statistical thermodynamics. Prigogine, Résibois, and others of the Brussels school have played a leading part in developing kinetic theories that are applicable to all fluids. One of the principal tools of this research has been to exploit the analogies between the Liouville equation, which describes how a molecular system evolves, and the time-dependent Schrödinger equation of quantum mechanics.

A second line of attack has been to push the macroscopic treatment of Onsager beyond the narrow range of situations in which flows depend linearly on forces. If this could be done then a whole range of new phenomena would come within the scope of non-equilibrium thermodynamics, such as the turbulent flow and convective instabilities of hydrodynamics, and chemically reactive systems that oscillate in space or time. However a macroscopic description implies that we can define such statistical properties as pressure, temperature and entropy even if the system is far from equilibrium. Prigogine showed that such an assumption is a sufficient condition for the use of thermodynamic methods and justified it in certain cases, for example, by showing that even in fast gas reactions the molecular distribution of velocities shows little departure from a local Maxwellian distribution.

The behaviour of fluctuations of these local properties distinguishes stable from unstable systems. Spontaneous fluctuations are always occurring but, except at a critical point, are usually unimportant. In a system with weak potential gradients each fluctuation quickly regresses to the steady-state behaviour, but when gradients are large then the fluctuations can grow until a new pattern of flow is established, for example the Bénard cells of rotating elements of fluid in a liquid heated strongly from below. Prigogine has sought to marry the classical theories of

stability of structures with a generalised thermodynamics which would encompass such dissipative systems. He does this by introducing a 'local potential', which is a generalisation of the more familiar chemical potential, and then by using a variational principle to calculate the flows. The boundary between the stable or steady states and the dissipative structures is described by an 'excess entropy production' which is positive for the former and negative for the latter.

These new methods encompass many of the traditional ones used in discussing hydrodynamic instabilities, but their more interesting applications lie in the field of chemical reactions. This is, first, because reaction rates are, in practice, never linear in differences of chemical potential, and secondly because of the biological occurrence of systems in which complex chemical reactions are coupled to flows of matter and energy. He and his colleague, G. Nicolis, have used these methods to investigate the conditions under which reaction systems can oscillate in space and time with the aim of developing a thermodynamics that is applicable to biochemical systems.

Whatever new results emerge it is clear that Prigogine, both by his writings and by his enthusiastic advocacy, has changed the ways in which we can discuss a variety of difficult problems. He is, above all, a man of original ideas. In his book (with P. Glansdorff) *Thermodynamic Theory of Structure, Stability and Fluctuations* (1971), he quotes Bergson's saying of 1907 that the second law of thermodynamics is the most metaphysical of all laws of nature. He adds, "Whether a compliment or a criticism, this applies also to the 'generalised thermodynamics' we develop in this monograph".

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The Nobel prizes (3): Physiology and Medicine

Starting a revolution

Jesse Roth and J. E. Rall on Rosalyn Yalow

DR Rosalyn Yalow was awarded a Nobel prize for medicine and physiology in 1977 for the development of the radioimmunoassay. The introduction of the radioimmunoassay for plasma insulin in humans (R. S. Yalow and S. A. Berson, *Nature* **184**, 1648; 1959; *J. Clin. Invest.* **39**, 1157; 1960) started a revolution in endocrinology which spread from insulin to other peptide hormones including substances previously thought not to be antigenic, to steroid and thyroid hormones and to the cyclic nucleotides. Like other great revolutions it spread rapidly to encompass other fields including clinical pharmacology, enzymology, oncology, virology, immunology and haematology. The recent explosion of studies of cellular receptors for hormones, neurotransmitters, lipoproteins and drugs has its technical and intellectual roots in the radioimmunoassay.

Missing from the Nobel citation is the name of Dr Solomon A. Berson who died in 1972. Nobel prizes are not awarded posthumously, but historians and scientists everywhere recall the hundreds of joint publications of Yalow and Berson in the two decades that flank the publication of the seminal papers that introduced the radioimmunoassay.

To appreciate the revolution that the radioimmunoassay wrought it is necessary to recall the incredible state of endocrinology in 1960. The peptide hormones, which constitute about 80% of all hormones, could not, with rare exception, be measured in blood or other biological fluids. If one wished to study the dynamics of insulin *in vivo*, one could only guess from measurements of the blood glucose, or

some other very distant component in the complex of reactions that regulate the blood glucose. Biological assays were available to measure the high concentrations of hormones in extracts of glands but these assays were orders of magnitude too insensitive and lacked the necessary specificity for measurements of hormones in blood.

How was it possible to measure peptide hormones at concentrations of 10^{-10} M in a sea of contaminating proteins at 10^{-3} M, when these hormones were virtually indistinguishable from thousands of other peptides and proteins in the blood? To solve this problem Berson and Yalow used antibodies to insulin, which they had recently characterised and had shown were capable of binding insulin but no other substances. Insulin that they labelled with radioactive iodine was reacted with antibody that had the desired specificity and the then unheard of affinity constant 10^{10} L/M. Conditions were set so that minute concentrations of unlabelled insulin competed with the labelled insulin for binding to the antibody. By measuring the ratio of radioactively-labelled insulin that was bound to antibodies to that which was free, the precise concentration of unlabelled insulin in the system could be determined.

This simple method of measurement of hormones in the blood was made possible by a series of conceptual leaps and technical innovations by Yalow and Berson in the preceding five years. They discovered that all insulin-treated patients generated antibodies to the hormone and recognised the problem of species specificity among insulins. They recognised the need to find antibodies with affinities so high as to be undreamed of by immunochemists of those days. They introduced methods to protect and purify proteins that were being labelled at high specific radioactivity. They devised a rapid precise method for separating antibody-bound hormone from free hormone and characterised in detail the kinetics and thermodynamics of insulin antibody interaction.

With precise and specific measurements for plasma hormone, it became clear that many of the earlier guesses were incorrect. For example, the radioimmunoassay proved that only a minority of diabetics have an absolute deficiency of insulin. Most diabetics have normal or supernormal amounts of insulin which is biologically intact but the cells of these diabetics are subnormally responsive to insulin. Yalow and Berson not only introduced the radioimmunoassay for insulin but applied the method to study the physiology of many other peptide hormones, including growth hormone, parathyroid hormone, adrenocorticotropin and gastrin. They also used this approach to devise a very sensitive method for detecting hepatitis virus and its antibodies in blood, which is widely used in blood banks in the United States and elsewhere. Other applications to problems of infectious diseases are now emerging. Although just beginning, the extension of radioimmunoassay to measure blood levels of drugs, including cardiac glycosides, anticonvulsants and antibiotics, has made it much more feasible for physicians to achieve therapeutic effects without sustaining serious untoward effects of these agents. The principle of competitive binding assays has been extended beyond antibodies to other binding substances of appropriate specificity and affinity.

In the light of these extraordinary scientific accomplishments, it is interesting to recall Dr Yalow's own modest personal and academic background. Born in 1921, she was raised in the South Bronx, the area that is now recognised as the most devastated in the urban United States. She was the first physics major at Hunter College, and although she graduated *magna cum laude* and *phi beta kappa*, her future was clouded by the fact that she was both Jewish and female, two traits which were not considered to favour success in physics in those days. In part because the military draft was depleting the ranks of eligible males, Dr Yalow was accepted by the University of Illinois, and after receiving her Ph.D in physics she returned to New York, where she worked until the end of the Second World War. In 1947, when applications of radioactive isotopes to clinical medicine were in their infancy, Dr Yalow joined the newly formed radioisotope unit of the

Veterans Administration Hospital in the Bronx where she has worked ever since.

Dr Berson, from a similar background, joined the radioisotope unit in 1950. His participation in the research was much less direct after 1968 when he assumed the chairmanship of the Department of Medicine of the Mount Sinai School of Medicine. In spite of his sudden death four years later, there has continued a flood of exciting new studies from the laboratory (renamed the Solomon A. Berson Research Laboratory) at the Bronx Veterans Administration Hospital under Dr Yalow's solo leadership. It has become clear that each peptide hormone in the blood is not a single substance but is rather a family of related peptides that include the active hormone, modifications of the active hormone, precursors and degradation products, as well as phylogenetically related peptides. Dr Yalow has been the major contributor to this area over the last decade and has extended these observations to numerous biological problems *in vivo*.

Her achievements are the subject of editorials in *The Daily News* and *The New York Post* as well as the subject of hundreds of sermons in churches and synagogues throughout the area. Dr Yalow is being viewed as an example of how talented and determined people of modest background can become world champions even in today's America. Women's groups all over North America have turned to her as a symbol. The Urban Crisis Task Force, which has its headquarters in the South Bronx, sees her as an ideal and has decided to name one of their new housing projects in her honour. □

Yalow

Inadvertent collaboration

George Fink on Roger Guillemin and Andrew Schally

DR Roger Guillemin of the Salk Institute and Dr Andrew Victor Schally of the Veterans Administration Hospital, New Orleans, were awarded the Nobel prize in physiology and medicine for isolating, characterising and synthesising three polypeptides which mediate the neural control of the anterior pituitary gland. The discoveries of Schally and Guillemin have already proved significant for clinical and basic medical science and are likely to offer new and safer methods for the control of population size.

The delight of neuroendocrinologists will only be dampened by the fact that the untimely death in November 1971 of Geoffrey Wingfield Harris, FRS, prevented him from sharing the fruits of his labours. As a medical student at Cambridge, Harris was the first (1937) to provide experimental proof for the then tentative view that the anterior pituitary gland was controlled by the central nervous system. The elegant studies carried out by Harris in the 1940s and early 1950s, alone and in collaboration with Dora Jacobsohn and the late John Green, established beyond doubt that this control was mediated by a neurohumoral mechanism involving the transport by hypophysial portal

vessel blood of chemical substances from the hypothalamus to the anterior pituitary.

The three polypeptides and their amino acid sequences are: thyrotrophin releasing factor (TRF) pyro Glu-His-Pro-NH₂; gonadotrophin releasing factor (GnRF) pyro Gly-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH₂; and somatostatin (or somatotrophin release inhibiting factor, SRIF) H-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH. Synthetic TRF and GnRF are now widely used in the investigation of thyroid dysfunction and infertility, respectively. Because TRF releases prolactin as well as thyrotrophin, the tripeptide is also used for investigating patients in whom prolactin secretion appears to be abnormal. Conceivably, antagonists of TRF may prove useful for controlling hyperprolactinaemia, a condition frequently associated with infertility in women, and for the control of hormone dependent tumours of the breast.

Superactive analogues of GnRF, made by substituting a D-amino acid (for example D-Trp, D-Ala or D-Leu) for Gly⁶ and an ethylamide group for Gly¹⁰, are being investigated mainly by Schally's group with a view to improving the precision of ovulation in women who prefer to or must use the rhythm method of fertility control. The parent decapeptide has already been used successfully for the treatment of certain types of infertility in men and women. Because GnRF will only discharge the amount of luteinising hormone (LH, the hormone which triggers ovulation) normally available for release, the risk in terms of pro-