UNIVERSITY NIGERIA

Inaugural Lecture Series 39

PLAIN PHARMACOLOGY

by V. Olufemi Marquis

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Vice-Chancellor, Deputy Vice-Chancellor, Registrar, Colleagues, the University Community:

This inaugural lecture is the second emanating from the Faculty of Pharmacy of this University and not only that, the chair which I have the greatest pleasure and honour to inaugurate this evening is the first one at Ife.

Some of my colleagues who have had the opportunity of delivering such lectures have stated that "an inaugural lecture is an academic response to a particular environment" (Ogunlana, 1976), and this will become evident as the discourse continues. Ekundare in 1978 also succintly put it "that it can be rightly regarded as an academic christening ceremony, with the Vice-Chancellor as the officiating minister and, the victim of the occasion reciting the creed". I am, however, happy to deliver such lectures to a wide spectrum of the University society.

At this juncture a brief account of how I became a Pharmacologist or a purveyor of drugs will be useful. I qualified as a pharmacist 25 years ago from the then Yaba School of Pharmacy, Lagos, which incidentally was the forerunner of our present Faculty of Pharmacy. On qualifying in 1954, I taught for three years in the school before proceeding to United Kingdom where I obtained my B.Pharm in 1960, and in 1963 obtained my Masters Degree in Pharmacology from the University of London.

In that same year I moved on to work as a Research Fellow in Edinburgh University where I was priviledged to be associated with scholars like the late Sir John Gaddum, Sir Walter Perry, R. P. Stephenson (of the receptor fame), R. B. Barlow, B.L. Ginsburg and W. E. Brocklehurst to mention a few. In 1967 I joined the staff of the Department (now Faculty of Pharmacy).

The Department of Pharmacology has since then grown from two members of staff with no graduate students, even when it temporarily sorjourned in the Faculty of Health Sciences, and can now boast of a staff complement of seven with six post-graduate students in the Faculty of Pharmacy, this is an indication of developments to come.

I am sure that you will be intrigued by the title of my lecture "Plain Pharmacology". It has been chosen because it seems to offer me many approaches to the subject of pharmacology. By dictionary definition "plain" means—easy to see or understand,—simple, ordinary without luxury or ornament—straightforward or frank.

Pharmacology is the science that deals with drugs, and a drug is substance used in the prevention, diagnosis, treatment or cure of disease

in man or other animals, and is derived from the French word, *drugue*—a dry herb or as put by Feldberg in 1929, 'a drug is something which when injected into a cat produces a scientific paper'. Pharmacology in its broadest sence embraces all the knowledge concerning drugs. The word pharmacology itself is derived from the Greek words *pharmakon* (drug) and logos (a discourse or treatise), hence it includes such allied fields as:

Pharmacy (Pharmaceutics) which deals with the art of preparing, compounding and dispensing medicines.

Pharmacognosy

This is the study of the physical characteristics of crude drugs. You will not be expected to get up at dawn to collect toadstools and herbs before the sun rises or to grind dried lizards in pestles, but even the least dubious of you will wish to know the origin of some of the more potent drugs in use today. For example how William Withering found that an extract from foxgloves improved the failing heart, how curare is produced from a black gummy resinoid mass which has been produced with much ritual by the Indians of South America for centuries, from jungle creepers. A small amount of this poison on their arrow tips was sufficient to paralyse quite large animals and kill them by respiratory arrest. Again in South America for many centuries the Indians have chewed the leaves of Erythroxylon coca thereby extracting cocaine. Cocaine increased their endurance but no doubt anaethetised their tongues at the same time.

Toxicology, posology, chemotherapy, therapeutics and materia medica. Each of these subdivisions of pharmacology is a highly specialized fields and make its contributions to our composite knowledge of drugs.

The modern definition is that it is the study of the response of living organisms to chemical stimuli. One may further divide the subject from a medical viewpoint, into pharmacodynamics and pharmacotherapy. The former is concerned with the response of living organisms to chemical stimuli in the absence of disease and the latter branch—pharmacotherapy, deals with the response of the organisms in a pathologic state to chemical stimuli. This is the phase of pharmacology which is of special interest to the physician.

With these definitions I hope at the end of the lecture I should have made some aspects of pharmacology plain enough for you to appreciate the problems emanating from its study.

In 1898 Langley wrote "I propose the term autonomic nervous system for the sympathetic system and the allied nervous system of the cranial and sacral nerves and for the local nervous system of the gut. The term did not, however, gain general acceptance at first and Gaskell in 1916 called it 'the involuntary nervous system'. However, the passage of time has favoured Langley and today the autonomic nerves are generally regarded as the motor nerves of sympathetic and parasympathetic systems.

But more has been added since then, for in 1972, Burnstock described a system of 'purinergic nerves', which are not sympathetic or parasympathetic. These will be fully clarified in the course of this lecture. Nerves are now believed to act by liberating at their terminals—a chemical substance, a transmitter which passes on the nerve impulse either to another nerve a 'synapse', or to an end organ such as muscle, to produce a change in the organs activity. Thus nerves may be said to have a similarity to the doctor's syringe which injects a drug into the body. The nerve is a device to enable the brain to release a drug at a distance which may be as great as from head to foot and to release it at a precise spot.

The term "humoral transmission" was used by Otto Loewi (1921) in describing the first direct demonstration of the natural process of release of a specific stimulant into the tissue fluids. In any case, I shall have to consider some instances in which the chemical transmitter of nervous effects appears to be released in such immediate proximity to the receptive cells that the use of the term "humoral" would risk a misleading implication. For this reason the more general term "Chemical transmission" for the process has been employed, and shall refer to the agents concerned as "chemical transmitters".

The transmission of the effects of impulses in nerve fibres, to awaken or to modify the activity of cells in relation to which the nerve fibres end, is one of the classical problems of physiology; and the classical subject for its experimental study has been the familiar preparation of motor nerve and voluntary muscle.

Since the experiments of Claude Bernard it has been known that the point where the nerve fibre ends, on the endplate of the muscle fibre, has special physiological properties. If the response of the muscle to a nerve impulse is paralysed by curare or by fatigue, it is here that the excitatory process is blocked, while nerve fibre and muscle fibre are still normally responsive, and are still normally conducted. The fact that the transmission of excitation is peculiarly liable to interuption at this point would not by itself imply that a different process or

mechanism of transmission have intervened. It might merely indicate that structures using the same process of conduction as nerve and muscle were here most readily accessible to certain poison or to the depressant effect of fatigue. It is right to suppose that the conception of the excitation of a voluntary muscle fibre by a nervous impulse assumed that the wave of physio-chemical disturbance, propagated along the nervous impulse, passes directly to the muscle fibre, and there excites contraction as it is further propagated.

This conception of the unbroken physical transmission of the excitation wave from nerve to muscle might well seem to receive support from the analogy between the nerve-muscle junction and a synapse of the nervous system. In both cases we have the terminal branching of a nerve fibre, the axon process of a neurone, making contact with another cell—the cell body of another neurone or a muscle fibre. In the case of synapse the response excited is a nerve impulse in the axon of the second neurone, essentially similar to that which is conducted to the synapse by the axon of the first. The suggestion of unbroken propagation is strong; and if such continuity of conduction occurs at a synapse there is no obvious reason why it should not occur at a nerve-muscle junction.

Further, with regard to the transmission of excitation from motor nerve to voluntary muscle, Adrian in an article in 1933, admits that it may not be so fundamentally different from that which we shall presently consider in the case of autonomic nerves, but that "an excitatory substance liberated at a nerve ending, but destroyed within a few thousands of a second . . . would account well enough for the known properties of a nerve ending".

The direct evidence, however, for the intervention of such a chemical transmitter between nerve impulse and effector cell came, in the first instance, from studies of the nervous control of the activities of involuntary muscle and gland cells by nerves of the autonomic system.

Naturally I cannot, in a lecture, attempt a comprehensive and detailed record of the evidence to which many have contributed and I must select for mention, not necessarily those items which are important than others, but those which seem to suit my purpose of telling a coherent story.

The suggestion that nervous effects might be transmitted by the release of a specific chemical stimulant was first made in 1904 by T. R. Elliott, who then was working as a student of George Henry Lewes in the department of physiology at Cambridge, he advanced, in explanation, the daring idea that sympathetic nerve fibres liberate adrenaline at their endings, to act as the transmitter and immediate agent of their effects. The years have justified his courageous insight because it was only Dixon who alone at that time seized the idea with eager conviction. Dixon (1906, 1907) went further to argue that parasympathetic nerves must similarly release a chemical transmitter of their effects. There was nothing then known in the body to play this part, and Dixon could only think of the parasympathetic transmitter as muscarine. He did, however, make an experimental attempt to find evidence of its release in the mammalian heart when the vagus nerves were stimulated. Removing a dog's heart while it was under vagus inhibition, he made, concentrated, and partially purified an extract from it; and he found that this, when applied to the beating frog's heart, has an inhibitor effect which atropine antagonised.

Nobody can say now what he had in his extract, though we may be pretty sure that it was not the labile substance now known to transmit vagus effects, and its presence had little, if any, connection with the inhibition of the heart from which it was extracted. Probably it was choline. It is beyond doubt, however, that Dixon, following Elliott's suggestion concerning adrenaline, had at that early date a conception of the general nature of the mechanism which later evidence completely justified.

From 1906 to 1921 there was a gap in the record of direct contributions to the theory of chemical transmission. The idea had been at the back of many minds, but is waiting for direct evidence to stimulate its further development.

Mention should be made, however, of two investigations on the action of a substance which was to play a part of central importance in these developments when they came. As long ago as 1900 Reid Hunt had begun experiments on depressor constituents of the adrenal gland. He could not find enough choline to account for the depressor action of an extract, and he was led, in 1901, to suggest that the excess of activity might be due to an unstable and more active derivative of choline. Since the additional activity was not abolished by atropine, it now seems more probable that Hunt was dealing with histamine the action of which was not known till much later; but he had the idea of a choline derivative, and it led him to try the action of a number of esters, which were made for him by Taveau (Hunt and Taveau, 1906). Among these was the acetic ester, acetylcholine, which Hunt found to have an action like that of choline, but about one thousand times as strong. This observation was published in the same year, and, indeed, at the same meeting of the British Medical Association as Dixon's first tentative mention of his heart-vagus experiment.

One other happening in 1906 should be noted in passing. It was then that Howell (1906, 1908) began to put forward the evidence which led him to suggest that vagus impulses inhibit the heart by mobilizing potassium ion.s Some seven or eight years later, Dale (1914) came across acetylcholine accidentally, as a constituent of a particular sample of ergot and therefore as a product of nature. This led him to make a detailed study of its action (Dale, 1914). This, I think, gave the first hint that acetylcholine might have an interest for physiology. It was found to be a very unstable substance, even outside the body; but when it was injected into the circulation its effects, though immediate and intense, were so extraordinarily evanescent that he suggested, rightly as it now appears, that it was probably hydrolysed with great rapidity by an esterase in the blood, being split into acetic acid and the comparatively inactive choline. The remarkable fidelity with which it reproduced the various effects of parasympathetic nerves, inhibitor on some organs and augmentor on others—a fidelity which was compared to that with which adrenaline reproduces the true sympathetic division of the autonomic system. Thus we now have knowledge of two substances, both with intense activities: both, by reason of their liability to the actions of different enzymes having similarly evanescent effects: and each reproducing, with a similar fidelity, the effects of one of the main anatomical divisions of the autonomic nervous system. There was this difference between the two cases. However, that adrenaline was already known as natural substance, formed in and secreted from the cells of the adrenal medulla into the blood and thus, by its direct action from the blood stream, supplementing the effects of sympathetic nerves which it so accurately reproduces. This natural occurence gave an added plausibility to Elliott's suggestion that adrenaline intervened in the direct effects of sympathetic nerve impulses; whilst up to 1914, there was no evidence at all that acetylcholine was a constituent of any part of the animal body, and many years, in fact, elapsed before it was found in the body.

There was yet another action of acetylcholine, which seemed at the time to have no relation to any physiological function. Its parasympathetic effects, produced by extremely minute doses, were all readily antagonised by a small dose of atropine. Only when these had thus been suppressed was it recognized that larger, but still small, doses of acetylcholine had a stimulating action on ganglion cells, recalling that of nicotine. This is an action shown by many bases of the quarternary ammonium type, to which acetylcholine belongs. To the nicotine-like action of acetylcholine belong also its later-described stimulating effects on voluntary muscles of mammals (Riesser, 1921, Frank, Nothmann, and Hirsch-Kauffmann, 1922, 1923, Dale and Gasser, 1926). We shall see later that this action also has quite recently acquired a physiological significance of very great interest. For the time, however, it was possible to recognize the fact that acetylcholine, in common with other choline esters indeed, but with a unique intensity and evanescence, exhibited these two types of action, which are now referred to as its "muscarinic" and "nicotinic" actions.

These observations were completed in the fateful year 1914, when the outbreak of war diverted all scientific energies from their normal applications. It was not until 1921 that Otto Loewi published his simple elegant and convincing work that the vagus nerve produced its effect on the frog's heart by liberating an inhibitor substance. He showed that this substance, as obtained in the fluid filling the heart can be transferred to another heart, and there reproduce the vagus effect.

This classical experiment formed the starting-point for a series of others, in Loewi's laboratory and elsewhere, in which the liberation of a substance having properties similar to those of the vagus substance, and similarly transmitting parasympathetic effects has been shown to accompany the reflex production of the autonomic actions of the third cranial nerve (Engelhart, 1931), and the production by artificial stimulation of the effects of the chorda tympani on the salivary gland and the tongue (Babkin, Alley, and Stavraky, 1932), Gibbs and Szeloczey, 1932, Bain, 1932, Henderson and Roepke, 1933, and Feldberg, 1933).

Loewi not only demonstrated the liberation of an inhibitor substance transmitting the effect of the vagus to the frog's heart; he was able, even with the minute traces obtained, to examine the properties of the substance in several directions; and these properties were found to correspond, in every test, to those of acetylcholine. Atropine antagonised the action of the transmitter, but did not prevent its liberation by the vagus. The transmitter was rapidly destroyed by an esterase present in the heart muscle, and its activity could be restored by acetylating the residue. Of special interest, and of great value for further progress, was the discovery that eserine (physostigmine) inhibited the action of the esterase; so that the actions of atropine and eserine, in antagonising and potentiating respectively the action of the vagus on the heart, were fully explained by the new knowledge that this action was transmitted by something indistinguishable from acetylcholine. This effect of eserine was given a more general application, when Engelhart (1930) in Loewi's laboratory, and Matthews (1930) in Dale's laboratory showed that, even in very high dilutions, it blocked the destructive action of a blood esterase on acetylcholine. Eserine was therefore regarded as an indicator of "cholinergic" effects. Acetylcholine has since been found and confirmed as a natural chemical

substance in the body.

Nicotine actions of Acetylcholine

Mention of the pseudomotor phenomena leads us to the other aspect of the action of acetylcholine—what has been termed its "nicotine" action—the physiological interest of which has been mounting over the years. The question which puzzled many pharmacologist and physiologist is that why should Nature use, as the transmitter of parasympathetic effects to involuntary muscle and gland cells, such a substance as acetylcholine, having not only the action directly appropriate to this purpose, but in addition, a "nicotine" action on ganglion cells and voluntary muscle which seemed entirely irrelevant to it? The ruling conceptions of the mode of transmission of nerve impulses across synapses to ganglion cells, or from motor nerve endings to the end-plates of voluntary muscle fibres, made it difficult to speculate on any intervention of acetylcholine in extracts of sympathetic ganglia, and Chang and Gaddum (1939) came across it again, using tests which gave clearer evidence of its identity. In both cases it was found also in the cell-free nerve, and the significance of this observation was not clear until Kibjakow in 1933, published a description of experiments in which he had artificially perfused the superior cervical ganglion of a cat, and found that, when the preganglionic nerve was stimulated, something appeared in the venous fluid which acted as a stimulus to the ganglion cells on reinjection, as shown by the contraction of the nictitating membrane He suggested that the impulses were transmitted across the synapse by the release of this substance, and Chang and Gaddum, in the light of their own observations, suggested that Kibjakow's substance might be acetylcholine.

Feldberg and Minz's (1933) further discovered that, when the splanchnic nerve supply to the adrenal medulla was stimulated, acetylcholine appears in the blood of the adrenal vein, if its destruction is prevented by eserine; so that acetylcholine here transmits, to the medullary cells, the nerve impulses causes them to secrete adrenaline into the blood. It is now known that the adrenal medullary cells are morphologically equivalent to sympathetic ganglion cells, and at least some sympathetic preganglionic fibres appear to end in direct relationship to them.

Similarly, Acetylcholine has been confirmed as the chemical transmitter from motor nerves to striated muscle at the Neuromuscular junction.

Transmission of Impulses at Ganglionic Synapses

With this analogy before them, Feldberg and Gaddum (1933) have

proceeded to a direct test of the possibility of Acetylcholine being present at the ganglion. The significance of these findings are illustrated in this slide.

A. MUSCARINIC BELLADONNA ALKALOIDS		ATROPINE HYOSCINE (i) Cosmetology (ii) Ulcer—Aludrox SA —Mist Mag Triscil Et Bellad (iii) Before surgical operations to dry up most secretions
B. NICOTINIC GANGLIA	—	Antihypertensives ganglion blocking drugs.
NERVE-SKELETAL MUSCLE JUNCTION	—	Tubocurarine)) Muscle relaxants Succinylcholine) Pre operative aids

III

From Loewi's experiments on the perfused frogs heart, he noted that the vagus nerve of the frog contains fibres which join it from the sympathetic chain, and that the effect of these sometimes predominates, so that stimulation of the mixed nerve may cause acceleration of the heart would transmit an accelerator adrenaline-like effect on the second heart, so that Elliott's speculation, as to the meaning of the similarity of sympathetic effects to those of adrenaline, received at last a direct experimental justification.

Further progress in our knowledge of this chemical transmitter of the peripheral effects of true sympathetic nerves have emanated largely from Cannon's laboratory at Harvard, and from the researches of visitors from other countries who have worked there. Cannon's work have been largely concerned with the demonstration that, when the lower end of the sympathetic chain is stimulated in a cat deprived of its adrenal glands, something passes into the blood which produces, at a distance, effect of sympathetic stimulation on other organs (Cannon and Bacq, 1931). To avoid a premature suggestion as to its chemical nature. Cannon referred to this transmitter of sympathetic effects as "sympathin".

There is an obvious probability in favour of its being the substance, natural to the body, and reproducing sympathetic effects with such remarkable precision as adrenaline itself.

Bacq in 1933 showed that when the cervical sympathetic nerve is stimulated "sympathin" appears in the aqueous humour of the eye just as Engelhart had found that, when the pupil was caused to constrict by the incidence of light, something like acetylcholine appeared in the same fluid. On analysing this "sympathin" by chemical and spectrographic tests, Bacq found out that the substance contained a catechol derivative and an amino side chain. He therefore concluded that it is either adrenaline itself or a very closely related substance.

T. R. Elliot once said to Henry Dale: "Dale, you won't have done anything towards an ultimate solution until you have discovered why acetylcholine and adrenaline should, each of them, augment the activity of one tract of involuntary smooth muscle and inhibit that of another, which in all respects appears to be an entirely similar tract".

In the past seventy years several hypotheses have been advanced to account for the dual reaction pattern to catecholamines, but the exact nature of the tissue components with which they interact and of the biochemical mechamisms mediating the final effect of such interactions are still largely unknown. Very much like the effect of adrenaline itself, these theories lend themselves to be grouped into two main lines, according to whether the split is offered at the level of sympathins and although some of the remote effects of sympathetic stimulation observed by Cannon & Resenblueth still resist interpretation based solely on the different receptor concept, much of our present understanding is based on the postulation of two main classes of tissue responses and the block of these responses by selective antagonists. Both prerequisites for associating drug responses with a given type of receptor were introduced by Dale in (1906) who first described the selective block by ergot alkaloids of most excitatory but none of the inhibitory adrenergic responses and who, with Barger, was the first to determine the order of potency of various agonists on different test organs as well. (Barger & Dale (1910))

The framework for our present understanding of adrenergic responses is based on the dual receptor theory of Ahlquist (1947). In this, the most important step beyond Dale's classification has been the recognition that cardiac excitatory and inhibitory smooth muscle responses can be grouped together on the basis of the similar order of potency of a series of agonists in eliciting them. In retrospect, the analogy may appear strained in view of the separation later of B_1 receptors in the heart (adrenaline = noradrenaline) and B_2 receptors in smooth muscle (adrenaline > noradrenaline). The picture is even further complicated by significant overlaps between β-receptor subgroups and by a

lack of homogeneity among a-adrenoceptors in different tissues. However, the basic distinction between a- and β-adrenergic responses has proved extremely useful in the development of a new class of drugs, the *β-adrenoceptor antagonists* which, in turn, have been looked upon as the strongest support for Ahlquist's theory. This class of drugs are now mainly used as antihypertensives and antiarrhythmics.

The large body of evidence allowing pharmacological classification of adrenoceptors has created an illusion of morphological reality in the minds of many pharmacologists. Although the nature and localization of a- and β-adrenoceptors are still unknown, a strong implication of functionally and morphologically distinct, well defined static membrane structures has been inherent in many studies.

β-adrenoceptor blocking agents

The antihypertensive effect of the B-adrenoceptor blocking agent propranolol, was first reported by Prichard & Gillam (1964) and this has since been confirmed by several workers (Prichard & Gillam, 1966; 1969; Frohlich, Tarazi, Dustan & Page, 1968; Zacharias & Cowen, 1970; Hanson et al,. 1972; Lydtin, et al, 1972; Zacharias, et al., 1972). Paterson & Dollery (1966), Richards (1966) and Weal (1966) found that propranolol produced only mild antihypertensive effects no greater than that obtained with the thiazide diuretics.

Although most of the work concerning the antihypertensive properties of β-adrenoceptor blockers has been done using propranolol, these properties have been reported for several other β-blockers. (see review by Day & Roach, 1974). The clinical value of these drugs has been enhanced by the lack of either orthostatic or exercise hypotension in their antihypertensive action. Rare side effects include central effects such as nightmares, hallucinations, insomnia, and depression, (see review by Simpson, 1974). Asthma and cardiac failure may result from the use of β-blockers in susceptible patients.

Although there has been a spate of publications reporting the anti hypertensive effects of this group of drugs in human hypertensives, the demonstration of this effect in animal models has been disappointing Thus Farmer & Lecy (1968) could find no hypotensive effect after acute and chronic administration of doses of propranolol and sotalol which cause effective β-adrenoceptor blockade in conscious hypertensive dogs and rats although bradycardia was evident. No effect could also be detected in Grollman rats with chronic propranolol treatment (Menard, et al., 1973). In fact, pressor effects have been reported in normotensive rats (Dasgupta, 1968; Yamamoto & Sekiya, 1969, 1972; Regoli, 1970) and in DOCA- saline treated hypertensive rats (Lydtin &

Sommerfeldt, 1972, Dusting & Rand, 1974) after acute administration of propranolol. The later workers suggested that the pressor effects may be due to noradrenaline released from sympathetic nerves. However, in the SHR and pinealectomised hypertensive rat, hypotensive effects have been reported after large doses of B-adrenoceptor blockers (Roba, Lambelin & De Shaepdryver, 1972; Vevra, Tom & Greselin, 1973; Karppanen, 1974). Recently Dusting & Rand (1974) reported substantial falls in blood pressure in DOCA-saline treated hypertensive rats after chronic administration of low doses of propranolol.

IV

PURINERGIC TRANSMISSION

As has been previously mentioned the autonomic nervous system system consists of two components, cholinergic and adrenergic nerves. However, in the last two decades, a third transmitter system has been postulated—purinergic nervous system.

First indications that some of the inhibitory fibres to the vertebrate stomach were not adrenergic appeared when adrenergic neurone blocking drugs were used on the guinea-pig stomach in the early 1930's. The inhibitory response of the guinea-pig stomach to vagus nerve stimulation was not prevented by these drugs except by high concentrations of bretylium sufficient to block transmission in ganglia. Similarly, Paton and Vane (1963) showed that relaxations in response to transmural stimulation of intramural nerves in the stomach of cats, mice and guinea-pigs were resistant to blockade by xylocholine.

In 1929, Drury and Szent-Gyorgy discovered that adenosine and related compounds affected the mechanical activity of various tissues. A comprehensive account of the complex pharmacological effects of these compounds, which include relaxant actions was discussed in a comprehensive review by Gillespie in 1934. Axelsson and Homberg (1965), Bueding Bulbring and Gercken (1967) carried out experiments on the taenia coli of guinea-pig by applying ATP extracellularly. They found that it inhibited spontaneous spike discharge and also the contractures maintained by the depolarised taenia coli of guinea-pig.

The presence in the intestinal wall of intramural non-adrenergic inhibitor neurones have been postulated by many workers including Burnstock, Campbell, Bennett and Holman (1964) who reported that in the taenia coli of the guinea-pig the inhibitory responses to transmural stimulation which persist in the presence of bretylium and guanethidine, are mediated by intrinsic nerves which are distinct from the sympathetic system. According to Burnstock, Campbell and Rand (1966) the taenia coli of the guinea-pig is also innervated by intramural inhibitory nerves with their cell bodies in Auerbach's plexus. These nerves could be excited by electrical stimulation of the taenia or by the application of ganglion stimulating drugs. The intramural inhibitory nerves had different properties from sympathetic adrenergic nerves because relaxations to stimulation was maximal at low amplitudes and were not blocked by bretylium, guanethidine or dimethylphenyl piperazine.

Bennett in 1966, Bennett, Burnstock and Holman also in 1966 presented evidence for the existence in the guinea-pig coli of inhibitory nerves distinct from sympathetic perivascular nerves. The evidence was based on the observations that the pattern of the inhibitory junction potential was not changed by anti-adrenergic agents and the hyperpolarisation produced by intramural stimulation was different from that produced by perivascular stimulation. The existence of non-adrenergic inhibitory nerves has been shown to be present in the stomach wall of guinea-pigs by Martison (1965a & b), Campell (1966), Bulbring and Gershon (1967), and have also been described in rabbit ileum by Day and Warren (1968).

Experimental evidences accumulating from the 1960's when trans-

mural stimulation of the guinea-pig taenia coli with single pulse of short duration has shown the presence of large hyperpolarisation or inhibitory junction protentials in smooth muscles which persisted in the presence of both atropine and guanethidine. Such evidences led to the use of low concentration of tetrodotoxin in abolishing the nerve stimulated responses or by storage of tissue at 4°C for more than 100 hours.

Evidence that these inhibitory responses are not due to adrenergic nerves is now conclusive. Relaxation of intestine produced by stimulation of perivascular sympathetic nerves is prevented by low concentration of alpha-and-beta-adrenoceptor antagonists or by adrenergic neurone blocking drugs, without affecting the inhibitory responses to transmural stimulation. Inhibitory junction potentials and relaxations in response to transmural stimulation are unimpaired in the guinea-pig colon after degeneration of sympathetic adrenergic nerves. Relaxation of the guinea-pig taenia coli in response to transmural stimulation or nicotine persists in organ cultures and in anterior eye chamber transplants after all adrenergic nerves have disappeared. In addition, transmission from intrinsic inhibitory neurones have been demonstrated in avian gizzard and mammalian anal sphincter, which are contracted by catecholamines.

More recent studies of the nervous control of the stomach and the effect of ganglion stimulants and blockers on isolated gut segments provide strong evidence that the cell bodies of non-adrenergic inhibitory nerves are located in Auerbach's plexus. In the stomach and distal rectum, the non-adrenergic inhibitory neurones are controlled by preganglionic, parasympathetic nerves running in the vagus and pelvic trunks respectively. It has now been conclusively confirmed that the transmitter agent is ATP (adenosine triphosphate).

V

Sorjourn in the Faculty of Health Sciences

In 1971, the Faculty of Pharmacy was informed that the department of pharmacology has been absorbed and transferred to the Faculty of Health Sciences. The transfer on its own was welcomed by some as a change for good, because of the expectations that there will be funds available to encourage intensive scientific research in a newly created Faculty, but alas, as far as I am concerned my stay in that Faculty were the five most traumatic and agonising years of my twelve years in this University. However, I will leave the rest of that story to my autobiography.

Like the biblical Daniel I was in the lions den or like Job I had no friends, but like Michak, Shaddrack and Abednigo and others too many to mention, help came in the form of some bearded apostles who are easily recognisable in that Faculty. Probably this help came as a result of meditations over the Psalm of David which states that "I will lift up my head unto the hills, from whence cometh my help. My help commeth from the Lord who made heaven and earth" (Ps. 121). For no sooner after a period, did I discover to my amazement that some of these bearded colleagues were interested in the anatomical aspects of non-mammals—animals which I have suggested for use in our laboratories as far back as 1969. Without much hesitation I began to put my thoughts to action and evolved systematic pharmacological investigations into non-mammals such as the Rainbow lizard (*Agama agama*), Giant African Snail (*Achachatina achachatina*), African Land Tortoise, (*Kinixys crosa*) and the fruit eating bat (*Eidolon helvum*), with the collaboration or well meaning students and colleagues. I have up to now been considering substances which are released after or during nervous stimulation and have served as important pharmacological tools, particularly in the analysis of drug action, there are more which occur along with those mentioned previously which are present both in the peripheral as well as the central areas of the body and are as important as acetylcholine and adrenaline. Amongst these are histamine, 5-hydroxytryptamine, prostaglandins to mention a few. I will cite histamine in this lecture because it has been studied in more details particularly with respect to the non-mammalian work.

HISTAMINE: Histamine or β-imidazolylethylamine is an endognous ubiquitous and enigmatic simple natural base found widely distributed in plants (e.g. stinging nettle), bacterial cultures and animal tissues. Histamine is in fact "an ENIGMA of pharmacology". Although its role has been repeatedly demonstrated in various pathological phenomena, its physiological role remains obscured. It was first synthesized as a chemical curiosity (Windaus and Vogt 1970) before its biological significance was recognised. It was first detected as a uterine stimulant in watery extracts of ergot (a product of the fungus—Claviceps purpurea that grows on rye and other grains) and was isolated from these extracts in pure form by Barger and Dale, 1910. It proved not to be a specific principle of ergot but a causal contaminant due in this instance to

bacterial decarboxylation of histidine, a phenomenon demonstrated by Ackermann in 1910).

In 1912, Mellanby and Twert observed that the flora of intestinal tract of man could decarboxylate histidine and produce histamine.

When Dale and Laidlaw (1910, 1011) subjected histamine to intensive pharmacological study, they discovered, inter alia, that is stimulated a host of smooth muscles and had an intense depressor action on the cardiovascular system. With rare acumen they drew attention to the fact that the pharmacological activity of histamine resembles that of many tissue extracts, and further, that the immediate symptoms with which an animal responds to an injection of a normally inert protein to which it has been sensitized are to a large extent those of poisoning by histamine. Their comments anticipated by many years the events that were to thrust histamine to the centre of physiological interest, namely, the discovery of its occurrence in the body and its release upon cellular injury. Although histamine had been identified chemically in extracts of intestinal mucosa by Barger and Dale as early as 1911, and also later, in extracts of the posterior lobe of the prituitary by Abel and Kubota (1919), it was suspected that it might have arisen from putrefaction.

It was not until 1927 that Best, Dale, Dudley, and Thorpe isolated histamine from impeccably fresh samples of liver and lung, thereby establishing beyond doubt that the substance was a natural constituent of the body, Thorpe (1928) reported further demonstrations of its presence in a variety of other tissues, Lewis (1927) found that a substance (designated "H-substance") with histamine-like properties was liberated from cells of the skin by injurious stimuli.

Given the chemical evidence of histamine's presence in the body, there remained little impediment to supposing that Lewis' "H-substance" was histamine itself. This conception was advanced by Dale in his Croonian lectures of 1929 and stimulated the growth of interest in histamine to a rare luxuriance. Some four decades later, histamine continued to fascinate biologists and to offer new facets for study.

The responses to histamine of different regions of the gastro-intestinal tract of the lizard were recorded and the modification of these responses by specific histamine antagonists, mepyramine and burimamide were investigated. The following results were obtained. It was found that histamine at relatively high doses elicited a mild mepyramine sensitive contraction of the oesophagus and a marked dose dependent and also mepyramine sensitive contraction of the rectum. On the

stomach and large intestine histamine had relatively no effect, on the other hand the duodenum and intestine responded to histamine in a complex manner.

These responses were either monophasic (i.e. contraction or relaxation), biphasic (relaxation followed by contraction) and they were both sensitive to mepyramine but not to burimamide. The complexity of the duodenal and ileal responses to histamine and the similarly complex modification exhibited by mepyramine have been thoroughly analysed. It was at first thought that the responses were either due to seasonal variations as indicated by Jovett (1963) in the case of 5-HT responses of the chick crop, but these experiments were carried out throughout the year to show if there were any such effects.

Present indications show that this is not the case. We also considered the striking similarity between these complex responses and the effects of the autonomic ganglion stimulants nicotine and tetramethylammonium in isolated preparations of rabbit ileum and those of nicotine on bat ileum as observed by Grillo, Marquis and Sanya (1975), rabbit colon (Gillespie & Mackenna, 1960) but hexamothonium had no effect Similar complex responses have been obtained by transmural stimulation in segments of rabbit isolated intestine (Day & Warren, 1967), cat stomach (Martison, 1965), guinea-pig isolated taenia coli (Burnstock, Campbell & Rand, 1966), guinea-pig isolated stomach (Campbell, 1966) and isolated chick duodenum (Ebong and Okpako, 1976).

Suggestions that inhibitory responses to histamine might be brought about by the stimulation of some adrenergic inhibitory neurones probably present in the wall of these parts of the tract have since been dismissed, because of the failure of both Dibenamine and Propranolol to inhibit these relaxations. Electron microscopic and histochemical studies will hopefully determine the validity of this suggestion.

We have therefore suggested the presence of at least two sub-types of Histamine H_1 receptors or that only one of the two types of responses to histamine (relaxation in particular) is actually mediated by histamine H_1-receptors in this species. We are of the opinion that the former concept will hold because the present experiments appear to support the concept of two types of H_1 receptors. Thus, it is being suggested that a sub-type of histamine H_1-receptor, is responsible for contraction and this is designated as α-H_1 receptor, and that a second type designated β-H_1 receptor is responsible for relaxation. These receptors could then be viewed as differing in:—

(i) distribution density—the β-receptors being relatively commoner, more predominant and of wider distribution

(ii) spatial localization—such that the β-receptors lie more peripherally than the α-receptors in both the lizard duodenum and ileum.

In addition there could be variations within the species such that

(i) the α-receptors are more numerous and also displaced more peripherally such that contractions is almost the rule.

(ii) both a and β-receptors predominate in almost equal proportions.

Lastly we suggest that the β-receptors are more sensitive to histamine and mephyramine than the α-type and that in lizards where the α-receptors predominate they respond more effectively to histamine (by contraction) than β-receptors (by relaxation).

Hence the relaxation introduced in tissues with a preponderance of β-receptors overrides the activity of the α-receptors and only relaxation is observed and vice versa for histamine induced contraction. In tissues with approximately equal proportion of α-and β-receptors, histamine produced both relaxation and contractions with the relaxation mediated by the more peripheral β-receptors preceding contraction hitherto postulated to be mediated by the more deeply located α-receptors.

Mepyramine a specific H_1 receptor blocker appeared to act antagonistically in three dose dependent phases. In low doses, it had little or no effect. Intermediate doses reduced the histamine induced response while higher doses seemed to give way to the opposite type of response depending on the initial response to histamine. The mechanism of action of mepyramine still remains obscure, nevertheless, it is observed that it readily blocked histamine induced relaxations and in a few cases, it not only inhibited relaxations but gave way to contractions in higher doses. It also blocked the seldom histamine induced contractions and also in a few cases gave way to relaxation as its concentration was increased. Furtherwork is being done to clarify this complex mechanism.

The results of these efforts culminated in a one day symposium organised by the department of pharmacology in November 1978 where scientists of repute in the persons of Profs. Aboderin, Segun (from Ife) Okpako (Ibadan), Bamgbose (Lagos), Dr Okon (of the bat fame) and a host of others, not forgetting my colleagues in Pharmacy and Health Sciences who contributed in no small measure to its success. Such a symposium on non-mammals is the first in Nigeria, if not in Africa.

In pursuance of the departments objective of furthering basic research into animals within our environment it agreed to host the 9th Annual International Conference of the West African Society for Pharmacology in this University, which takes place in about a fortnight from today with the theme "Non-Mammalian Comparative Pharmacology".

At this year's conference, there will feature for the first time ever, a symposium on non-mammalian/comparative pharmacology which will attract international scientists from Great Britain and France. The symposium is designed to focus detailed attention on the non-mammals that abound in our immediate environment. For a meaningful routine use of these locally available laboratory subjects, there is need for a critical appraisal of the basic and therefore reference data compiled from the studies done on them so far. There is also the need to do comparative evaluations to see how they behave pharmacologically from the traditionally used mammals. This departure from tradition has been deemed necessary by this University's department of pharmacology not only because of the natural sense of scientific enquiry about animals living in our environment but also because of the rising cost of utilization of mammals for routine investigation and teaching in pharmacology. We do not for one moment envisage substituting non-mammals for mammals in investigations leading to the use of novel medicinal agents in man but surely, the basic screening and primary investigations can be carried out on non-mammals that abound in our environment and which are relatively cheaper to obtain. Apart from the usefulness of such basic data on our fauna for investigational uses in traditional medicine, the exercise will show that we are concerned and we do know our environment about which basic primary data is painfully and at most times embarrasingly scanty or non-existent.

It is gratifying that in continuation of the pioneering role of this University, this new challenge has been taken by the department of pharmacology and we hope to blaze a trail for others to follow.

VI

Lastly I would want to make a brief comment on the call of some government functionaries on the pages of newspapers about research into our herbs or medicinal plants. It is not sufficient to make such pronouncements without active financial backing by the way of grants and subventions to carry out meaningful and thorough research into the fauna and flora of Nigeria.

There is need, I agree, for more careful and meaningful research into our Natural products and Medicinal plants. Not only this, we need to know more about the animals which exists in our environment, the biologists, the pharmacognosists, phytochemists, chemists, must rally round to make concerted efforts to achieve this goal. My department as mentioned earlier, has already initiated detailed fundamental research into the non-mammals as well as mammals within the Ife University environment, though a humble beginning, yet we hope to collect enough data to be able to use in later work. Furthermore my department has collaborated with the Drug Research and Production Unit of the Faculty in some detailed applied pharmacological work, some of which have the backing of the O.A.U. and W.H.O.

In any drug or pharmaceutical industry, pharmacology with all its allied subject areas stand at cross roads between the developmental scientists and the consumer of such drugs. A major function of pharmacology and indeed the pharmacologist is to be able to marry both the fundamental and the applied aspects of research into drugs and medicinals. It is also true that other members of the developmental team should come forward with sufficient enthusiasm to get such ventures off the ground, if anything at all to prove that we are not just oblivious to the problems around us.

Pharmacology has no problem at Ife, the subject is vigorously encouraged at the undergraduate level, and a graduate programme also exists for specialisation in various areas of the subject. It is my hope that bright youngmen and women will be attracted to the department in order that our efforts shall begin to yield fruits.

Vice-Chancellor, Deputy Vice-Chancellor, Registrar and the University Community:

"Truth forever on the scaffold,
Wrong forever on the throne,
Yet that scaffold swayeth the World,
Behind the dim unknown
Standeth God watching His Own".

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