system was studied in the experiments on normal rabbits under the electric stimulation (alternating current of 60 Hz) of the posterior limb with a frequency of 2 stimuli per second, each stimulus having a 10 ms duration. The number of stimuli of given amplitude causing a flexion of the stimulated limb was recorded.

It was found[5] in experiments on rats that some derivatives of tropane in the intraperitoneal dose of 15 mg kg^{-1} caused a marked decrease of the pain reaction threshold and a reduction of the analgesic effect of morphine and other analgesics differing from morphine both chemically and as to the degree of their analgesic effect including azidomorphine, and trimeperidine. In experiments on rabbits the same compounds at a dose of 4 mg kg^{-1} intravenously, restored impulse summation in the central nervous system reduced or completely suppressed by morphine at a dose of 0.5–1 mg kg^{-1}. When the drugs were administered to the animals prior to morphine the latter did not cause a reduction of the impulse summation. The same effect was observed with azidomorphine and trimeperidine.

The anti-morphine activity of tropane derivatives was compared with the activity of the classical morphine antagonists, nalorphine and naloxone. Using the impulse summation test it was found that nalorphine and naloxone are slightly more potent than tropane derivatives but with the analgesia test the tropane compounds were more potent.

The ability to reduce opiate analgesic effect was found in many tropane derivatives; the character of the lateral chain was of no importance and this property of the compounds mentioned appeared to be determined by the tropane fragment. Therefore, it was of interest to test the role of this fragment in the anti-morphine action of other agents. With this aim, atropine and cocaine were studied in the same way and both appeared to reduce the influence of morphine on the impulse summation in the central nervous system. It is noteworthy that *N*-methylpyrrolidine and *N*-methylpiperidine being tropane molecule fragments also have an anti-morphine effect. However, they cannot be responsible for the anti-morphine effect of tropine derivatives since the tropine molecule does not degrade in the organism.

The experimental findings presented indicate that many tropane derivatives have a marked affinity for opiate receptors because they not only reduce opiate analgesic effects but also prevent the development of the analgesic action of opiates.

Another confirmation of the concept that some tropane derivatives are antagonists of narcotic analgesics is provided by our findings obtained with morphine-like polypeptides. In our experiments we used the enkephalin amide analog Tyr-Dala-Gly-Phe-NH_2 which caused in the dose of 5 mg kg^{-1} intravenously a marked analgesic effect of 40–60 min duration. This tetrapeptide also causes a reduction of the impulse summation in the central nervous system. Tropane derivatives eliminated the reduction of the impulse summation caused by the tetrapeptide indicated. Thus the antagonism by tropane and its derivatives is developed not only to exogenous opiates (morphine, azidomorphine) but also to ones which occur endogenously (peptides with morphine-like activity).

Since endogenous morphine-like compounds are opiate receptor ligands and tropane derivatives reduce and eliminate their effects it may be suggested that they are also opiate receptor ligands.

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The physiology and pharmacology of the anococcygeus muscle

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When the rat anococcygeus was first introduced as a preparation for pharmacological studies some ten years ago it was suggested that it should prove 'useful both for teaching and research'[1]. How far has this proved true?

The first preparation was the *in vitro* rat anococcygeus muscle. Since then the range has been extended to include an *in vivo* preparation in the rat and *in vitro* preparations from the rabbit, cat, dog, and recently, we have made some observations on the bovine anococcygeus muscle. All have in common a motor adrenergic innervation and inhibitory nerves whose transmitter remains unknown. While their innervation is similar, the properties of the muscle fibres themselves differ widely from the rat anococcygeus with no spontaneous tone and few receptor types through the dog muscle which is also atonic but now possesses inhibitory β-adrenoceptors and motor H_1-histamine receptors, to the rabbit which has considerable spontaneous tone, H_1 motor receptors and now β-adrenoreceptors, muscarine receptors and weak H_2-histamine receptors all mediating relaxation (Table I).

Table I also illustrates the difficulty in suggesting a likely inhibitory transmitter from agonist action. On the assumption that it will be the same in all species, candidates such as acetylcholine, dopamine, histamine, 5-HT, GABA and glycine can be excluded since in the rat they are either ineffective or mediate contraction. Two possibilities are a peptide or ATP. Normally ATP has little effect other than a weak contraction at high concentrations. In the presence of indometacin to inhibit prostaglandin synthesis, however, its effect is reversed to inhibition and on this basis it has been suggested as the inhibitory transmitter[2]. Why, in the absence of indometacin, ATP released from nerves should be powerfully inhibitory while exogenous ATP is ineffective or motor, remains a problem which may be explained by access to different receptors. Convincing identifi-

TABLE I.
Species differences in postsynaptic receptors.

Receptor	Rat	Dog	Rabbit	Cat	Ox
α-Adrenoceptors	Motor	Motor	Motor	Motor	Motor
β-Adrenoceptors	0	Inhibitor	Inhibitor	Inhibitor	Inhibitor
Dopamine	Motor	Not tested	Not tested	Not tested	Not tested
Muscarine	Motor	Motor	Inhibitor	Inhibitor	Not tested
H_1-Histamine	0	Motor	Motor	0	Motor
H_2-Histamine	0	Not tested	Inhibitor	0	Not tested
5-HT	Motor	Motor	Motor	Motor	Not tested
ATP	?	Not tested	Inhibitor	Inhibitor	Not tested
Prostaglandin E_1, E_2	Motor	Not tested	Not tested	Inhibitor	Inhibitor
Prostaglandin $F_{2\alpha}$	Motor	Not tested	Not tested	Inhibitor	Inhibitor
Bradykinin	Inhibitor	Not tested	Inhibitor	Not tested	Not tested
Substance P	Inhibitor	Not tested	Not tested	Not tested	Not tested
Vasopressin	Motor	Not tested	Not tested	Inhibitor	Not tested

cation of the inhibitory transmitter remains, I believe, the most fascinating aspect of this preparation.

What use has been made of the preparation? In teaching, several pharmacology departments in the U.K. have introduced the rat anococcygeus into their laboratory classes as an example of adrenergic nerve-smooth muscle transmission. The rat muscle is universally preferred for several reasons; it is cheap, easily isolated and robust in student hands. The absence of spontaneous tone is an advantage in providing a constant base-line for measuring responses. With this preparation direct and indirect sympathomimetic effects are readily and reproducibly obtained, presynaptic inhibition by agonists such as clonidine can be demonstrated together with their reversal by selective antagonists such as yohimbine and, finally, various forms of drug supersensitivity involving either a shift in the dose–response curve or an increase in the maximum response can be demonstrated. A particular convenience in these experiments is the fact that muscarinic agonists also cause contraction and provide a useful control for the selectivity of the effect on adrenergic responses.

In research, as in teaching the rat muscle has overwhelmingly been preferred. Many have used the tissue as a substitute for the vas deferens free from the controversy which surrounds the motor transmitter in the vas. Indeed, some have taken advantage of the difference and used the preparations to complement one another, the vas deferens to measure presynaptic inhibition free from the complications of postsynaptic excitation and the anococcygeus to measure postsynaptic effects[3]. From the literature the research uses fall into three groups:

(1) Studies on the structure, physiology and pharmacology of these muscles and their innervation. Much of our own efforts have been in this area; Kohyi and his colleagues have described the dog muscle and Garrett the histochemistry of cholinesterase.

(2) Studies on neurotransmission. Drugs affecting both adrenergic motor and inhibitory transmission have been examined by groups including Ambache and Zar; Doxey and his colleagues; Doggrell, Woodruff and Paton; Drew; Leighton and his colleagues; and McGrath and his colleagues.

(3) Studies on drug supersensitivity. Most work on this has been done by Gibson and Pollock.

Structure, physiology and pharmacology

In each new species the original description has of necessity included physiological information such as the presence of spontaneous tone and the nature of the innervation as well as a pharmacological description of receptors (see Table I). Subsequent research, for example on the ultrastructure and the electrical and ionic basis of excitation and inhibition, has been almost entirely on the rat and most of what follows applies to that species.

The rat muscle is composed of parallel bundles of smooth muscle fibres unusually arising in a true tendon from the coccygeal vertebrae. In all species some of these fibres end by merging with the longitudinal muscle of the colon. In some, such as the rabbit, there is little or no extension beyond the colon but in the rat, dog and ox some muscle fibres in the male continue, to end either in the perineum or by forming the retractor penis muscle. As a consequence the anococcygeus is heavier and stronger in the male than the female and if this is not taken into account an unnecessarily large variance is introduced into dose–response curves. Each muscle bundle contains between two and eight fibres with numerous gap junctions between fibres possibly representing regions of electrical continuity. In the narrow tissue clefts between bundles run the autonomic nerves within Schwann cell sheaths. Many of these are adrenergic as shown by their formaldehyde fluorescence, by the presence of dense-cored vesicles within their varicosities, by the ability to enhance these dense cores with 5-hydroxydopamine and their disappearance after chronic treatment with 6-hydroxydopamine or reserpine. In the first description of the fine structure no other nerve profiles attributable to the inhibitory nerves were seen[4]. More recently varicosities containing larger, electron-opaque vesicles have been described contributing up to 40% of the total and most probably representing the inhibitory nerves[5]. A third type of varicosity with mainly clear vesicles accounted for less than 5% of the nerve profiles and may represent a true cholinergic innervation. If so, this does not seem an important neural control since neither motor nor inhibitory responses to nerve stimulation are influenced by atropine. The origin of these motor and inhibitory nerves in the spinal cord has been identified: the motor are characteristically sympathetic arising in the upper lumbar outflow; the inhibitory equally characteristic, arising from the sacral cord between L5 and S3[6]. Both are interrupted by ganglia as judged by the action of ganglion blocking drugs *in vivo*. The organization is, therefore, that of the autonomic nervous system with the inhibitory fibres conforming anatomically to the parasympathetic division. The localization of the ganglion synapses, however, is not entirely clear. *In vitro* the responses to extrinsic nerve stimulation are insensitive to hexamethonium up to a concentration of 3×10^{-5} M suggesting the fibres are postganglionic with the ganglion relay some distance from the muscle. Indirect support for this conclusion was the observation *in vivo* that it was possible to stimulate postganglionic sympathetic fibres via an electrode in the vertebral canal several centimetres cranial to the muscle, consistent with a postganglionic location in the ganglion chain close to the vertebral column. Ganglion cells, however, are present on and just beneath the surface of the muscle[4] and recently it has been reported that (+)-tubocurarine reduces and cholinesterase inhibitors potentiate the motor response to extrinsic nerve stimulation but not to field stimulation with the implication that some of the extrinsic motor fibres are preganglionic[7]. There was no effect on the response to inhibitory nerve stimulation. These are puzzling results. One would have

expected the inhibitory fibres, if these are parasympathetic in organization, rather than the sympathetic motor fibres to have ganglion cells close to the tissue, though the arrangement could be comparable to the vas deferens where the sympathetic nerves do synapse close to the muscle. More work is needed to clarify these conflicting observations but at the end of the day I believe the large majority of fibres close to the muscle will be found to be postganglionic.

The electrical properties of the muscle and its response to nerve stimulation have been examined in the rat and the rabbit with very different results. In the rat the resting membrane potential is high, about 62 mV, and stable, corresponding to the absence of spontaneous mechanical activity. In the rabbit the membrane potential is l 48 mV in the atonic muscle and falling even lower when tone is present, and with superimposed rhythmic waves of depolarization with frequent spike potentials at their peak. Nerve stimulation in the rat produces graded depolarizations without spike potentials and these give rise to graded contractions. Guanethidine blocks the adrenergic nerves, depolarises the muscle and raises tone. Nerve stimulation now produces mechanical inhibition but little or no hyperpolarization. These responses are quite unlike the large hyperpolarizations in the guinea-pig taenia from stimulating the non-cholinergic non-adrenergic nerves in that tissue, suggesting that the transmitter might also be different. It was a surprise, therefore, to find in the rabbit responses to inhibitory nerve stimu- ı ~ on almost identical to those in the guinea-pig taenia, large hyperpolarization as well as mechanical inhibition. Passive displacement of the membrane potential altered the magnitude of both the depolarization associated with adrenergic motor nerve stimulation and the hyperpolarization of inhibitory nerve stimulation in a way which suggested a reversal potential of −20 mV for the former and −80 mV for the latter. Such results suggest an increase in permeability to some ion with an equilibrium potential close to these reversal potentials. Measurement of input resistance through the microelectrode during excitation or inhibition failed to show any convincing change but the more sensitive measurement of membrane conductance by passing longitudinal current through the muscle and measuring electrotonic decay did show a fall in membrane resistance in the rabbit, though a much smaller fall in the rat[8].

These results suggest that if a rise in intracellular calcium is responsible for contraction and a fall for relaxation, then in the rat, spike potentials contribute little to the former and hyperpolarization is unlikely to be the direct cause of the latter. Transmembrane movement of calcium as a consequence of depolarization may be the cause of contraction in the rat though even here single stimuli produce such small depolarizations that intracellular release of calcium may be more important, at least for the twitch response. In the rabbit large depolarizations with spike potentials are common and might be the immediate cause of calcium entry and contraction and equally the large hyperpolarizations by cancelling this calcium entry could be directly responsible for inhibition.

Drugs affecting neurotransmission

Table II illustrates two points: first, the preponderance of work on the motor, adrenergic side compared with the poverty of information on the inhibitory innervation. When the inhibitory transmitter is identified and agonist and antagonist analogues are made available this disparity will no doubt quickly disappear in a wave of new work. Second, the drugs have been arranged in groups to underline the suitability of the preparation for the study of almost all aspects of adrenergic transmission. Pre- and post-synaptic α-agonists and antagonists, neurone blockers, indirect sympathomimetics and drugs blocking neuronal uptake have all been successfully demonstrated. It is unnecessary to go through each of these groups in detail. Three slightly unusual features are perhaps worth commenting on. First, the relative sensitivity of pre- and post-synaptic α-receptors to agonists. Several workers have studied this either *in vivo* or *in vitro*[9]. One problem brought out in Table I is that while the sensitivity of the presynaptic α-receptors is similar to other adrenergic nerves, the postsynaptic α-receptors have a rather high sensitivity so that only for clonidine and guanfacine is it possible to show depression of the nerve response free from postsynaptic excitation. No doubt it is for this reason that others have used the vas deferens, whose postsynaptic sensitivity to noradrenaline is low, to measure presynaptic inhibition and the anococcygeus for postsynaptic excitation. A second unusual feature is the ease with which indirect sympathomimetic actions are produced. Not only is the list of indirect sympathomimetics in Table II long (but by no means exhaustive), it also includes all of the neurone blockers and other drugs such as cocaine, labetolol, the peptide eledoisin and TEA, none of which is commonly considered an indirect agonist. With LSD and cocaine there is an element of doubt as to whether their mode of action is truly through neuronal noradrenaline release even though their action is abolished by phentolamine and, therefore, involves the α-receptor. For example, the excitatory effect of LSD was still present in muscle from reserpinized animals[10] yet had previously been completely absent in muscles treated with 6-hydroxydopamine[11]. More recently an increased release of [^{3}H]noradrenaline by LSD but not by equicontractile doses of $BaCl_2$ suggests that at least part of the effect of LSD is a true indirect sympathomimetic action. Why indirect sympathomimetic effects are so readily seen in this tissue is unclear. The explanation should lie either in a high density of adrenergic nerves, an avid neuronal uptake, a particularly narrow synaptic cleft or a high postsynaptic receptor sensitivity to noradrenaline. Perhaps this is one occasion for a multifactorial explanation since all four factors are favourable though no single one uhiquely high. The final unusual feature concerns the actions of dopamine. As an agonist dopamine is highly effective, almost as effective as noradrenaline, and both it and apomorphine are antagonized by haloperidol suggesting an action on true dopamine receptors. Bromocriptine, however, is ineffective but acts as a preferential antagonist of noradrenaline as does pimozide suggesting some interactions between dopamine and noradrenaline receptors.

Noradrenaline uptake and drug supersensitivity

Neuronal uptake of noradrenaline is to be expected in a tissue with a dense adrenergic network evenly distributed throughout the muscle. Exposure to low concentrations of radioactive noradrenaline confirms this with tissue/medium ratios rising as high as 8/1. This retention is reduced by cocaine or desmethylimipramine suggesting that most is held within nerves but an even greater reduction in retention, especially with high concentrations of noradrenaline, is produced by phenoxybenzamine which blocks both neuronal and extraneuronal uptake suggesting that some noradrenaline is taken up into muscle cells. Neuronal uptake can be blocked not only by cocaine but also by a variety of antidepressants (see Table II)[12] and the retained radioactive noradrenaline can be released by nerve stimulation or by indirect sympathomimetics, confirming once again its neuronal location.

From these results one would expect the

TABLE II. Some drugs active in the rat anococcygeus muscle preparation.

	Motor effects	
	Presynaptic	Postsynaptic
Adrenoceptor agonists		
Noradrenaline	10^{-9}–10^{-6} M inhibits twitch + noradrenaline release	10^{-6}–10^{-4} M contraction
Clonidine	10^{-9}–2×10^{-6}M inhibits twitch + noradrenaline release	8×10^{-8} M contraction
Guanfacine	0.4 μg kg^{-1} inhibits twitch	144 μg kg^{-1} contraction
Oxymetazoline	2×10^{-8} M inhibits twitch + noradrenaline release	6×10^{-9} M contraction
Tetrahydrozoline	5×10^{-8} M inhibits twitch + noradrenaline release	9×10^{-8} M contraction
Naphazoline	8×10^{-7} M inhibits twitch + noradrenaline release	2×10^{-8} M contraction
Methoxamine	10^{-6} M no effect	2×10^{-7} M contraction
Phenylephrine	10^{-6} M no effect	3×10^{-7} M contraction
Adrenoceptor antagonists		
Phentolamine	5×10^{-8} M increases noradrenaline release	2×10^{-8} M inhibits twitch + noradrenaline
Phenoxybenzamine	3×10^{-7} M increases noradrenaline release	2×10^{-8} M inhibits twitch + noradrenaline
Yohimbine	10^{-7} M increases noradrenaline release + twitch	5×10^{-7} M inhibits twitch + noradrenaline
Piperoxan	10^{-5} M increases noradrenaline release	
Prazosin		10^{-9} M inhibits noradrenaline
Dopamine agonists and antagonists		
Dopamine		Contraction
Apomorphine		10^{-6} g ml^{-1} contraction
Haloperidol		10^{-6} g ml^{-1} inhibits DA and noradrenaline
Bromocriptine		Inhibits noradrenaline
Pimozide		Inhibits noradrenaline
Neurone blockers		
Guanethidine	10^{-6} M inhibits twitch	
LSD	10^{-9}–10^{-6} M inhibits twitch	
Labetolol	10^{-5} M inhibits twitch	
Guanoxan	Inhibits twitch	
Indirect sympathomimetics		
Tyramine	10^{-6} M contraction, releases noradrenaline	
Amphetamine	10^{-6} M contraction	
Guanethidine	10^{-5} M contraction, releases noradrenaline	
LSD	10^{-9}–10^{-6} M contraction	
Labetolol	10^{-5} M contraction	
Cocaine	3×10^{-5} M contraction, releases noradrenaline	
TEA	10^{-2} M contraction	
Eledoisin	10^{-6}–10^{-5} g ml^{-1} contraction	
Noradrenaline uptake blockers		
Cocaine	10^{-6} M potentiates twitch + noradrenaline	
Nortryptiline	10^{-8} M prevents [^{3}H]noradrenaline uptake	
Protryptiline	6×10^{-8} M prevents [^{3}H]noradrenaline uptake	
Desipramine	4×10^{-8} M prevents [^{3}H]noradrenaline uptake	
Imipramine	3×10^{-7} M prevents [^{3}H]noradrenaline uptake	
Amitryptiline	2×10^{-8} M prevents [^{3}H]noradrenaline uptake	
Guanethidine	10^{-6} M potentiates noradrenaline	
Other active Drugs		
Acetylcholine		10^{-5} M contraction
Carbachol		3×10^{-6} M contraction
Neostigmine		10^{-7} M potentiates ACh
5-HT		10^{-5} M contraction
$BaCl_2$		3.8×10^{-2} M contraction
KCl		5×10^{-2} M contraction
Reserpine	200 μg kg^{-1} depletes noradrenaline 90%	
Tris	10^{-2} M inhibits twitch response	
PGE_2	10^{-7}–3×10^{-6} M inhibits twitch	
	Inhibitory effects	
TEA	10^{-3} M potentiates inhibitory response	
KCl	5×10^{-2} M relaxes high tone	
Ethanol	200 mM reduces inhibitory response	
PGE_2	10^{-7}–3×10^{-6} M reduces inhibitory response	
Bradykinin		Inhibition
Papaverine		10^{-6}–10^{-4} M inhibition
Sodium nitroprusside		10^{-9}–10^{-7} M inhibition
Sodium nitrite		Inhibition

preparation to demonstrate at least one form of supersensitivity, that due to loss of neuronal uptake and confined to agonists subject to neuronal uptake. This is so; the noradrenaline supersensitivity produced by cocaine, 6-hydroxydopamine or some neurone blocking drugs does not extend to either oxymetazoline, which is not subject to neuronal uptake, or to carbachol[13]. Two other forms of supersensitivity have been demonstrated by the same workers. First is a non-selective increase in sensitivity produced by chronic reserpine or thyroxine treatment which causes a supersensitivity to acetylcholine and KCl as well as to noradrenaline, a situation similar to that produced by chronic denervation in other tissues. The mechanism here, as in other tissues, is obscure. Second, an increase in the maximum contractile response with no change in the dose–percentage response is produced by morphine withdrawal, by single doses of reserpine or by corticosterone. The common link in these apparently dissimilar situations may be an increase in plasma corticosterone since the supersensitivity following morphine withdrawal or reserpine is absent when steroid synthesis is inhibited by metyrapone or when the adrenals have been removed, and the mechanism may be to alter the tissue distribution of sodium since either blocking the sodium–potassium pump with ouabain or raising extracellular sodium levels will similarly raise the maximum response. In addition to these major forms of drug supersensitivity other minor effects have been reported. Morphine withdrawal causes some hypersensitivity to ACh apparently from inhibition of cholinesterase by corticosterone and an even more puzzling observation is a specific hypersensitivity to ACh produced by the antidepressant mianserin.

In conclusion, the years since its introduction seem to confirm the anococcygeus as a useful preparation for both teaching and research. So far its usefulness has been mainly in the study of adrenergic neurotransmission. This situation will surely be transformed when more is known of the inhibitory nerves and transmitter.

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The clinician's role in patient compliance

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A large number of therapies are currently available which, when used in accordance with the established details of the regimen, are reasonably efficacious in preventing and treating illness. However, as the focus of medical practice has shifted from acute illnesses to chronic diseases, patients can no longer be only passive recipients of medical care, but instead, must take an active role in managing their own care (with physician guidance). Thus progress in treatment and in achievement of desired medical outcomes depends heavily upon patient adherence (or 'compliance') to recommended or prescribed regimens.

An extensive literature exists documenting generally low rates of patient compliance. Although these rates vary for different conditions, treatments, patients, and settings, reviewers have noted that at least a third of the patients in most studies failed to co-operate with their physicians' advice. Moreover, when the medication regimen is long term, only about 50% of patients are generally found to be compliant, and this figure can drop to 25% or lower where the condition is asymptomatic (as, for example, is frequently the case with a medication regimen for hypertension)[19]. Other research efforts have clearly demonstrated that physicians cannot predict the probable degree of their patients' adherence to regimen at levels of accuracy better than would be attained by chance; moreover, they substantially *over*estimate the compliance rates of their own patients, and often express both little desire to understand the problem and little sympathy for the unco-operative patient (although, as medical students, their own drug-taking behaviors and compliance-related attitudes closely mirror those found for patients in general).

Noncompliance creates significant barriers to attainment of therapeutic goals: by disrupting or invalidating the potential benefits of the regimen, by exposing the patient to additional medical tests and alternative therapies which may be duplicative or unnecessary, and which may result in iatrogenic outcomes, by interfering with the doctor-patient relationship (e.g. patient dissatisfaction resulting from poor medical outcomes caused by poor compliance, and negative reactions by physicians to 'problem' patients) and by interfering with attempts to evaluate the quality of the treatment.

A considerable amount of the research on noncompliance has examined the role of the patient's sociodemographic characteristics (e.g. age, sex, religion, race, mari-