The Nobel Prize in Physiology or Medicine 1977

Press Release

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The Karolinska Institute has decided that the Nobel Prize in Physiology or Medicine for 1977 should be divided, one half being awarded jointly to

Roger Guillemin and Andrew Schally

for their discoveries concerning "the peptide hormone production of the brain" and the other half to

Rosalyn Yalow

for "the development of radioimmunoassays of peptid hormones".

This year's Nobel Laureates in Physiology or Medicine have made their discoveries within the field of peptide hormones (peptides being substances built up by chains of amino acids). Many hormones in the body belong to this group and are produced by the hypophysis, the thyroid gland, the parathyroid glands, the placenta, the gastro-intestinal tract and other tissues. New such hormones are still being discovered.

While chemical methods for quantitative analysis of other hormones in blood and urine were in common use in the middle 1950's, such specific analytical procedures were not available for peptide hormones. The main, but not the only reason for this was their occurrence in blood in extremely low concentrations. For example, the molar concentration of pituitary ACTH under basal conditions is 1×10^{-12} . To measure such a

small amount of ACTH with prevailing biological methods as much as 250 ml of blood was necessary!

The lack of specific procedures to measure peptide hormones in blood with some degree of accuracy brought about stagnation within a large section of biological and medical research. And what was worse, on the basis of unreliable biological determinations of peptide hormones, hypotheses on physiological mechanisms and pathological events were advanced which led research astray.

The contributions of **Rosalyn Yalow** have to be regarded in the light of this context. Together with her late coworker, Solomon Berson, she was able to pull down this barrier to development - and this was accomplished in a most unexpected way. Yalow and Berson, towards the middle 1950's made the surprising finding that people who had received injections of the polypeptide hormone insulin - be it for diabetes or for treatment of schizophrenia - had developed antibodies against the hormone. This conflicted with the prevailing concept which was that such a small protein as insulin could not be antigenic. It took considerable time before this was accepted. In addition, some other findings were made that would become crucial to this whole field of research: the insulin antibodies formed a soluble complex with added insulin labeled with radioactive iodine and, furthermore, when non-labeled insulin was added to this mixture it could displace the labeled insulin bound to the antibody. This may be expressed in another way: the percentage binding of labeled insulin to the antibodies is a function of the total insulin concentration in the solution. This was to become the starting-point for radioimmunological determination of insulin and, later, for all peptide hormones in blood, other fluids and tissues.

In a series of brilliant, now classical papers between 1956-60 they described the radioimmunological assay method (or RIA) in detail. It was accomplished by a spectacular combination of immunology, isotope research, mathematics and physics. RIA is so sensitive that it allowed determination of insulin in amounts as small as 10-20 pg and ACTH in an amount less than 1 pg (or one thousand-billionth g) per ml.

RIA brought about a revolution in biological and medical research. We have today at our disposal a large number of RIA-like procedures, so-called ligand methods, for determination of almost anything we wish to measure: peptide hormones, hormones that are not peptides, peptides that are not hormones, enzymes, viruses, antibodies, drugs of the most different kinds etc. This has brought about an enormous development in hitherto closed areas of research.

But Yalow's contributions were not limited to presenting us with RIA. In a series of classical articles she and her coworkers, with the aid of RIA, were able to elucidate the physiology of the peptide hormones insulin, ACTH, growth hormone, and also to throw light upon the pathogenesis of diseases caused by abnormal secretion of these hormones. Thus, they directed diabetes research into new tracks and gave it a new dimension. This was pioneering work at the highest level. It had an enormous impact. We were witnessing the birth of a new era in endocrinology, one that started with Yalow. This modern

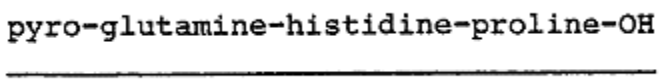
endocrinology continues to develop and gives us continuously new outlooks on the causes and nature of diseases within the whole spectrum of medicine.

The discoveries of **Roger Guillemin** and **Andrew Schally** deal with another sector of peptide hormone physiology and medicine.

The pituitary gland secretes a number of hormones which are transported with the blood to most hormone producing glands in the body. In these, they stimulate their specific function - to produce and release hormones. It has long been known that the central nervous system in some way could modulate endocrine functions and that, probably, the brain stem - the hypothalamus - acted as an intermediary in this process. In some way, information was passed to the hypophysis which, by way of its specific hormones, transferred the information to the other endocrine glands. As early as 1930, it was discovered that small blood vessels connected the hypophysis with the hypothalamus, and that these might be the route of transport of the information from the brain to the hypophysis.

Towards the end of the 1950's, Guillemin and Schally, each in his own laboratory, were able to extract from the hypothalamus of sheep and pigs some compounds which, when administered to pituitary tissue, brought about release of its hormones. One extract made the pituitary release ACTH, another TSH (**T**hyroid **S**timulating **H**ormone), a third one LH and FSH (the gonadotrophic hormones) etc. They termed these substances "releasing factors or hormones", RF or RH. The one inducing the release of TSH, thus was called TSH-RF or TRF.

However, it was not until 1969 that the nature of these hypothalamic factors would be established. Guillemin was working with 5 million hypothalamic fragments from sheep, and Schally with the same amount of material but from pigs. They concentrated their efforts to the search for one of the releasing factors, TRF. After years of struggle, during which the two groups established a formidable race, they stood there one day with 1 mg (!) of a pure substance with one single mode of action: it released TSH from the hypophysis. This was TRF. After another few months the structure of TRF was established. It is an extremely small peptide composed of three amino acids in a special fashion:



Within the same year TRF was synthesized by the Guillemin group.

The ice was broken. Within two years LH-RH was isolated, sequenced and synthesized, firstly by Schally and shortly afterwards by Guillemin.

Guillemin's and Schally's discoveries laid the foundations to modern hypothalamic

research. The experiences from animal research was rapidly transferred to humans and brought into clinical work. Several new peptides were isolated from the hypothalamus, the foremost one probably being the first inhibitor of pituitary function: somatostatin, which decreases the production of pituitary growth hormone.

As an extension of Guillemin's and Schally's discoveries may be regarded the exciting finding of peptides in the brain with morphine-like activity, the endorphines. Peptides with hormone-like activity have also been identified in other parts of the brain. The central nervous system more and more moves forward as an endocrine organ, which opens fascinating perspectives in medicine. We are looking forward to an enormous development in this field, to which Guillemin and Schally opened the door.

The important discoveries by the 1977 Nobel Laureates in Physiology or Medicine has led to a formidable development of their own fields of research. Further, they have opened new vistas within biological and medical research far outside the borders of their own spheres of interest.