Nobel Prizes

Cell cholesterol wins the day

WHEREAS the division of the spoils is often controversial when it comes to Nobel Prizes, there will be no argument about the sharing of this year's Physiology and Medicine award between Michael S. Brown and Joseph L. Goldstein, for their collaboration has been remarkable by any standards. Since meeting as medical students in the 1960s, they have been apart only for a brief spell while Brown boned up on biochemistry and Goldstein on genetics, before setting up, in 1972, a joint programme on cholesterol metabolism at the University of Texas Health Services Center in Dallas where they continue to collaborate as equals. Of the "discoveries concerning regulation of cholesterol metabolism" for which the prize has been awarded, pride of place must go to Brown and Goldstein's relentless study of the cell-surface receptor for low-density lipoprotein (LDL). LDL is the major transporter of blood cholesterol and the LDL receptor is the key to the transfer of cholesterol from the blood to the interior of fibroblast and liver cells.

Brown and Goldstein have hounded the receptor with a combination of biochemistry, genetics, microscopy and, most recently, molecular genetics. As a result, the LDL receptor is more thoroughly understood than any other receptor and its study has been highly influential in promoting the general investigation of receptor-mediated endocytosis — the process by which many extracellular molecules are delivered to the interior of cells. In essence, Brown and Goldstein have demonstrated that complexes of LDL and receptor concentrate in "pits" formed in the cell-surface membrane and thence in vesicles that are pinched off from the pits. After fusion of vesicles in the cell's interior, the receptor and LDL part company. The receptor is recycled to the cell surface whereas the LDL is degraded in the cell, freeing the cholesterol from the protein constituents of LDL, so that it can be utilized in the cell.

Without a doubt these studies have benefited enormously from the existence of rare hereditary defects in the receptor, which result in the condition known as familial hypercholesterolaemia. Through molecular genetics, Brown and Goldstein have been able to discover exactly what is at fault with the receptor's gene in some patients, and therefore precisely why their receptors are defunct (*Science* **227**, 140; 1985, and *Cell* **41**, 735; 1985). For patients with a pair of defective genes, the result is excessively high blood cholesterol and LDL, with the development of coronary atherosclerosis usually before the age of twenty.

Not content with studying the receptor-mediated uptake of cholesterol into cells, Brown and Goldstein have recently collaborated with Paul Berg, a 1980 Nobel laureate, in cloning the gene for the key enzyme of cholesterol synthesis in tissue (*Nature* **308**, 613; 1984). The enzyme, known chiefly as HMG CoA reductase, is of particular importance because its production is subject to negative feedback regulation by cholesterol. If the mechanism of that feedback can be understood in terms of the gene, it will be possible to explore the possibility that gene defects are a factor in some cases of hypercholesterolaemia.

While it is still too early to be certain of the relevance of much of Brown and Goldstein's work to the prevention and treatment of atherosclerosis, their work has been of great fundamental importance and highly influential. So far all attempts to lure both of them from their opulent Dallas surroundings to more distinguished institutions have failed. Nobel prizes seem unlikely to make any difference nor to split such a close working partnership that no paper is published by either partner without the other. **Peter Newmark**

US diet

Back to the stew-pot

Washington

A PUBLIC row has erupted in the United States because the National Research Council has rejected the conclusions of a dietary study it commissioned five years ago to make new Recommended Dietary Allowances (RDAs) for nutrients and energy. The chairman of the study committee, Henry Kamin of Duke University, questions the competence of the research council's anonymous reviewers and accuses them of being "scared" of the policy implications of his report. Among other things, he would reduce RDAs for vitamins A and C, as the study wanted. Kamin blames the decision not to publish the committee's report on the "vulgarization of nutrition" in the United States.

Kamin's study was to have been the 10th edition of the research council's *Recommended Dietary Allowances*. Since they were first issued in 1941 as a guide for planning national food supplies, RDAs have expanded both in number and variety of applications, and are now central to many federal food assistance schemes. Kamin's committee was asked to derive RDAs "adequate to meet the unknown nutritional needs of practically all healthy persons".

The figures Kamin eventually arrived at differ — though usually by small amounts — from existing RDAs, but were "both rigorous and original", according to Kamin. Reviewers appointed by the Research Council believed, however, that modifications to RDAs should be made only in the light of "compelling new evidence" — which, they said, Kamin failed to provide.

After six months of revisions and re-revisions, reviewers and study authors were still unable to agree on what should be the proper RDAs for vitamins A and C, with some unresolved questions over the RDA for calcium (which, in contrast to those for the vitamins, the study authors wanted to increase). Frank Press, chairman of the research council, then stepped in to call a halt, and will now establish a new committee with a revised brief to take up the question raised.

One of the key differences between Kamin and the reviewers is whether the evidence needed to justify changing an existing RDA should be stronger than that needed to establish a completely new value. Some of the changes recommended by Kamin's committee were based on reinterpretations of the studies on which the existing RDAs are based; not all of these were accepted by the reviewers. But, according to Kurt Isselbacher, chairman of the research council's Food and Nutrition Board, Kamin's committee was "reluctant to accept criticisms" and displayed "tremendous inflexibility". Given the differences of opinion, the research council then had to decide whether it should issue new recommendations that were "scientifically no better than the old ones".

Another area of dispute was the weight that should be attached to the public impact of the recommendations. Despite Kamin's accusation that he was effectively asked "to steer the science to fit the policy implications", Isselbacher maintains that policy worries "were not a concern that was felt by most". Nevertheless, policy implications did provoke the question whether the scope of the study was adequate to formulate new RDAs, given new evidence about the relation between diet and some chronic diseases. For example, Kamin, concerned only with protection against nutritional deficiency, proposed a lowering of the RDA for vitamin A, but another report from the research council says that vitamin A might help to prevent cancer. Some reviewers were concerned about the effect on the public of such apparently contradictory recommendations.

For these and similar reasons, according to Frank Press, the next edition of the RDAs will include "a more encompassing analysis of data pertaining to nutrients and health". The new study group is to be chosen in consultation with the National Institutes of Health. In the meantime, writes Press, the public "should rest assured that there is no cause for concern". **Tim Beardsley**