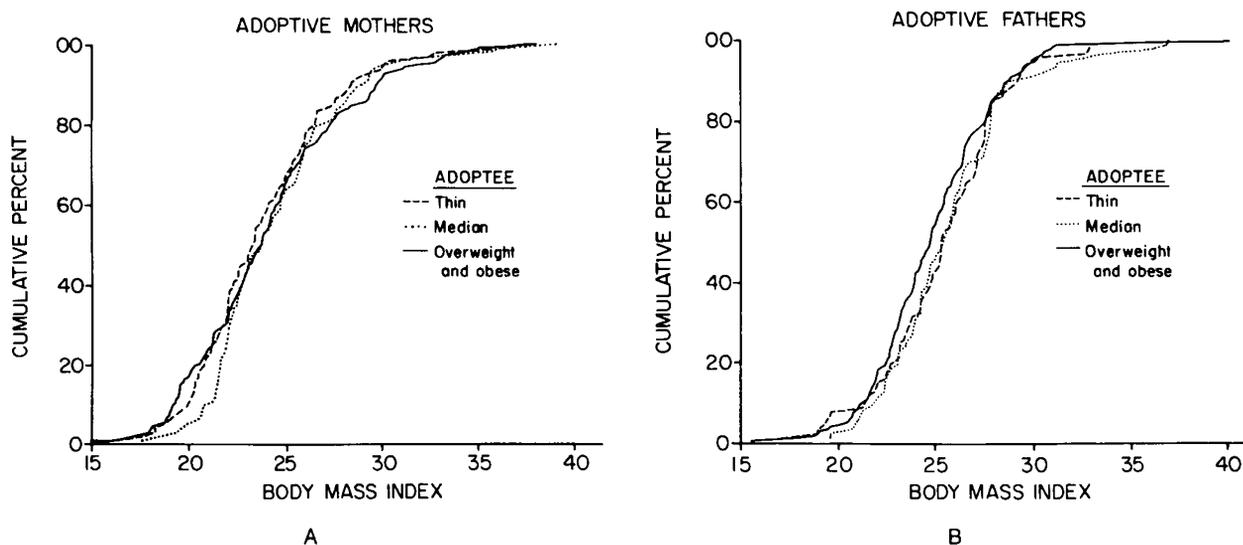


Figure 3. Cumulative Distribution of Body-Mass Index of Adoptive Parents According to Adoptee Weight Class.

The body-mass indexes of parents of overweight and obese adoptees have been combined. There was little difference among the distributions except for a tendency for the adoptive parents of overweight and obese adoptees to be somewhat lighter than the adoptive parents of thin and median-weight adoptees.

Table 3. Proportions of Overweight plus Obese and of Obese Parents, According to Adoptee Weight Class.

PARENTS*	ADOPTEE WEIGHT CLASS			P VALUE
	THIN	MEDIAN	OVERWEIGHT PLUS OBESE	
Mean body-mass index	17.8	23.0	31.4	
Overweight plus obese				
Biologic mothers				
% Who were overweight	18	35	41	0.001
Total no.	87	86	171	
Biologic fathers				
% Who were overweight	35	38	49	0.04
Total no.	68	65	136	
Adoptive mothers				
% Who were overweight	34	37	35	0.98
Total no.	96	103	199	
Adoptive fathers				
% Who were overweight	57	53	45	0.04
Total no.	93	88	174	
Obese only				
Biologic mothers				
% Who were obese	6	8	14	0.03
Total no.	87	86	171	
Biologic fathers				
% Who were obese	3	9	10	0.10
Total no.	68	65	136	
Adoptive mothers				
% Who were obese	7	6	10	0.27
Total no.	96	103	199	
Adoptive fathers				
% Who were obese	5	9	6	0.84
Total no.	93	88	174	

*"Overweight" is defined as a body-mass index of 25 or more, and "obese" as a body-mass index of 30 or more (the overweight category includes obese parents). "Total" refers to the total number of parents within each adoptee weight class.

adoptive parents, but no such relation was found. Late placement was rare: 90 percent of the adoptees had been transferred to their adoptive homes within the first year of life, and 55 percent within the first month. In addition, there were no differences in mean age of transfer among the four weight classes. Contact of adoptees with their biologic parents also did not appear to have had an important influence. An earlier study of this population had revealed that only 21 percent of the adoptees had had contact of any kind with their biologic parents (in person, by mail, or by telephone).²⁹ Furthermore, the adoptees who did have such contact did not differ from the others (79 percent) in the psychological measures that were the focus of that study. A final measure of the quality of the register is that it has been used successfully for many studies of genetic influences on psychopathologic factors, without revealing any important biases.^{11,30-33}

Practical Consequences: The Prevention of Obesity

Better understanding of the determinants of human obesity will be useful in preventing this disorder because it will help to restrict the size of the target population. Current efforts to prevent obesity are directed toward all children (and their parents) almost indiscriminately. Yet if family environment alone has no role in obesity, efforts now directed toward persons with little genetic risk of the disorder could be refocused on the smaller number who are more vulnerable. Such persons can already be identified with some

assurance: 80 percent of the offspring of two obese parents become obese, as compared with no more than 14 percent of the offspring of two parents of normal weight.³⁴

A relevant example of a similar preventive effort is the use of diet to control a disorder with very strong genetic determinants — phenylketonuria.³⁵ Prevention of obesity may be more difficult in some ways than prevention of phenylketonuria because, with obesity, the period of vulnerability is not restricted to childhood. Thus, prevention of obesity may require a life-long effort for persons who have obese parents.

Yet, prevention of obesity may be less difficult in some ways than prevention of phenylketonuria because it need not be confined to dietary measures. Increased physical activity is useful in the control of human obesity, and Stern et al.³⁶ have shown that it is also effective in the prevention of a type of genetically determined obesity in mice. These researchers found that simply increasing physical activity prevented the development of obesity in 50 percent of yellow obese mice, and that it greatly limited the extent of obesity among the other 50 percent.

Demonstration of the genetic determinants of human obesity not only allows development of better-informed programs of prevention. It also provides a basis for the understanding and eventual control of this disorder.

We are indebted to Drs. Seymour Kety, David Rosenthal, and Paul Wender for the use of the Danish Adoption Register, and to Margit Lyngby Christiansen, Anne-Lise Petersen, and Birgit Leth Jensen for assistance.

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RED-CELL LITHIUM-SODIUM COUNTERTRANSPORT AND RENAL LITHIUM CLEARANCE IN HYPERTENSION

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Abstract Red-cell lithium-sodium countertransport is increased in patients with essential hypertension. It has been proposed that sodium-hydrogen ion exchange in the brush border of the renal proximal tubules is analogous to red-cell countertransport. To investigate the rate of sodium reabsorption by the proximal renal tubules in hypertension, we measured lithium clearance (a measure of proximal tubular reabsorption of sodium), as well as red-cell countertransport, in 14 patients with untreated essential hypertension and in 31 controls. As a group, the hypertensive patients had a higher average (\pm SEM) rate of red-cell countertransport (0.378 ± 0.030 mmol of lithium per liter of cells per hour, $P < 0.01$) and a lower renal fractional lithium

clearance (13.96 ± 0.69 percent, $P < 0.01$) than normotensive subjects (0.317 ± 0.015 mmol of lithium per liter of cells per hour and 17.75 ± 0.81 percent, respectively). Within the normotensive group, subjects with hypertension in at least one first-degree relative had significantly lower fractional lithium clearances than subjects with no hypertensive relatives (15.37 ± 0.84 percent vs. 19.06 ± 1.07 percent, $P < 0.05$). We conclude that hypertensive patients have heightened proximal tubular reabsorption of sodium and that red-cell countertransport is a marker of the renal abnormality. Enhanced proximal tubular sodium reabsorption may precede the development of essential hypertension. (*N Engl J Med* 1986; 314:198-201.)

IN 1980 Canessa et al. first described an association between elevated erythrocyte lithium-sodium countertransport in vitro and human essential hypertension.¹ The in vivo function of the lithium-sodium countertransporter has been envisioned as a facilitated diffusion process mediating sodium-sodium exchange in red cells and possibly in smooth muscle.² Because changes in countertransport activity cannot alter net sodium transport and therefore cannot affect the transmembrane sodium gradient, and because increased cell sodium is an attractive mechanistic trigger for hypotheses relating disorders of

cellular sodium metabolism to hypertension,^{3,4} lithium-sodium countertransport has been viewed as an epiphenomenon in the pathophysiologic sequence leading to hypertension.

Recently, the possibility that countertransport may be of pathogenetic importance was raised by Aronson⁵ and by Mahnensmith and Aronson.⁶ Noting similarities between red-cell lithium-sodium countertransport and cation countertransport mediated by the sodium-hydrogen ion exchanger of the renal proximal tubular brush border, they speculated that if increased red-cell countertransport was paralleled by increased proximal tubular sodium-hydrogen exchange, net proximal sodium reabsorption could be increased. Such a disorder could be related to the initiating renal stimulus central to several of the currently popular hypotheses of the basis of human hypertension.^{4,7-10} Although the direct measurement of proximal tubular

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