INTRODUCTORY REMARKS: REGIONAL ECONOMY AND FAMILIES OF NEUROREGULATORY SUBSTANCES

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THE PROGRAM Committee have indeed been generous to its Chairmen. In an inordinately hard pressed and concentrated program they have given them the most precious commodity of time: An unusual concession, for which I am grateful.

Looking at this program, I suspect that we are passing through a historic phase. The information explosion alone suggests that something important is afoot: Never has the growth curve been so steep. Yet, size and complexity do not change the givens and basic purposes of a field. Let me explain:

Nearly twenty years ago, in April 1954, the First International Neurochemical Symposium was convened at Magdalen College, Oxford, England. Drs. Seymour Kety, Jordi Folch-Pi, the late Heinrich Waelsch (whose death was such a loss to Neurochemistry), and Louis Flexner were the American partners of the Committee. In Britain, there were Drs. Derek Richter, Geoffrey Harris, and myself (who acted as organising secretary). The field was sparse in those days; yet we located sixty-nine colleagues from nine countries to attend what proved a most useful exchange.

Writing in the introduction to the Proceedings, we put our purpose this way:

> 'We agreed also that from the start it would be well to consider the brain as a biological entity in all its complexity of morphology and function, rather than as a homogenate, or an engineering problem. For that reason, we felt that the most useful contribution of a Symposium of this kind would be an attempt to reintegrate biochemical process with structure and function, particularly with respect to the chemical topography of the brain, which, to us, seemed of greatest moment in an understanding of function. The program thus not only represents the framework of a conference, but also expresses an attitude: and of necessity includes discussion of structural, genetic, and pathological aspects, as well as subject matter that, in the more limited sense, may be termed 'neurochemical'. We feel that this approach may be helpful in slowly building the foundations for a rational therapy of disorders of the nervous system'. (WAELSCH and ELKES, 1963)

We seem to be still at it; but it is significant that a little point on the horizon in 1954—what we called the CNS 'Sympathins' has now enlarged to a whole continent. The forces which brought us to this point are, in part, accidental and empirical, and in part, deliberate. It required the boot of empiricism (the discovery of some of the psychoactive drugs) to give us new facts. The dialectic began when new facts began to hunt for explanations; and here it is the evolution of new *methods* which brought us to the position we are in today.

These methods were, in part, anatomical and physiological, in part chemical, in part behavioural and in part clinical. In this respect, our field brooks no compromise, and compels conversation between various approaches like no other. It was a combination of Anatomy, Physiology and Behaviour which slowly bared the mosaic of the subsystems governing Sleep, Wakefulness, Arousal and focussed Attention. It gave us an anatomical scaffolding for an understanding of the control of Hunger, Thirst, Sexuality, Social play and Predatory Attack. It was the same combination, coupled with microphysiological approaches, which led to an understanding of the role of convergence, filtering and funnelling of signals in peripheral sense organs (such as Retina and Olfactory Bulb), integration at high central level (such as the cerebellum) or the assignment of significance and value in what we call Affective terms in pathways and structures of the Limbic System. It is here, too, that the organising power of the Reward and Punishment systems emerged; with still another field (the sequential organisation of motor performance, including speech) being related to the striatum and the dominant hemispheres.

If all this sounds like the language of the nineteenth century cerebral 'localisers' it both is, and isn't. The brain, to be sure, is an assembly of sub organs, a system of systems, a mosaic of biassed homeostats. It has its nodal areas, its cables, and connections; and presumably in certain respects is 'wired' for a purpose. But the wiring,' and control centers, should not mislead. For equally clear, and emerging in the light of recent experimental evidence, are diffuse and generalised effects in large areas of the brain, or in the brain as a whole; phenomena of modulation, gating, and slow potential drifts. It is these which may be related to the now established fact of differential cell populations in even small areas of the brain; and the influence, by way of widespread projections of some nodal midline areas (such as the locus coeruleus) over large areas.

While these developments were proceeding, a chemical map was being quietly superimposed upon functional anatomical findings. It started with the painstaking dissection of gross areas of the brain and bioassay. I still remember the excitement of reading the great paper of FELDBERG and VOGT (1948). It proceeded to the sampling of ever smaller areas, by the application of the LINDERSTROM-LANG techniques to the analysis of single cells (POPE, 1955; HYDEN and LANGEE, 1961). The use of radio isotopes added to this dimension, and further elucidated the regional chemical organisation within the C.N.S. But it did more. For by taking down the regional process to the organisation of sub-cellular components, by showing up the astonishing precision and economy of the processes governing release, reuptake, and storage, it related *spatial* sub-cellular organisation to turnover in *time*. It added the concept of quantal discharge of transmitters by differential synaptosomal populations (IVERSEN and SNYDER, 1968; KUHAR *et al.*, 1970; SHASKAN and SNYDER, 1970) thus introducing a much needed statistical, probabilistic element into our thinking. It also made much more real the concept of heterogeneous cell populations surmised by some of us early on. This proposition was literally illuminated by the advent of the path-breaking fluorescent and immunofluorescent techniques (FALCK, 1964; HOKFELT 1973) a proposition carried further by the iontophoretic application of drugs to single cells by multibarrel micro-pipette in several laboratories, including my own stamping ground of the NIMH, St. Elizabeths Hospital (SALMOIRAGHI and BLOOM, 1964).

It is, however, the combination of methods which again yielded special benefits: The combination for example of micro-pipette, radioisotope techniques in electromicroscopy (BLOOM and HOFFER, 1973) or the immunochemical approach and electron microscopy (HOKFELDT, 1973). Regional Neurochemistry, the subject of a special symposium at Varenna (KETY and ELKES, 1961) thus seemed to be coming of age.

If events studied by the above methods in the C.N.S. are very fast, the integer which we know as behaviour, including speech, is a very slow readout of such events. Here a refinement of methods, all the way from an automated approach to Skinnerian operant work, to the use of the Skinner Box as a metabolic cage, to self-stimulation, self-injection and self-infusion techniques can give one fine-grain analysis of behaviour over time. Ethological study of behaviour of animals in their natural surroundings, or in a controlled open environment, form the counterpart of such observations. They are particularly valuable in the study of the internalisation of early social cues in neurochemical terms. If, indeed, environment can produce chemical change in the brain of the developing animal, the first outlines of an environmental neurobiology may be at hand. Ability to cope, and inability to cope may have its early chemical counterparts, and thus open a direct link to the study of clinical states. Two days of the symposium are devoted to advances in this latter field alone. Here the combination of measurement of behaviour (and of subjective phenomena), with the refinement in the chemical estimation of hormones, neurohormones and metabolites in tissues, body fluids (SHARMAN, 1973) and post mortem material opens truly breathtaking possibilities. The use of stable isopopes in man (SEDVALL *et al.*, 1973) should add a further dimension. I believe that already we have clearer reference points for an understanding (and rational treatment) of affective disorders than we have, for example, for the genesis of coronary disease. Grant agencies, investing in scientific 'Growth Stock' might well take note of these facts.

You will have noted that I have gone on so far without mentioning Dopamine, which is to occupy us a good deal this morning. The reason for this is because I am, once again, reminded of the way mental habit operate in our field.

Once again, a personal example may serve by way of illustration: Between 1949 and 1953, Bradley and I had studied the effects of cholinergic and noncholinergic drugs, including the amphetamines and LSD-25 on the electrical activity of the brain, and on behaviour in the conscious animal, and in acute preparations. We had surmised that amphetamine acted on amine receptors placed high up in the so-called Arousal system which was being developed at that time by MORUZZI and MAGOUN (1949) and that LSD-25 was acting elements peculiarly related to a medial afferent system whose function was primarily inhibitory (BRADLEY and ELKES, 1953, 1957). Imagine our excitement when at a meeting of the British Physiological Society we saw for the first time Dr. MARTE VOGT's (1954) diagram on the distribution of sympathins in the CNS; or when, in a personal communication, the late J. H. GADDUM (1953) told me of the antiserotonin action of LSD-25; an observation he published the following April. Between 1954 and 1957, I proposed (ELKES, 1953; 1958; BRADLEY and ELKES, 1957) a view of the existence of three families of neuroregulatory substances within the C.N.S. As we said at the time:

> 'Perhaps rather than thinking in unitary terms, it may at this stage, be advisable to think in terms of the possible selection by chemical evolution of small

families of closely related compounds, which by mutual interplay would govern the phenomena of excitation and inhibition in the central nervous system. Acetylcholine, nor-adrenaline and 5-hydroxytryptamine may be parent molecules of this kind; but one has only to compare the effects of acetylcholine with succinylocholine, or nor-adrenaline with its methylated congener to realise how profound the effects of even slight changes of molecular configuration can be. The astonishing use which chemical evolution has made of the steroids is but another example of the same economy. It is likely that neurons possessing slight but definite differences in enzyme constitution may be differentially susceptible to neurohumoral agents. Such neurons may be unevenly distributed in topographically close, or widely separated areas in the central nervous system; these differences probably extending to the finest level of histological organisation. Phylogenetically older parts, and perhaps, more particularly, the mid-line regions and the periventricular nuclei may, in terms of cell population and chemical constitution be significantly different from parts characteristic of late development.

As yet, little information is available of the chemistry of the mosaic of cells, and cell groups making up the so-called reticular activating system. The neurons of this system, which is really a system of systems, bear a somewhat special and reciprocal relation to the afferent pathways which impinge upon them by way of collaterals. They are activated by these, but equally, through their activity, determine the ultimate perception of the signal arriving at the cortex by way of the sense-linked pathways. The translation of afferent signals into perception may well depend on the interaction of cortical and reticular elements, and may have its neural counterpart in the three dimensional apposition, and patterning of excitory and inhibitory states in a very large cell population. The reticular formation are distinctive for the diffuseness of their connections and of their effects. Equally, in this dense reticular field self-excitory phenomena may predominate, and the powerful operation of vectorial and spatial influences is likely. Slight variation in local titre of a neurohumoral agent in these key mid-line areas may thus profoundly affect the excitability of large neurone pools at a distance. It would perhaps be permissible to speak of the operation of chemical fields in these regions, which would depend on the rate of liberation, diffusion and destruction of locally-produced neurohumoral agents. The agents in question may be either identical with or, more likely, derived from neuro-effector substances familiar to us at the periphery. Their number is probably small, but their influence upon integrative action of higher nervous activity may be profound. The basic states of consciousness may well be determined by variations in the local concentration of these agents'. (BRADLEY and ELKES, 1957.)

The suggestion of the existence of three families of neuroregulating substances, one, related to cholinesters, of diffuse distribution; a second to catecholamines, related to the brain stem mid-line structures regulating attention and affect, and a third, an indole related to the afferent systems, exerting a regulating inhibitory, filtering role on afferent signals, was regarded a first crude approximation in a study in which cytochemistry, pharmacology, and electrophysiology are mutually complementary and interdependent. Since them many facts have appeared. Behind Serotonin there is Melatonin; behind Norepinephrine there is Dopamine; Histamine

and GABA, even glycine and other membrane active amino acids may play a part in neuroregulatory substances.

All substances mentioned have one thing in common, namely, the extraordinary care and precision of their intra and pericellular economy. New members continue to be added. They may perhaps make up a sort of alphabet which the nervous system uses to construct its membrane-located specific sensors and recognisers; possibly by conferring conformational changes onto glycolypids or glyco proteins in bimolecular leaflets. Inhibition is at the heart of information transfer in the C.N.S.; it is the nervous system's stupendous capacity to selectively store and to *ignore* which makes precise performance (the so-called 'readout' of programs) possible. It is the informed silence which carries the message, and tells the tale.

I do not think, therefore, that we should be unduly swayed by our own current interests (such as Dopamine), fully justified though it may be. The epochs of Acetylcholine, Norepinephrine Serotonin, GABA and Dopamine, which we have lived through confirm the value of each. The field has been tilled well, and the findings lie there, to be used wisely and conjointly. That we should pass through these special preoccupations attests both to our curiosity and to our need—our very human need—for the scaffolding and support of an explanation (ELKES, 1970). Explanations provide psychological safety—for a time. But they are also hazardous and transient; for I suspect, while using the '*Either/Or*', the language of our brain really is the language of the '*Also*' and the '*And*'.

This brings me to my last point: I have a feeling that our field may be passing through a phase not unlike that undergone by physics at the turn of the century; and it is the evolution of new and precise mathematical languages which made modern physics what it is. As yet, the languages we are using are clumsy and qualitative; but when phenomena accumulate beyond a certain point (and we may perhaps be reaching it at this very Symposium), a new look is needed at relationships. The linear or binary view no longer suffices; and a topology of multiple phenomena in time will require linguistic models not met by our present old verbal hardware. The mathematicians may be waiting in the antechambers, and may even be looking over our shoulder. One does not know how long it will be before mathematics interacts with neuro- and psychopharmacology. When it does, however, new and precise configurations will become apparent. Psychobiology will then have come of age; and, quite possibly, enlarge the realm of science itself in the process.

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