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THE USE OF GANGLION BLOCKING AGENTS IN RELATION TO THE NEUROGENIC FACTORS IN HYPERTENSION.

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One of the major dangers in the study of hypertension seems to be the ease of making misleading inductions, i.e.believing things to be causally associated which are not so in fact. It recalls the story of the little boy living by the seaside on the border between Ulster and Eire who used to play with a small girl on the other side of the border. They were only children and it was a lonely neighbourhood. One hot day, daringly, they decided to bathe without bathing suits. As the little girl undressed an expression of amazement crossed the little boy's face. "gosh" he said, " I didn't know that Catholics and Protestants were so different." Confronted with such complexities, I would like to avoid the wider aspects of hypertension and simply to examinein some detail a much narrower point, how to obtain from the use of ganglion blocking drugs information about the neurogenic factors in hypertension.

First there are some special features of ganglionic block which have to be mentioned. Ganglia differ in their sensitivity. In cats, for instance, the ganglia supplying the nictitating membrane are more resistant than those suppliying the salivary gland. In man, after a dose of hexamethonium one subject will faint on standing without there being anyeffect on the eyes, while another has his accommodation paralysed without any fall in blood pressure on standing. There is no established explanation for this. But if microscopical sections of ganglia are examined they obviously do not conform to the simple usual diagram; they consist instead of a very complex basket work of dendritessurrounding the ganglion cell with many small supporting glial cells carried aming them. If, then, there is something of a cellular barrier round some or many ganglion cells, this would mean that these particular cells might well prove relatively inaccessible to an injected quaternary salt (because of the impermeability of cells to such compounds). The practical consequence of course is simply that one cannot assume , if one has blocked one ganglion, that the other ganglia will be blocked to the same degree.

One must be careful that the blocking agent used is specific. Any drug sufficiently like acetylcholine to compete with it at the ganglion synapse is liable to have actions related to acetlycholine at other places. Thus one sees with d-tubocurarine action at the neuromuscular synapse a feeble atropine and anti-cholinesterase action as well as the ability to releasehistamine (which is possessed by a good amny bases). Nicotine is somewhat betterbut possesses significant stimulant as well as blocking actions and is active at the neuromuscular junction.

Tetramethylammonium is better still but has a number of curious actions: a curare-like effect, the eliciting of paraesthesiaeand the stimulation of noradrenaline ectretions. Hexamethonium is a good deal better; if one defined a specific drug as one in which the principle action was exerted in a dose 100 times smaller than any other action, it would pass the test. This is one of the most important facts about hexamethonium, and it seems to be more or less true of all the other compounds related to it. In one special respect almost all these compounds are specific, in that they penetrate only very slowly into the central nervous system; this means that one can largely discount central actions in the interpreting of their effects.

It must also be remembered that ganglion block will paralyse the efferent side of the buffer nerve system. It is this which accounts for the potentiation of the actions of adrenaline and noradrenaline , or even of acetylcholine on the blood pressure, and it is obviously liable to modify the response to many drugs.

An important point is that the effect of hexamethonium depends particularly on two factors; the rate of excitation of the ganglion, and the duration of the exitation. Firstly the block is much greater the faster the rate of stimulation. Secondly, if you compare the initial peak post-ganglionic response with the response at the end of a minute's excitation, whereas the normal ganglion the excitation rate must exceed 25 shocks a second before fatigue begins much earlier: and fatigue is actually detectable after a large dose of hexamethonium even at a rate as low as half a shock per second. This means that if you determine the rate of excitation at which the maximum post-ganglionic response can be obtained , a rather startling "law of diminishing returns" comes into operation; whereas the normal ganglion can yield an increasing postganglionic discharge with increases of stimulation rate up to 25 per second, the deeply blocked ganglion merely becomes weaker if the rate of discharge is accelerated

beyond half a shock per second.

These results have two implications: first that the more active a ganglion is the more sensitive it will become. This may explain the considerable response one sometimes sees with very small doses of ganglion blocking agents in a hypertensive patient. Second, the only reactions to a substantial block which are likely to show themselves are either non-ganglionicones, or else the activation of new ganglionic pathways at a slower rate, which might only produce a transient effect. From this it seems probable that the tolerance developed to hexamethonium is largely humoral. If the superior cervical ganglion, which is quite a resistant ganglion, can be paralysed more or less completely even to so slow a rate as half a shock per second, it is unlikely that any ganglion in the body will fail to be paralysed by the large doses of hexamethonium used in the tolerant patient.

Tests for the Neurogenic Component in Hypertension.

Having armed oneself with a specific ganglion blocking agent ,the question arises of how to use it to assess the neurogenic component. Obviously any tests must be done on a supine patient, so that one studies the hypertensive processes (rather than postural reflexes). Since hexamethonium has only a slight or no effect in normal subjects lying down, one could then attribute the fall seen in hypertensives to removal of abnormal autonomic tone.

But clearly one would like to make this quantitative. Three types of test suggest themselves:-

(a) To determine the threshold dose, in which one would assess the intensity of the autonomic drive by finding out how far it had sensitised the ganglia. This is attractive because it is very safe and would not be complicated by reactions to a big fall in pressure; but it would be liable to individual variations in sensitivity.

(b) To determine the maximal fall in blood pressure obtainable by ganglionic block, increasing the dose of blocking agent until no further effect was obtained. This is attractive, theoretically,because with a big dose, allowed to act for a sufficient time , it is unlikely that any significantly active ganglia would be spared. Variations in sensitivity between subjects mught thus be minimised, but of course the method would have its dangers particularly in elderly people.

(c) The slope of the dose response line. Professor Pickering has suggested, on the basis of the dose response curves obtained by Morrison and myself (1953) that the different slopes might correspond to different degrees of neurogenic activity. In these particular experiments this may well not be th case, since they were based on standing systolic blood pressures, and probably measured the capacity of the venous bed, the muscle tone, and the vigour of postural reflexes as much as anything else. But with a supine subject it is likely that the bigger the maximal fall obtainable, the steeper would be the line relating to the fall in blood pressure produced to dose of hexamethonium given. Combined with a measurement of threshold dose this might provide a most useful measure of autonomic tone in hypertension.

One is uncertain how these simple tests compare with the tests using tetraethylammonium or serotin that Dr. Page has mentioned. But I am confident that the factors mentioned above are important, and that a test of the kind outlined could be useful. In any case it seems a wicked waste, now that we have a fine population of reversible sympathectomized patients, not to use them to try to put some precision into the much abused term "neurogenic".

Reference.

Morrison B.,and Paton W.D.M. (1953) Brti. Med. J. i. 1299.