The Economist

Are laboratory mice too clean?

The hygiene hypothesis may also apply to animal experiments

THE hygiene hypothesis posits that certain diseases—notably asthma, eczema and type-1 diabetes—which are becoming more common than they once were, are caused in part by modern environments being too clean. The diseases in question result from misfunctions of the immune system. The hygiene hypothesis suggests such misfunctions are the result of children's immune systems being unable to learn, by appropriate exposure to viruses, bacteria, fungi and parasitic worms, how to respond properly.

If modern human homes are unnaturally clean, though, they are as nothing compared with the facilities in which experimental mice are housed. Those are practically sterile. That led Lili Tao and Tiffany Reese, two researchers at the University of Texas Southwestern Medical Centre, in Dallas, to wonder if such mice would display extreme versions of the predictions of the hygiene hypothesis.

This would matter, because mice are often used in medical experiments on the assumption that their reactions are similar enough to those of human beings for them to act as stand-ins. Conversely, laboratories' spotlessness might also mean mice are sometimes too healthy to act as useful models for disease. As they explain in *Trends in Immunology*, Dr Tao and Dr Reese therefore combed the scientific literature to look for both phenomena.

A nice example which the two researchers found of the hygiene hypothesis at work is that stopping laboratory mice being infected with murine cytomegalovirus, which is common in their wild kin, damages their immune response to a host of other pathogens, bacterial as well as viral. Mice so infected will survive subsequent exposure to otherwise-lethal doses of *Listeria monocytogenes* (a soil- and food-borne bacterium) and *Yersinia pestis* (the bacterium that causes plague). These mice are also better able than others to handle retrovirus infections. And the effects on them of multiple

sclerosis—an illness the underlying cause of which is suspected to be an inappropriate immune response—are reduced.

On the other hand, early infection with a different common pathogen, *Yersinia pseudotuberculosis*, affects murine immune systems in a way that leaves mice more open to subsequent attack, rather than less so—the reverse of the hygiene hypothesis. By unknown means, such infection permanently diverts immune cells called dendritic cells from their normal homes in lymph nodes and to the wall of the gut, where they cause sustained inflammation. Similarly, early exposure to certain herpes viruses, also common in the wild, can result in latent infections that cause no perceptible symptoms unless a kind of parasitic worm called a helminth also turns up. That reactivates the infection. Anyone attempting to mimic human worm infestations using mice should be aware of this.

Those studying vaccines, too, need to be aware of the confounding effects of hygiene. Laboratory-bred mice have fewer memory T-cells than those brought up in the outside world. Memory T-cells are the parts of the immune-system that remember prior infections, thus enabling a rapid response if the agent which caused that infection is encountered again. Generating such T-cell memories is a vaccine's job.

Moreover, an experiment done by Dr Reese herself showed that exposing young mice to human pathogens, such as herpes and influenza viruses, altered their subsequent responses to vaccines for other diseases. Animals so exposed produce fewer antibodies against a yellow-fever vaccine than do pathogen-free mice.

As is often the case with these sorts of preliminary literature reviews, the outcome is a grab-bag of intriguing results, rather than a coherent hypothesis or prescription for action. But the evidence Dr Tao and Dr Reese have assembled suggests there is something going on here that needs investigating. It seems to be a classic example of the law of unintended consequences. The point of raising mice hygienically is to eliminate as many uncontrolled factors from an experiment as possible. That hygiene itself might be such a factor has not, until now, crossed people's minds.

How to respond is unclear. Running trials twice, with “dirty” and “clean” mice, could be one approach. Another might be to agree on a set of bugs to which early exposure is permitted. What this work does show, though, is that in research, cleanliness is not necessarily next to godliness.