Editorial

Chemotherapy of Hypertension: Yesterday—Today—Tomorrow

ON A LOVELY DAY in September 1962, I was strolling with Professor J. V. O. Reid and Dr. John Walsh on the grounds of King Edward VIII Hospital in Durban, South Africa. In the midst of our discussions on human pathology unique to this part of the world, my attention was drawn to an attractive bush, which I photographed. It wasn’t a large bush but it was in full bloom with pretty purple, blue, and white flowers. It was called the “yesterday-today-tomorrow” bush or “Brunfelsia uniflora.” While inspecting one of the blue flowers, I was told that it had originally come out purple and after a day or so had turned blue. Tomorrow it would be all white.

Viewed in perspective, the renaissance in the treatment of hypertension with drugs may be considered in a chronology similar to that of the flowering bush. Although the present discussion will be mainly at a generic level, the practical object of concern is the patient with severe hypertension, with or without cardiovascular complications. It is in this type of case that widest agreement exists concerning the beneficial effects to be achieved with drug therapy. In what follows there is an arbitrary omission of precise annotation and emphasis is given to major categories of drugs and concepts of their mechanisms of action.

Yesterday was in essence the era of ganglion-blockade. Prior to the beginning of this era, about 1950, the therapeutic situation was a barren one, indeed. In management of severe hypertension, one was confronted with such undesirable alternatives as observing the natural history of the “disease” (plus phenobarbital) or recommending surgical sympathectomy, the latter tending to be reserved for malignant cases. This changed radically and chemical therapy began to flower following discovery of the ganglion-blocking properties of the quaternary ammonium ion and the advent of the methonium compounds, the best hypotensive being hexamethonium. The crossover from demonstrable inhibition of autonomic nerve function with such compounds in animals to effective orthostatic lowering of blood pressure in man was predictable, and there followed as a consequence a host of compounds with similar actions but differing in potency, duration of effect, and metabolic fate. These included quaternaries such as chlorisondamine (Ecolid) and pentolinium (Ansolysen), the short-acting tertiary amine compound, trimethaphen (Arfonad), and the well-absorbed secondary amine, mecamylamine (Inversine).

Because these compounds interfere with cholinergic transmission at parasympathetic as well as sympathetic ganglia, an unusual degree of persistence and enthusiasm was required by the patient, who often had blocked bowels, blurred vision, dry mouth, sexual impotence, etc., as well as by the physician, who

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was kept busy antidoting these "side effects" and arranging an optimal hypotensive dosage schedule. Considering these difficulties as well as widespread skepticism in the early days as to whether it was worth all the effort anyhow, I look on the work of physicians who first pursued the drug approach in hypertension as being well nigh heroic. The adjunctive use of the veratrum alkaloids, hydralazine, and the rauwolfia alkaloids did much to ease the burden of ganglion-blockade and broaden the base of effective management of severe hypertension. A real milestone was reached conceptually with the demonstration that reserpine and other rauwolfia alkaloids release the amines, serotonin and norepinephrine, from tissue depots in animals. Correlation of sympathetic-blocking effects in animals with diminished tissue levels of the transmitter substance, norepinephrine, served to stimulate further approaches to treatment of hypertension based on chemically induced alterations in the metabolism of this amine.

Today, of course, encompasses the extensive experience of yesterday but mainly concerns the addition of two types of drugs introduced during the past 5 years, the selective inhibitors of sympathetic nerve function and the thiazide diuretics. The development of selective sympathetic inhibitors has occurred coincident with an upsurge of interest and knowledge concerning the biochemistry of norepinephrine, which is generally thought to be the peripheral transmitter of the sympathetic neurone. Factors governing the release of this substance on to the receptor (blood vessel) have been subjected to detailed investigation. Since postganglionic sympathetic neuronal transmission is adrenergic (really noradrenergic) while that of the entire parasympathetic system is cholinergic, interference with adrenergic transmission should result in selective sympathetic inhibition. That this is so became apparent with the introduction in 1959 of bretylium tosylate and guanethidine (Ismelin). Both compounds were found in animals to produce specific adrenergic blockade, which was confirmed in man by the predominantly orthostatic blood pressure response in the absence of evidence of parasympathetic block. Since both are strongly basic compounds which do not enter the brain, there is no question that their sites of action are peripheral. Bretylium, a benzyl quaternary ammonium compound, does not alter the peripheral stores of norepinephrine, but acts to prevent physiologic as well as certain types of pharmacologic release of the adrenergic transmitter at nerve terminals. Guanethidine, in addition to having a bretylium-like action in inhibiting neurogenic release, also has norepinephrine-releasing and depleting effects. Though not proved, it is probably the latter effect that accounts for its long-lasting hypotensive action in patients. The effect on norepinephrine stores is somewhat different from that of large doses of reserpine, e.g., on intravenous injection guanethidine produces an initial pressor effect indicating that some of the norepinephrine released is gaining access to receptors, and the metabolic fate of norepinephrine released by the two drugs is different. The complexity of events at the nerve ending may be illustrated by simply mentioning some of the terminology used by workers in the field, such as: compartments or pools of norepinephrine, turnover rates, tissue-binding versus oxidative deamination and O-methylation, and ease of releasibility. Concepts are changing and the need for further clarification is obvious. The important practical point is that guanethidine is currently the preferred potent hypotensive agent, whereas clinical toxicity and frequent development of tolerance have returned bretylium to the realm of research interest only.

While their mechanisms and sites of action are not known precisely, another category of compounds which appear to be selective sympathetic blockers in patients are the enzyme inhibitors-monoamine oxidase inhibitors and the decarboxylase inhibitor, \( \alpha \)-methyl-dopa. These compounds readily enter the brain and it is not certain to what extent their blood pressure effects are mediated centrally. Curiously, these agents exhibit little hypotensive...
effect in animals. Monoamine oxidase is one of the enzymes involved in the metabolism of norepinephrine and a decarboxylase is essential to synthesis of the amine. The relationship between monoamine oxidase inhibition and hypotensive effect has not been adequately explained. A recent postulate on mechanism is that of a bretylium-like action in blocking release; several other explanations have been offered, none being based on conclusive evidence. Be that as it may, it has been possible to achieve orthostatic lowering of blood pressure with several different monoamine oxidase inhibitors in patients with hypertension. While the over-all role of monoamine oxidase inhibitors in therapy is probably a minor one, this depends considerably on the physician's preference. They are useful particularly in selected patients who may benefit from the antidepressant effects of the drugs. Factors of potency and toxicity make isocarboxazid (Marplan) and pargyline (Eutonyl) the inhibitors of choice for lowering blood pressure.

A large number of favorable reports have appeared on the new drug, \( \alpha \)-methyl-dopa (methyl-dopa, Aldomet). Certain unique aspects of this agent, particularly regarding its hemodynamic effects, are summarized elsewhere in this issue by Weil, Barbour, and Chesne. While numerous investigations suggest that methyl-dopa is a useful drug, extensive experience by the practicing physician will be required before one can be certain of its place in therapy. It is recommended that methyl-dopa be reserved initially for the severe hypertensive patient and that the precautions suggested by the manufacturer be followed carefully. From the standpoint of mechanism of action, methyl-dopa is frequently represented as a new approach to hypertension based on decarboxylase inhibition. Though this point of view is still worthy of some consideration, it is not supported by available data. In animals, the drug does deplete norepinephrine in the brain as well as in peripheral sympathetic terminals, but this is by a reserpine-like mechanism which is un-related to the enzyme-inhibiting effect. Several other decarboxylase inhibitors have been shown not to have norepinephrine-depleting properties in animals and to be devoid of hypotensive action in man. Possibly, the effects of methyl-dopa on blood pressure are mediated chemically (norepinephrine depletion) or pharmacologically by amine metabolites formed by decarboxylation of the drug itself. Decarboxylase inhibition occurring concurrently in the patient is probably inadequate to alter significantly the synthesis of norepinephrine.

It will be recalled that chlorothiazide, the original thiazide, was introduced into therapeutics on the basis of diuretic properties in the dog. While the predicted diuretic effect was confirmed in man, of equivalent interest was the coincidental observation of a blood pressure-lowering effect in patients with hypertension. The development of several more potent diuretics, most of them close analogs of chlorothiazide, has not resulted in a better hypotensive agent, thus far. The hypotensive actions of these drugs are generally considered to be secondary to their diuretic and natriuretic effects, with resultant diminution in plasma volume. On the other hand, it is noteworthy that one analog (diazoxide), which in the hands of several investigators has exhibited hypotensive properties, actually produces sodium retention. The great contribution of the thiazide diuretics to management of severe hypertension lies in their potentiation of the effects of other agents, permitting either a reduction in dosage of the primary drug or better blood pressure control at the same dose.

Thus, in the management of severe hypertension today, the physician has available for use a variety of new and old drugs. While the newer drugs appear to be in the direction of simplifying therapy, treatment in a given patient is still very much an individual matter, and one must be prepared to use any of the agents mentioned thus far, alone or in combination.

Tomorrow will be looked upon chiefly in
terms of what is needed and what is likely to become available. There is a real need for better agents for the acute management of accelerated hypertension. Intravenous therapy with short-acting compounds such as nitroprusside and methaphen requires constant observation, whereas with other agents (parenteral Reserpine, Aldomet, or ganglion-blockers) the desired effect often is either delayed in onset or accompanied by unpleasant side effects. Since antihypertensive therapy as presently constituted is usually required continuously for the duration of the patient’s life, initiation of chemotherapy in any patient cannot be taken lightly. In most patients we are still a long way from the goal of uniform and easy control of blood pressure without discomfort or hazard.

In the near future we may expect further refinements in the area of sympathetic neuronal inhibition. Other guanidine compounds are already being studied in patients in the hope of finding an agent that does not possess the disadvantages of guanethidine, such as diurnal variation of response and occasional production of severe diarrhea. Investigations of chemical and physical events at the sympathetic nerve ending and the effects of drugs thereon will undoubtedly yield further practical results in the same general area. Attempts to inhibit synthesis of norepinephrine with enzyme inhibitors is tending to shift away from the decarboxylase step toward the final step, the hydroxylation of dopamine by dopamine-β-oxidase. Several compounds that inhibit this enzyme in animal tissues have been discovered, but in general they appear to be too toxic for clinical trial. It is only a matter of time before potent, safe agents are found. A better understanding of the mechanism of action of current drugs, such as α-methyl-dopa, might be rapidly translated into development of even more effective agents. The worthwhile acute action of parenteral diazoxide is deserving of further study. Over the horizon may lie a compound with the hypotensive properties of the thiazides but without troublesome effects on electrolyte balance. Also, the area of aldosterone antagonists may prove rewarding.

When one gets beyond the considerations just mentioned, predicting becomes most difficult. While most experts consider that many factors are involved in the pathogenesis of hypertension, fields of investigation other than electrolyte metabolism and autonomic function have not yielded potent antihypertensive drugs. Developments applicable to treatment may be expected to appear in studies in other research areas that superficially may appear unrelated to the problem of hypertension. A broad perspective would be required to make extrapolations to therapy. Said in another way, a degree of strabismus may prove more rewarding at times than clear and direct vision. Then again, though we may prefer the logical and sequential, history indicates the importance of the accidental discovery and the screening program. Rest assured, however, that regardless of how we get there, some day the flower will be all white.

Albert Sjoerdsma

General Principles

An underlying philosophy, when it can be found, is invaluable in practice, not only because it quickens and maintains interest, but because it forms a stable guide to action when experience fails, as it often will in face of the unusual, to give precise or particular direction.—Sir Thomas Lewis. Diseases of the Heart. New York, The Macmillan Company, 1933, p. vi.
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