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.

Yalow

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 degraduation 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. □

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 aminoacid 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-aminoacid (for example D-Trp, D-Ala or D-Leu) for Gly^6 and an ethylamide group for Gly^{10}, 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-

ducing multiple pregnancy is negligible compared with that of administering exogenous gonadotrophins. Concern about the safety of the steroid contraceptive 'pill' has added impetus to the search for other chemical contraceptives.

As well as inhibiting the release of growth hormone, somatostatin inhibits the release of thyrotrophin, prolactin, insulin, glucagon and gastrin. In spite of these widespread effects, early trials suggested that the tetradecapeptide may prove useful for the control of certain aspects of diabetes mellitus. An inhibitory effect of somatostatin on platelet aggregation has, however, made it mandatory for clinicians to proceed with caution.

As expected, access to large amounts of the three peptides, which are relatively easily synthesised, has proved invaluable for investigating the physiology and biochemistry of the hypothalamic-pituitary system. Perhaps of greater importance, however, is the fact that the peptides have reawakened interest in extra-hypothalamic peptidergic neurons, a field which has largely remained dormant since the studies of Gaddum and Von Euler on substance P (1931). Using antisera to TRF, GnRF and somatostatin, immunoassay and immunohistochemical studies have shown that relatively large amounts of these peptides are present in areas outside the hypothalamus, including the cerebral cortex and spinal cord.

The small amount of polypeptide in the hypothalamus (nanogram quantities), the protected N and C terminals of TRF and GnRF, and the fact that the hypothalamus contains more pharmacologically active substances than any other tissue, made the isolation of the three peptides exceedingly difficult. Both Schally with Murray Saffran at McGill, and Guillemin in Houston, started their isolation studies on corticotrophin releasing factor (CRF). Subsequently, at Baylor University, they collaborated on this project, but, by the early 1960s, they realised that for various technical reasons, notably the lack of a specific assay for CRF, it would have been better to leave the investigation of this potentially important factor until last.

After Schally became chief of the Veterans Administration Endocrine and Polypeptide Laboratory in New Orleans (1963), the alarming rivalry which soon developed between the two Laureates provided the necessary stimulus for the completion of their Herculean task. Almost every result obtained by one was checked by the other, and, although separated more by passion than distance, much of the work proved inadvertently to be collaborative. Thus, for example, Guillemin and his co-workers were the first to show that hypothalamic extracts could release thyrotrophin (*C.R. Acad. Sci. Paris.* **255,** 1018, 1962). Schally's group revealed that His, Glu and Pro were the aminoacids present in porcine TRF (*Biochem. Biophys. Res. Commun.* **25,** 165, 1966). On the basis of the activity of various synthetic tripeptide isomers of these acids, both groups reached the conclusion in 1969 that TRF was likely to be pyro Glu-His-Pro-NH2.

Shortly afterwards, Guillemin reported that the structure of natural ovine TRF was identical to that of the active isomer as assessed by infrared, mass and nuclear-magnetic resonance spectrometry (*C.R. Acad. Sci. Paris* **269,** 226, 1969; *Nature* **226,** 321, 1970). Schally, found that natural porcine TRF was also identical to pyro Glu-His-Pro-NH2 as assessed by identical Rf values in various chromatographic systems (*Biochem. Biophys. Res. Commun.* **37,** 705, 1969) and by spectral analysis (*Biochemistry* **9,** 1103, 1970).

Samuel (Don) McCann in 1960 and Geoffrey Harris in 1961, using respectively the ovarian ascorbic acid depletion method of Albert Parlow (an assay used extensively by Guillemin and Schally) and the rabbit ovulation test, reported that hypothalamic extracts released LH. After ten years of intense work carried out by several groups, Schally was able to announce in 1971 that his team had determined the structure of porcine GnRF (*Biochem. Biophys. Res. Commun.* **43,** 393 and 1334). The amino-acid sequence was confirmed by Guillemin's group who used ovine tissues (*Proc. Natn. Acad. Sci.* **69,** 278, 1972). Both groups agreed that the decapeptide releases LH and follicle-stimulating hormone (FSH) (hence Schally's preferred term, LH–RH/FSH–RH). Earlier evidence for the existence of a separate releasing factor for FSH appeared to be due to the non-specific effects of polyamine contaminants. So far there is no convincing biochemical evidence for the existence of a FSH–RF distinct from the decapeptide, and this is disappointing since it makes remote the possibility of developing an acceptable male contraceptive 'pill'.

McCann and his co-workers (*Endocrinology* **83,** 783, 1968) first demonstrated the presence in fractions of sheep and rat hypothalamic extract of a growth hormone inhibitory factor and a growth hormone releasing factor. The structure of ovine growth hormone inhibitory factor (somatostatin) was reported by Guillemin's group in 1973 (*Science* **179,** 77). In spite of extensive studies the structure of growth hormone releasing factor remains unpublished.

Since the isolation of the three polypeptides, Schally's team have focused attention on the development of potent agonists and antagonists of GnRF, as well as on the isolation of prolactin-inhibitory, corticotrophin-releasing and growth-hormone-releasing factor. As well as developing analogues of the peptides, Guillemin has concentrated his efforts on the endorphins, his most significant recent contribution being the isolation of a pituitary protein (MW 31000) which appears to be a common precursor of β-endorphin and ACTH.

Apart from their expertise in chemistry and physiology, and their tenacity and perseverance, the success of the two Laureates depended on the recognition in the early sixties that the isolation of each hypothalamic factor required an all or none approach. They had the capacity to attract research funds amounting to many millions of dollars which enabled them to assemble large teams of competent chemists and biologists, and as well, purchase the many hundreds of thousands of hypothalamic fragments necessary for successful isolation.

Since the late 1950s, when he began to test ovine hypothalamic fragments for LH-releasing activity, Geoffrey Harris was determined to isolate LH–RF. He managed to secure only one senior chemist at a time : first Peter Fawcett at Mill Hill and then (1966) Harry Gregory at ICI. In the light of the resources available to the American teams, it is perhaps remarkable that, using only a few thousand fragments, Gregory had by 1970 isolated six of the aminoacids in GnRF and had shown that this factor had no free α amino groups (*Control of gonadal secretion*, eds. Baird and Strong, page 15). Is there a lesson here for the funding of British biomedical research?

Guillemin, Schally