100 YEARS AGO

I should be obliged by your inserting the following experience if you think it remarkable. Yesterday we killed an adder (?) here, about 38 inches long; and seeing that he had made a meal evidently some little time before, out of curiosity we opened him, and extracted a large toad, which was about half-way down the snake's interior, or about 18 inches. The toad, whose head was much wider than the snake's, and whose body was many times as large as his enemy's head, we of course all thought must be dead; and we laid him on a flowerbed, wondering how he could have got inside the snake at all, for it certainly seemed a case of the greater being contained in the less. Of course we knew the marvellous stretching powers of a snake's jaws, but this seemed to eclipse them all. As we watched the toad he seemed to move, so we bethought ourselves of trying to revive him, and, after pouring water freely over him, and whisky and water down his throat, we were intensely astonished to see him revive; so much so that he stood up on all-fours, blown out like a balloon, and made a kind of a dart at a stick in the most comical way. Eventually "Jonah," as we promptly christened him, disappeared amongst the flowers. Can any of your readers quote a like case of resuscitation? Perhaps some of them might be able to afford information as to the probable duration of the toad's entombment.

From *Nature* 11 August 1898.

50 YEARS AGO

For nearly eighty years, one of the most prominent items of anatomical evidence in support of the antiquity of man in Australia has been a fragment of a supposed human molar, found by Krefft in the Wellington Caves of New South Wales. ... Recently, the human origin of the fragment has been questioned by Dr. T. D. Campbell, and I have considered *de novo* its possible relation to the lower mammals. ... After direct comparison with relevant material, I have no doubt that Krefft's find was derived from the posterior half of the upper fourth premolar or seccator, of the right side, of *Macropus (Protemnodon) anak,* Owen, a giant Pleistocene 'wallaby'....

From *Nature* 14 August 1948.

Thermodynamics

Cool sounds

Peter T. Landsberg

The turbines and crankshafts of the mechanical engineers have proved to be very useful, as everyone knows. But they produce noise, and unfortunately need oiling every now and again. How much better if engines could be constructed whose moving parts have been eliminated! Solar cells, for the production of electricity, are one way to go: the result is an elegant 'engine' in which only the electrons are the moving parts. In a paper[1] in *Physical Review Letters*, Reid, Ward and Swift describe another, but less familiar, transition to engines without moving parts. Moreover, by using a single gas both as the working part of the engine and as a heat-exchange medium, an old theoretical efficiency limit can be transgressed.

The principle that they explore is embodied in the thermoacoustic thermal engine and the closely related thermoacoustic refrigerator[2]. In a thermoacoustic heat engine, sound waves are generated by a heat flow, and the oscillatory motion of the gas in the sound wave is the only moving part in the thermoacoustic set-up.

The sound wave is contained in a resonator, closed at both ends. The engine receives heat at a high temperature from a heat source via a hot heat exchanger, and rejects heat at a lower temperature via a cold heat exchanger to a heat sink. In each acoustic cycle, the sound wave moves the gas back and forth a small fraction of the distance between these two heat exchangers, within a third heat exchanger called the 'stack'. The stack consists of a number of parallel plates open to the gas flow and of high heat capacity. Any given parcel of gas absorbs heat from one location in the stack during one extremum of its motion, and rejects heat to another, cooler location in the stack while near the other extremum of its motion. In this way, heat is ferried from the heat source to the heat sink.

Each such parcel of gas absorbs its heat while the sound wave imposes high pressure, and rejects its heat while the sound wave imposes low pressure. Hence the gas enjoys thermal expansion at high pressure and thermal contraction at low pressure, producing work and thereby reinforcing the sound wave.

As with many types of heat engine, the thermoacoustic engine can be reversed to become a refrigerator. Like the heat engine, the thermoacoustic refrigerator uses a standing wave in a resonator, but with all the energy flows reversed: the system receives heat at low temperature and rejects it at higher temperature, while absorbing acoustic power supplied by loudspeakers. There is a theoretical lower limit (based on the Carnot cycle) to the work required to produce a desired cooling power, proportional to the temperature difference. In the special case that the cooling power is used to cool a gas stream from the refrigerator's own high temperature to its low temperature, the lower limit on the work required to process a given gas flow rate is proportional to the square of the temperature difference.

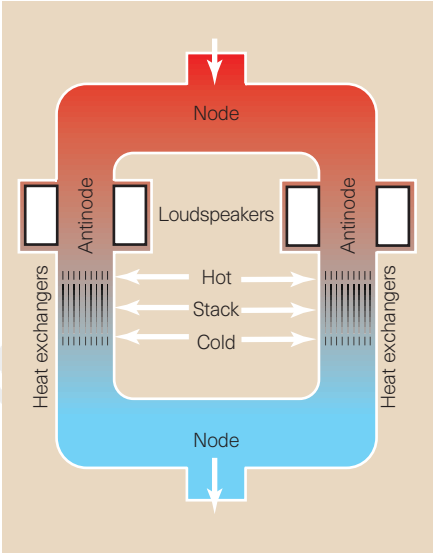

Figure 1 **A thermoacoustic refrigerator with an externally applied flow. By using the gas stream to be cooled as part of the mechanism, such a device could be more efficient than a conventional closed-off thermoacoustic refrigerator.**

But in a new development[1], experimentally demonstrated at the Los Alamos National Laboratory, the resonator is opened at both ends, and the flowing gas stream to be cooled is used as the thermoacoustic working gas (Fig. 1). This leads to the elimination of the cold heat exchanger that previously carried heat from the gas being cooled to the thermoacoustic gas. Furthermore, by providing almost a continuum of staged refrigerators to the flowing gas stream, this arrangement reduces the thermodynamic lower bound on the necessary mechanical power to half of the Carnot lower bound mentioned above. In the working model that the authors have built, the actual power required is still high, at about 25 times the ordinary Carnot lower limit, but with some simple refinements (such as increasing the size and pressure to reduce viscous losses) improvements are undoubtedly possible.

This technique won't revolutionize

ordinary air conditioning, as that is based on cooling air that is already inside a building, rather than pumping in warm air from outside and cooling that. But in-stream thermoacoustic cooling may find other more specialized uses, such as dehumidifying a compressed air stream. □

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1. Reid, R. S., Ward, W. C. & Swift, G. W. *Phys. Rev. Lett.* **80,** 4617–4620 (1998).
2. Swift, G. W. *Physics Today* **48,** No. 7, 22–28 (1995).

Immunology

Burnet's unhappy hybrid

Klaus Rajewsky

The clonal-selection theory[1] proposed by Burnet some 40 years ago holds that antibody-forming cells (B lymphocytes) are precommitted — before contact with antigen — to a single antibody specificity. The B cells then express antibody of that specificity as an antigen receptor on their surface. This theory was borne out by molecular analysis showing that individual members of families of gene segments called variable (*V*), diversity (*D*) and joining (*J*) are randomly assembled (so-called *V*(*D*)*J* recombination) into antibody variable-region genes during B-cell development[2] (Fig. 1). However, it has since become apparent that B cells can change their receptor specificity during development. Now, building on earlier evidence[3–7], Hertz *et al.*[8] (reporting in *Nature* last month) and Meffre *et al.*[9] (in the 17 August issue of the *Journal of Experimental Medicine*) suggest that mature B cells diversify their receptor repertoire in the antibody response. The cells do this by activating *V*(*D*)*J* recombination along with the well-established mechanism of somatic hyperpointmutation.

Somatic hyperpointmutation of antibody variable-region genes was the first mechanism of receptor modification to be discovered. It operates in T-cell-dependent antibody responses during proliferative expansion of the responding B cells in a particular microenvironment, the germinal centre. From the newly arising antibody mutants, those that show a high affinity for the immunizing antigen are selected into the 'memory' B-cell pool[10].

A second process by which B cells can change receptor specificity is based on 'secondary' *V*(*D*)*J* rearrangements. Each newborn B cell expresses a distinct antigen receptor, with a distinct combination of a V_H, a D_H and a J_H gene segment for the variable region of the antibody heavy chain, and a V_L and a J_L segment for that of the light chain ($V\kappa$ and $J\kappa$ or $V\lambda$ and $J\lambda$, depending on whether the cell expresses a light chain of class κ or λ)[2]. However, any B cell that expresses a particular κ chain can continue, or reinitiate, rearrangements of the variable-region genes to get rid of the $V\kappa J\kappa$ gene segment initially expressed. It can then express a new κ chain, or switch to expression of a λ chain. This is achieved either by rearrangements of upstream (non-rearranged) $V\kappa$ genes to downstream (non-rearranged) $J\kappa$ segments (Fig. 1), or by elimination of the $V\kappa J\kappa$ rearrangement carried by the cell, together with the κ constant-region gene on the same chromosome. Even in the case of the heavy chain, B cells can change specificity by rearranging a (non-rearranged) upstream V_H gene into the $V_HD_HJ_H$ complex that was initially assembled and expressed[10].

This change of receptor specificity by secondary variable-region gene rearrangements was initially identified as a process that eliminates autoreactive receptors in newly generated B cells in the bone marrow, and was termed receptor editing[11,12]. Receptor editing seems to be triggered when the receptor is engaged by (self) antigen, and it is now considered to be an important mechanism of immunological tolerance and also antibody diversification. Only cells that fail to revise an autoreactive specificity are 'clonally' eliminated, as was postulated by the clonal-selection theory. But it was subsequently discovered that variable-region gene rearrangements can also be reinitiated in peripheral B cells — both *in vitro* through appropriate stimuli, and *in vivo*, in the germinal-centre reaction[3–7].

Hertz et *al.*[8] and Meffre *et al.*[9] now point to an important difference in the control of receptor editing in early B-cell development, compared with what happens in peripheral B cells and the germinal centre. In peripheral cells undergoing editing, when ligands bind the receptor with high avidity, variable-region gene rearrangements are terminated, not induced. Meffre *et al.* showed this for human tonsillar B cells activated by CD40 ligand and interleukins. Hertz *et al.* did similar experiments with B cells isolated from mice with transgenic receptors. When these mice were immunized with antigen that bound the transgenic receptor with either low or high avidity, the authors found that *V*(*D*)*J* recombination was induced only when the avidity was low. So, the purpose of secondary *V*(*D*)*J* recombination in T-cell-dependent antibody responses does not seem to be (as one might have expected) the elimination of potentially harmful self-reactive antibody specificities arising in the germinal-centre reaction. Rather, *V*(*D*)*J* recombination diversifies the receptor repertoire in the responding cell population from which cells that bind antigen with high affinity are selected into the memory B-cell pool — similar to what is achieved by somatic hyperpointmutation.

Meffre *et al.* clearly show that, as in the mouse, gene rearrangements in human germinal-centre B cells are largely restricted to the 'centrocyte' subset, believed to originate from the proliferating 'centroblasts' in which somatic hyperpointmutation is occurring. But Hertz *et al.* document the initiation of *V*(*D*)*J* recombination in supposedly mature B cells *in vivo*, shortly (four days) after immunization, that is, before germinal centres usually develop. Thus, receptor diversification by secondary *V*(*D*)*J* recombination may be initiated before somatic hyperpointmutation.

We know that somatic hyperpointmutation occurs in most of the responding cells, but it is not clear to what extent receptor editing shapes the receptor repertoire upon antigenic stimulation. It could be restricted, for example, to a population of immature B cells drawn into the germinal-centre reaction — the editing cells resemble such cells to a surprising extent in terms of gene expression[5,9]. However, although the generation of a new antibody repertoire by rearrangements of variable-region genes in response to antigen was initially a displeasing thought to many of us, it could help to recruit useful antibody specificities into the memory B-cell pool. Most of the diversity of pre-germinal-centre antibodies resides in the complementarity-determining region III of the heavy chain (encoded by a *D* element, adjacent non-templated nucleotides and parts of *V* and *J*), and this region may be the main determinant of antigen binding specificity[13]. So, receptor editing — which seems mainly to affect the κ-chain loci — could produce an (initial?) set of antibody variants that express distinct light chains, but still bind the nominal, or a related, antigen. This may be an optimal substrate for somatic hyperpointmutation to produce a range of high-affinity mutants in response to an invading pathogen. Indeed, in the chicken, the germinal-centre reaction seems to involve a similar interplay of somatic hyperpointmutation and gene conversion[14].

Do these new results (and the process of somatic hyperpointmutation) challenge the clonal-selection theory, with its principle that antigen selects cells precommitted to an antibody specificity? Burnet, in his unique way, came close to where we now stand but did not seem to be happy with it[1]: "The only question that really arises is whether, on a background of … [clonal selection] …, a new mechanism has been