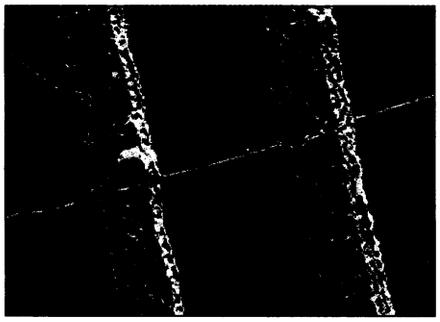

Atomic force microscope image of a single carbon nanotube crossing two platinum strips, which are used as source and drain contacts. On the right, a part is seen of a third electrode which could be used as a gate. The distance between electrodes is 200 nm. In the upper left corner a short tube is seen. [Courtesy of S. J. Tans *et al.*, Delft University of Technology]

and also supplied the nanotubes used in the two recent transport experiments. Tans and colleagues (*4*), from Delft, have studied a single nanotube, and Bockrath and colleagues (*5*), from Berkeley, measured a bundle of nanotubes (see page 1922). The two groups found similar electron transport properties.

So, what is special about these transistor characteristics? As we know, electrons in molecules only occupy quantized orbitals, which correspond to discrete levels in the energy spectrum. The current from source to drain contacts is carried exclusively by electrons that have exactly these particular energies. If one adds an electron to the molecule, one needs to pay more than just the finite energy to occupy the next available molecular state; one must also pay a so-called charging energy to compensate for the extra elementary charge that the molecule now contains. Therefore, both quantization of charge and quantized molecular states govern the electronic properties of a molecular transistor. The energy required to add an electron to the molecule can either be supplied by the voltage source between the two current contacts or by the voltage applied to the gate terminal. These voltages are the spectroscopic tools in the determination of the charging energies and the molecular states (*2–5*).

The physics of charging energies and discrete energy states has been exploited before by the mesoscopic community. These quantum effects were found in ultrasmall transistors known as quantum dots. Those quantum dot transistors are small electron boxes with zero dimensionality fabricated in semiconductor materials. Because charging energy and quantized states resemble so closely the ionization energy and excitation energies of an atom, quantum dots are often nicknamed "artificial atoms" (*8*). Following the same arguments, two or more coupled quantum dots can be regarded as "artificial molecules" (*9*). We can complete the connection between natural and artificial structures by naming the single-molecule transistor a "natural quantum dot." The finite length of the nanotubes makes them effectively zero-dimensional, that is, the same as quantum dots. And indeed, the present transport experiments on carbon nanotubes are well explained by the theory developed for quantum dots (*4*, *5*). The hope is that in future experiments, the physical consequences from the narrow and long geometry will be revealed. One-dimensional conductors have attracted a lot of theoretical interest because they are model systems for strongly interacting many-body physics. Maybe the carbon nanotubes will serve as the experimental system in which these exotic theories can be tested.

Whereas quantum dots show their quantum properties only when cooled to low temperatures (a few kelvin above absolute zero), the small size of single-molecule transistors allow them to operate at much higher temperatures. In fact, scanning tunneling studies on a C_{60} molecule by Porath and Millo (*2*) and on a carbon cluster by Soldatov *et al.* (*3*) still show transistor operation at room temperature. In this transistor, a single electron again makes the difference between an on state and an off state. Although the persistence up to room temperature is very promising, we still have a long way to go before we can integrate or couple different nanotubes to make a little electronic circuits. On the other hand, nanotubes have an interesting connection between their mechanical and electrical properties. For instance, a kink in a nanotube can change it from metallic to semiconducting (*10*). So, one can imagine building a specific electronic circuit by stretching and bending a couple of nanotubes here and there.

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IMMUNOLOGY

A Gut Reaction: Lymphoepithelial Communication in the Intestine

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Different parts of the body require different defenses against pathogens. The immune system is therefore regionally specialized and compartmentalized, in large part by the conditioning effect of the local microenvironment. On page 1937 of this issue, Wang and colleagues focus on the intestine and provide important new insight into the immunoregulatory effects on intestinal T cells of local hormonal networks, specifically thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH) (*1*). Their work illustrates the importance of studying the immune system in its natural environment.

The intestinal mucosa separates the external environment (the gut) from the internal milieu, forming the most extensive of such barriers in the body. The large surface area facilitates effective absorption of essential nutrients, but presents a problem—only a single layer of epithelium separates the intestinal lumen from the internal environment. So this anatomic design may not be optimal for excluding infectious, toxic, and otherwise harmless immunogenic material from the body. The dilemma is solved by adaptation of versatile immunologic and nonimmunologic defenses (*2*).

Strategic adaptation of the intestinal immune system is reflected in the molecular and cellular components of the mucosal immune system, which differ in several respects from their counterparts at other sites within the systemic immune system (*2*). Interspersed among the epithelial cells (enterocytes) lining the intestine are the intraepithelial lymphocytes (IELs) (see figure). The IELs are an important immunologic compartment; collectively, they represent a pool of cells comparable in size to that of all peripheral lymphocytes in the spleen. They are not only functionally and phenotypically distinct

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from peripheral lymphocytes, they also differ from lymphocytes within the lamina propria beneath the epithelium of the gut. The IELs, which have been referred to as "peculiar" and "curious" (*2*), have the features of activated and specialized cytotoxic cells. Almost all IELs are T cells, and most bear the CD8 surface receptor but exhibit considerable heterogeneity of surface phenotype (*3*).

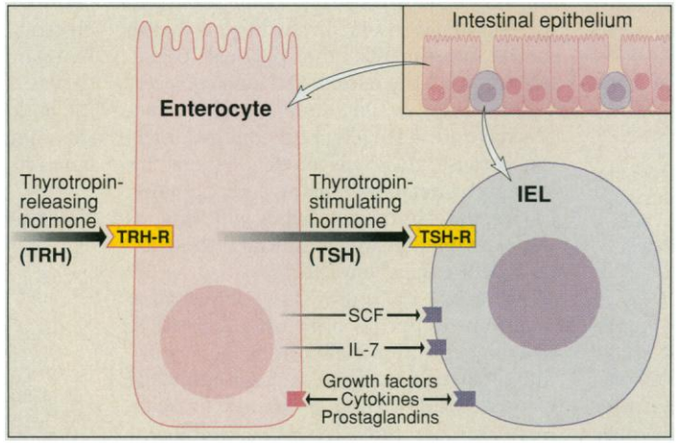
Details of the precise origin and pathways for development of IELs are still uncertain, but studies in mice have revealed two populations of IELs: one that is dependent on the thymic microenvironment for its differentiation and another that differentiates outside the thymus (*3*). As the thymic epithelial microenvironment is a site for self–nonself education and T cell differentiation, it appears that the gastrointestinal epithelium can serve the same function for a subset of IELs. In this way, the mucosal epithelium is a primary lymphoid organ. Indeed, the intestinal epithelium can justifiably be regarded as a component of the mucosal immune system. Enterocytes can present antigen, express secretory component, and transport immunoglobulin A into the intestinal lumen (*2*).

Specialization and maintenance of intestinal immune homeostasis is subject to the regulatory influence of the local microenvironment. Cellular communication networks within the intestinal mucosa are bi-directional, with mucosal immune cells transmitting and receiving regulatory signals to and from other residents of the mucosa. The report by Wang and colleagues now adds another layer of intrigue to intestinal lymphoepithelial interactions. These investigators have previously shown that nonimmunologic factors are involved in extrathymic development of so-called thymus-dependent IELs (*4*). Exogenous administration of the hypothalamic-derived neuropeptide TRH or TSH promoted the development of thymus-dependent IELs in athymic mice. In contrast, administration of thyroxin was associated with a strong tissue-specific immunosuppressive effect on precursor IELs, with minimal effects on differentiated IELs or other lymphocytes outside the intestine (*4*). This finding raised the prospect that TRH or TSH has regulatory effects on IELs that are independent of thyroxin, and that hormonal control of IEL development may occur locally after precursors arrive in the gut epithelium. The present work confirms the presence of a local paracrine network of hormonal regulation of IELs by intestinal enterocytes (see figure). TRH acts by way of receptors on enterocytes to elicit the release of TSH, which binds preferentially to IELs in comparison with other lymphoid and nonlymphoid cells. The central regulatory role of TSH was supported by the finding of selective impairment of IEL development in mice that have a defective TSH receptor caused by a congenital mutation of the TSH receptor gene (*hyt/hyt* mice).

This network occurs in the presence of numerous other epithelial-IEL interactions. Human intestinal epithelia express functional cytokine receptors, and their secretory and absorptive functions are modified by several cytokines and other immune-derived signals (*5*). IELs also regulate epithelial growth and development; mice lacking γδ IEL have severely impaired development of intestinal epithelia (*6*). Evidence for reciprocal communication from enterocytes to IELs is even more compelling. An example of tissue-specific homeostatic control of the immune system is epithelial-derived stem cell factor (SCF), which influences IEL maturation by acting on specific receptors on IELs (*7*). Local production of interleukin-7 by human enterocytes provides another receptor-mediated regulatory signal for IEL proliferation (*8*). Epithelial cells are also a potential source of several other cytokines and immunomodulatory factors such as complement components and prostaglandins (*2*). Some intestinal epithelial cell lines can deliver a death signal (the Fas ligand) to Fas receptor–bearing T cells (*9*). This suggests that some epithelial tumors can deliver a preemptive strike against activated T cells and thereby evade immune surveillance. Lymphoepithelial Fas ligand–receptor interactions may also be called into play in certain inflammatory states (*9*, *10*).

The new findings of a TRH-TSH network in the intestinal mucosa (*1*) present a challenge to current concepts of intercellular communication within the local immune system. The range of chemical signals that mucosal lymphocytes can respond to and transmit is now broader than previously considered. Cross-talk among immune and neighboring cells is achieved by shared ligands and receptors, and rigorous distinctions between growth factors, cytokines, local hormones, and neuropeptides are no longer appropriate (*11*). Additional issues that need to be resolved relate to the role of the TRH-TSH controlling network in mucosal inflammatory diseases. Does upregulation of neuropeptide receptors occur in inflammation? Are all subsets of IELs responsive to these regulatory signals? How does the finding that lymphocytes themselves can, under some circumstances, produce TSH (*11*) relate to the intestinal TRH-TSH network described here? Can the process be subverted by certain bacterial or viral infections?

For now, it is clear that a comprehensive understanding of the controlling influences on the immune system within mucosal and other tissues will require a look beyond the classical pathways of immunoregulation. Already well established is a bidirectional communication between the immune and neuroendocrine systems (*11*), but this is only one component of the immunoconditioning effect of the local microenvironment.



Cross talk in the intestine. Epithelial cells and intraepithelial lymphocytes (IELs) share several ligands and receptors that provide mutual, reciprocal regulatory signals. Coordination of this paracrine network is exemplified by the action of TRH by way of epithelial receptors (TRH-R) to elicit local release of TSH, which exerts a receptor-mediated (TSH-R) regulatory influence on adjacent IELs.

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