Obesity is a major health issue worldwide, but the background for this condition is more complex than commonly assumed. Dietary and genetic factors have but partial roles in the development of obesity, which is why the focus in recent years has turned to the trillions of microbes residing in the human intestine and their possible effect on energy harvest and metabolic signaling. A study by Cox and colleagues showed that the administration of low-dose penicillin in early life induces lasting effects on body composition by altering the intestinal microbiota.

Early life is a critical period both for the establishment of the intestinal microbiota and for metabolic development. The authors previously found that subtherapeutic antibiotic treatment of young mice altered their microbiota and body composition. However, the question remained whether age at the commencement of antibiotic treatment played a specific role in the development of obesity and whether obesity persists in the long term, after treatment. In a more recent study, Cox and colleagues found that mice are particularly vulnerable to exposure to low-dose penicillin during a critical time window around birth. Male mice whose mothers were treated with penicillin before the birth of the pups and throughout the weaning process had a markedly altered body composition in adulthood, with increased total mass and fat mass, increased ectopic fat deposition, increased hepatic expression of genes involved in adipogenesis, decreased bone mineral content, and increased bone area. By contrast, the body composition of adult male mice who had received penicillin after weaning and of female mice who had received penicillin at either phase of development (just before birth or after weaning) was more similar to that of controls. The results suggest that even transient changes to the microbiota caused by limited exposure to low-dose penicillin during a specific time window during development may have a sex-specific long-term effect on body composition.

Cox and colleagues went on to study whether treatment with prenatally administered penicillin added to the effect of a high-fat diet in the development of obesity. Low-dose penicillin and high-fat diet were found to have independent selective effects on the microbiota and body mass—in particular, fat mass—of male mice. Exposure to penicillin also resulted in substantially more fat mass in female mice fed a high-fat diet, as compared with penicillin-exposed female mice fed a low-fat diet. Penicillin and a high-fat diet in combination, but not separately, increased fasting insulin levels. These findings underscore the development of obesity depends on more than diet and genes. The identification of factors that modify the intestinal microbiota may help us to understand why individual persons have different vulnerabilities to high calorie intake.

Finally, Cox and colleagues examined whether the penicillin-moderated gut microbiota would have similar effects on body composition and metabolism if transferred to germ-free mice. Cecal microbiota were transferred from 18-week-old controls and penicillin-treated mice to 3-week-old germ-free mice (Fig. 1). The young mice that received penicillin-altered microbiota gained total mass and fat mass at a significantly faster rate than did the mice that received microbiota from controls. Recipients of penicillin-altered microbiota also had decreased expression of intestinal immune-response genes, similar to their donors. These results suggest that immunologic and metabolic changes are not caused by direct effects of antibiotics but rather by derived changes in the gut microbiota.

In humans, similar studies are difficult to conduct. Epidemiologic studies have suggested that interventions that influence the establishment of the intestinal microbiota, such as cesarean section and early treatment with antibiotics, increase the risk of overweight later in childhood. Currently, however, there is no direct evidence for a causal relationship in humans. And the translation of findings from mouse to hu-
Man is challenging. Although humans may be vulnerable to early treatment with antibiotics, sex differences may not be the same as in mice and the length of the critical time window may be different. Furthermore, the magnitude of the effect of antibiotics on obesity in humans needs to be weighed against the beneficial effects of clinically indicated treatment with antibiotics in infancy. It may even be speculated that in families in which obesity is a problem, specific antibiotic treatment at birth could reverse the adverse effect of obesogenic microbiota transferred from mother to infant during delivery.

Obesity and its causes are a puzzle; each piece makes our understanding of the causative factors more complete. The study by Cox and colleagues represents a valuable piece in the puzzle in that it provides evidence for the existence of basic research clinical implications.
tence of a critical window in early life, when the intestinal microbiota can influence the development of persisting metabolic traits.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Department of Epidemiology Research, Statens Serum Institut, Copenhagen, and the Department of Clinical Epidemiology, Aalborg University, Aalborg — both in Denmark.


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