Comment

Nobel prize criteria

All three recipients of this year's Nobel prize for medicine (see p 144) richly deserve the honour. At least two of them—Roger Guillemin and Andrew Schally—have clearly been in the running for several years. The third, Rosalyn Yalow, is associated with a technique that has already had an enormous impact on medical research and promises to revolutionise medicine in the future. Yet the awards also pinpoint weaknesses and inconsistencies in the way Nobellists are chosen.

The fact that the prize is not given posthumously deprives of Nobel status two scientists who would certainly have been included this year. All of Rosalyn Yalow's work was done during a 20-year collaboration with Solomon Berson, who died in 1972. And the man who created the field in which Guillemin and Schally won their honours, Geoffrey W. Harris, of Oxford University, also died in the same year. Harris's painstaking experimentations proved to his satisfaction that the brain communicates with the pituitary gland beneath it via a tiny system of blood vessels carrying chemical messengers. Others ridiculed the suggestion for many years. Harris was right, and Guillemin's and Schally's work in identifying the messengers stems directly from his achievement.

The fact that Guillemin and Schally lead large, variegated teams of senior and individually highly talented researchers raises a more difficult issue, one that is becoming more common as research by large groups displaces the lone scientist. Both men are aggressive, hard-driving, entrepreneurial scientists, putting together the problem, the team and—as importantly—the funding, to achieve their breakthroughs. Is it right that their more anonymous colleagues should be overlooked?

The last, and trickiest problem posed by this year's award, is the attribution of the discovery concerned. It is at least arguable that Yalow and Berson's radio-immunoassay is a specific application of a general—and novel—analytical technique developed independently by Roger Eakins and his group at the Middlesex Hospital, London, at the same time Yalow and Berson were working at the VA Hospital in the Bronx. Why then has Dr Eakins been omitted from a share of the award given to Rosalyn Yalow? *Graham Chedd*

Reactions to drug reactions

The need, in the light of the damage done by the heart drug practolol, for "earlier suspicions and recognition of adverse affects" is highlighted in the proposal advanced this week by the Association of British Pharmaceutical Industry for the post-marketing surveillance of reactions to new medicines *(British Medical Journal,* 15 October, p 1001). Strangely, the ABPI's starting point is to emphasise "the previous successes of various voluntary reporting methods". However, the "yellow card" system, whereby medical practitioners notify adverse effects to the Committee on Safety of Medicines (CSM), set up after the thalidomide disaster, failed lamentably to limit the damage done 15 years later by practolol.

The ABPI admits the need to explore ways of heightening doctors' awareness of possible harmful reactions and to report them. It does not discuss how the scale of such reporting might be increased considerably from its present pitifully low level. Great emphasis, on the other hand, is laid on the suggestion that, except when expressly forbidden by reporting practitioners, the value of such reports could be promoted by notifying them routinely to the drug company concerned.

If accepted, the ABPI's proposals would delay the introduction of large-scale schemes for monitoring the adverse effects of drugs in man in favour of pilot studies restricted to "new medicines that contain a new chemical entity and whose clinical indications require long-term administration". Given the thalidomide experience, it is difficult to understand why such studies have not been undertaken already.

Another surprising proposal is that to ensure *independent* assessment of data on drug reactions, and confidentiality of information, the agency responsible for registering treated patients could be "administered by one or more of the professional associations or colleges *or by the ABPI*" (my italics). This, the emphasis on cost-effectiveness, and the reservations about the number of patients that should be involved in following up the marketing of a new drug raise doubts about the ABPI's claim to scientific advantages over other systems. Fortunately, the subject will be thrashed out with other interested parties before the CSM finally decides on the form of a central scheme. It is to be hoped the suggestion that *patients* be directly involved in monitoring drug reactions will be given serious consideration in these discussions. *Ephraim Lesser*

Antarctic enlightenment?

Curiously inconsistent conclusions about the fate of Antarctica's resources emerged from the recent meeting in London of the 13 Antarctic Treaty Consultative Powers. On the positive side, a moratorium or ban on mineral exploration and exploitation was agreed until a framework for these activities had been established. The considerable environmental hazards attached to mineral recovery in this vulnerable area, combined with the aversion of certain powers to such restrictions, make this a particularly important achievement.

Turning to a more immediate prospect for exploitation—the living resources of the Southern Ocean surrounding the continent—the recommendations are distinctly less encouraging. There are good environmental grounds for introducing firm controls on Antarctic krill fishing. Although krill exists in large quantities, it constitutes the main food of many Antarctic marine creatures and our knowledge of its population dynamics is rudimentary. There is ample evidence of the speed with which commercial fisheries build up under normal conditions and today, with coastal state jurisdiction encroaching on traditional fishing grounds world wide, this process can only be accelerated. Yet, in part because they did not wish to invoke questions of sovereignty, the Antarctic Treaty Powers have ruled out any economic regulation of the krill fishery. Equally serious, no mention was made of the interest of the wider international community in this protein-rich resource, an interest which the UN Food and Agriculture Organisation is helping to articulate. What the Antarctic Treaty powers are in the process of farming is no more than a permissive regime in which benefit is monopolised by those with the capital and technology to harvest, process and market the krill.

Decisions to postpone Antarctic mineral exploration and exploitation and to respect the interests of the international community in these non-living resources are significant steps forward. Can we hope that some of this spirit will percolate thinking on Antarctic living resources before next Spring when Treaty Parties start drafting their definitive regime? Or must we conclude that such enlightenment is possible only when a resource has been written off technologically and economically for at least 15 years, and possibly indefinitely? *Barbara Mitchell*

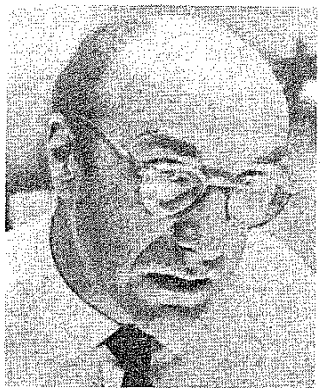
Nobel Prizes 1977
Medicine

. . . For the development of radioimmunoassays of peptide hormones

. . . For discoveries concerning the peptide hormone production of the Brain


AP
Schally


AP
Yalow


AP
Guillemin

The science and—increasingly—the practice of endocrinology have been revolutionised in the last decade by the two developments recognised by this year's Nobel awards for medicine. The first is an exquisitely sensitive analytical technique capable of detecting minute quantities of hormones in the bloodstream, quantities so tiny that the femtomole, just meaning 10^{-15} mole, has now become the routine unit of measurement. The technique, known as radioimmunoassay, has catapulted endocrinology into the forefront of medical research. It has also had an enormous impact on clinical medicine, permitting major advances in the diagnosis and treatment of thyroid disease, growth disorders and fertility problems. Some 50 to 60 million radioimmunoassays were carried out worldwide in 1976 alone. The second development has been the virtual founding of a new science, that of neuroendocrinology—the isolation, identification, synthesis and modification of the chemical messengers by which the brain exercises control over several of the body's major hormone systems, again including those involving thyroid function, growth and fertility.

In each of the areas covered by the awards, there is also the potential for even more spectacular future advances. The range of techniques covered by the term radioimmunoassay is extending into the measurement of almost any substance that is potent or significant at extremely low levels in the circulation. Interestingly, British researchers are at the forefront of this new technology, and several see the possibility in a few years of diagnosing a wide range of diseases by detecting minute abnormalities in the bloodstream before symptoms develop. The social and economic implication of such an ability would obviously be dramatic. From the science of neuroendocrinology, the optimists also see the prospect for a new class of highly specific and potent drugs permitting the fine tuning of several hormone systems, including a drug that could block fertility. Again, while the recognition of the Nobel committee went to two American researchers, this work had its origins in Britain and much of the pre-clinical testing of the compounds is being done in this country.

Rosalyn Yalow receives a half share in the prize for her work, conducted during a twenty-year collaboration with Solomon Berson at the Veteran's Administration Hospital in the Bronx, in developing the radioimmunoassay technique. Berson, who died in 1972, was trained as a physician; Yalow was a nuclear physicist with an interest in medicine. They came across the method almost by accident, when monitoring the fate of insulin administered to patients with diabetes. Antibodies produced in response to the insulin were binding to it in the patient's blood. By labelling the insulin with radioactive iodine, Yalow and Berson realised they could use the binding reaction to provide an assay for insulin.

At the same time, in the late 1950s, a team under Roger Eakins at the Middlesex Hospital in London were developing a parallel method, called by Eakins "saturation analysis". He explains the technique to his medical students by asking them to imagine a jug of water being poured into a cup, the excess water overflowing. The cup is the binding agent—in Yalow and Berson's method, an antibody; in Eakin's, any agent that will bind specifically to the compound being measured—in his analogy, the water. By visualising the water with a dye—or by labelling the compound with a radioactive tag—then looking at the distribution of the water between the cup of known size and the overflow, one can deduce the amount of water present initially in the jug.

Eakins first used his method to measure level of the thyroid hormone thyroxin and of vitamin B_{12}, in the blood. Yalow and Berson, using the method they called radioimmunoassay, employed it to detect and quantify insulin and later other peptide hormones. Yalow likens the impact of the technique in its ability to detect and measure substances previously beyond reach to the discovery of the microscope. Eakins says that until the technique became available, endocrinology "had been floundering around in the darkness". With it, the subject has taken off. The most important advances have come in the study of the peptide hormones produced by the front lobe of the pituitary gland, the grape-sized organ that nestles beneath the base of the brain. These hormones include ACTH, which has the adrenal gland as its target organ; growth hormone, important in regulating the size to which we grow; thyroid stimulating hormone (TSH); and the two fertility hormones, LH and FSH, which regulate the ovaries in women and the testes in men.

The radioimmunoassay technique has been crucial in allowing the study of these hormones in research, and is presently being employed, *inter alia*, to sort out the parenthood of the hormones, all of which appear to be chopped-down versions of larger molecules. But the analytical technique has also become an indispensable tool of modern clinical medicine, enabling these hormones and others to be rapidly and inexpensively quantified in a variety of disease states. For example, thyroid disease can now be simply diagnosed and its treatment monitored; the use of scarce and costly human growth hormone in the treatment of dwarfism can now be much more finely controlled; and the fields of both male and female infertility have been trans-

formed by the ability to measure LH and FSH levels. Indeed, one slightly embarrassed endocrinologist last week admitted that the technique was so powerful it has allowed his branch of medicine to progress perhaps beyond its actual importance in terms of the severity and frequency of hormone disorders.

And the story by no means ends with the peptide hormones, even though it is this application of the radioimmunoassay technique that is cited in the Nobel award. In Britain in particular, the method is being extended to detect and quantify a range of substances important even in femtomole concentrations in the circulation. For example, it can be used to monitor how much of a very potent and potentially toxic drug like digoxin is absorbed into the bloodstream of a patient so that his dosage can be accurately adjusted to be therapeutic and not lethal. It is used to detect alpha-fetoprotein, a molecule whose presence in the mother's bloodstream is used to diagnose neural crest disease (such as spina bifida) of the fetus. And, in the future, the technique is likely to be extended to spot and measure abnormalities in a host of molecules in the circulation, some of which—such as specific cancer antigens—may act as markers for diseases in their early pre-symptomatic state.

Roger Guillemin of the Salk Institute and Andrew Schally of the VA Hospital in New Orleans, who share between them the other half of medicine prize, are old rivals in a field pioneered by Geoffrey W. Harris of Oxford. Harris died five years ago, having lived to see his once controversial idea that the brain communicates with the pituitary via chemical messenger molecules vindicated by Guillemin's and Schally's identification of the first such messengers in the early 1970s. Both Guillemin and Schally adopted US-style solutions to the molecules' isolation: huge quantities of starting materials—in Guillemin's case, for example, hundreds of thousands of sheep's brains—and large research teams. Guillemin was first, with the messenger that triggers the release of TSH from the pituitary, called TSH-releasing-factor, or TRF. Schally stole the glory with LH-releasing-factor, or LRF, announcing a structure just weeks ahead of Guillemin. Guillemin took the lead again when his team isolated somatostatin, a factor that *inhibits* the release of growth hormone. (This was after an embarrassing episode in which Schally announced a growth hormone *releasing* factor, only to discover later it was a fragment of the haemoglobin molecule; such are the pressures of the rivalry.) Schally is now rumoured to be on the verge of claiming the most elusive of the releasing factors, that for ACTH.

Both Schally's and Guillemin's groups are very active in synthesising analogues of the releasing factors—molecules in which the structure of the native hormone is modified slightly. These analogues are being devised with two major goals in mind. First, to find long-lived and more potent versions of the natural hormones for use in replacement therapy of patients lacking this form of brain-pituitary communication. And second, to find antagonists of the brain's own releasing factors, so that the communication can be deliberately disrupted. The great hope here is for an anti-LRF drug, which could switch off the fertility hormones in men as well as in women. Because the regulations covering the testing of new compounds on human volunteers are less strict here than in America—and also because Schally has many personal contacts in this country—much of the testing of these releasing factor analogues is going on in Britain. Guillemin meanwhile has extended the research of his team to include the now highly fashionable field of neurally active peptides, in particular the endorphins, molecules apparently derived from the same parent molecules as some of the pituitary hormones, and possessing powerful, if still largely unexplained and undefined, effects on the brain.

Graham Chedd

Physics

. . . for fundamental theoretical investigations of the electronic structure of magnetic and disordered systems

Anderson

Van Vleck

Mott

There must be a better way of informing Nobel prize-winners that they've won the coveted award. John Van Vleck was awoken bleary-eyed by the *Boston Globe;* Nevill Mott was poised between meat course and sweet in a pleasant Marburg restaurant when the press agency rang; and Philip Anderson was enjoying a rustic moment's planting in his garden when the media descended with the news. It explains one thing: why the press photos of Van Vleck last week generally had him garbed in bathrobe and pyjamas.

Van Vleck, at 78, was suspicious of the *Boston Globe's* news. His prize is principally for the work he did on the quantum theory of magnetic materials before the Second World War. And, eyeing the reporters, he recalled an old colleague, Professor P. W. Bridgeman, who had been approached by the press in a similar way, blushed with pride and explained the import of his work, only to learn later that the press had been wrong: he hadn't won the prize at all. (Bridgeman did win it later, in 1946.)

This time, however, the news was right. Van Vleck was one of the tiny handful of American physicists who, before the efflux of refugee intellectuals from Europe, were in a position to apply the new quantum mechanics of Schroedinger and Heisenberg. Van Vleck told *New Scientist* that his doctoral thesis "was probably the first in pure mathematical atomic physics in the US". Submitted to Harvard in 1922, it concerned the application of the old Bohr quantum theory to the two-electron helium atom. It did not work, and "looking back I'm surprised I ever thought it might". But when Schroedinger's equation was published in 1924, launching modern quantum theory, Van Vleck was prepared. "I was very lucky".

Van Vleck became a master craftsman of quantum