We are in a period in which the management of mild and moderate hypertension is being reevaluated. The U.S. Veterans Administration studies initiated nearly 20 years ago indicated that drug treatment of hypertension clearly reduced morbidity and mortality. Large scale controlled studies since that time have either compared the effect of one drug with another or of one or more drugs with that of usual care in the community. There is, however, an increasing uneasiness that many of the million of patients taking drugs with known and unknown long-term side effects may be doing so inappropriately.¹

Some years ago in an extended trial of withdrawal of hypertension drugs or substitution of a placebo, Dus- tan et al.² found that relatively few hypertension patients could sustain their reduction of blood pressure without medication. However, more recently Finnerty³ has shown in a large series of patients that the total dosage or the number of antihypertensive drugs can be reduced without impairing the antihypertensive effect and with considerable reduction in adverse symptoms of medication. In neither of these studies, however, was an attempt made to substitute nonpharmacologic for pharmacologic measures. It is noteworthy that hypertensives tend to be an overweight group of patients, with a mean of 30% above ideal weight in most large series, and that metabolic derangements such as noninsulin-dependent diabetes and hyperlipidemia are often associated.

The 1979 Report of the Hypertension Task Force of the National Institutes of Health⁴ urged that attention be given to the special problems of the overweight hypertensive individual, and a recent report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure emphasizes the potential value of nonpharmacologic management.⁵ Several of the large national prospective studies are revising their protocols to include more emphasis on this approach. In October, 1980, the first meeting entirely devoted to hypertension and obesity was held in Florence, Italy; the reader is referred to the Proceedings as an additional source of basic references.⁶ The present review will briefly consider several questions: Are there subtypes of overweight hypertensive patients in whom particular mechanisms bring out a latent hypertension? May particular endocrine disturbances of the obese contribute to the hypertensive state? If so, can these be reversed by nonpharmacologic measures such as weight reduction, increased physical activity, and restriction of sodium intake? What is the relative value of dietary management as opposed to physical training? What are the indications for future research in this field?

General Considerations

Not all obese persons are hypertensive, but the association between obesity and hypertension is a close one.⁷ Obesity is a risk factor for development of hypertension and for its progression, and hypertensives tend to become obese.⁸ The two conditions may be genetically linked. Measures that favorably affect obesity also tend to reduce the hypertension. If a patient's hypertension can be corrected by nonpharmacologic measures directed toward metabolic derangements, one may well ask whether the condition should still be labeled "essential" hypertension?

As Berglund et al.⁹ have shown, middle-aged hypertensives tend to be hyperinsulinemic. Their mean fasting blood glucose concentrations are normal, but they tend also to have glucose intolerance. Thus, they have varying degrees of insulin resistance. Disorders of carbohydrate and lipid metabolism are more prominent in persons with obesity of the hypertrophic adult-onset
type in which there is predominantly adipocyte enlargement, rather than hyperplasia, and in which the distribution of fat is upper truncal rather than universal. Data from the 1st National Health and Nutrition Examination Survey (HANES I) include blood pressure measurements as well as measurements of subscapular and triceps skinfold thickness, which can give some indication of the distribution of fat. The subscapular measurement was found to be the best predictor of both systolic and diastolic blood pressure in each race-sex group and has significant predictive power unshared by the triceps measurement (Baird, Sylwestrer, Habicht, and Sims, in preparation). Earlier, Albrink and Meigs had shown by the correlations between ulnar and subscapular skinfold measurements that hyperlipidemia was also associated with central disposition of body fat.

The hyperinsulinemia and other endocrine changes often associated with spontaneous obesity which include suppression of growth hormone response and the changes in concentration of substrates, can be produced by experimental overfeeding and weight gain in normal volunteers, and they are readily reversible. This simply means that the changes may be brought about by overeating, but does not exclude the probability that other mechanisms are operative in some of the subtypes of obesity and in noninsulin-dependent diabetes.

**Mechanisms in the Overweight Contributing to Hypertension**

**Renin-Angiotensin-Aldosterone System**

Contributing factors to hypertension in obesity are shown in figure 1. Plasma renin activity (PRA) has been variously reported to be unchanged in obesity or reduced in inverse proportion to weight. All three laboratories have found the aldosterone concentration in plasma the same in obese hypertensives. Tuck et al. and Hiramatsu et al. have found that both PRA and aldosterone are reduced during acute weight loss, although aldosterone diminishes to a lesser degree and correlates poorly with change in blood pressure. There is disagreement with respect to blood volume. Messerli et al. relating this to height and to weight, reported an increase, and Mujais et al., relating blood volume to surface area, found reduced volumes. Perhaps the discrepancies would be resolved if the values were related to fat-free or lean body mass. Unless this is done, a physically inactive stockbroker will apparently have a reduced blood volume in comparison with a football guard of similar weight, height, and surface area, whereas the volume might be appropriate for his lean body or fat-free mass. It is possible that the reduced blood volume in relation to weight reported in patients with essential hypertension may be explained by an increase in fat mass and decrease in lean body mass, even though the total weight is within normal range. Berglund et al. found that hypertensives of comparable weight have increased fat mass and reduced body cell mass, which again suggests that fat-free mass would be a more appropriate reference. Persons with normal weight by conventional standards may still resemble the obese physiologically and functionally.

**Adrenocortical Steroids**

The central distribution of body fat acquired in adult years, the diminished glucose tolerance, and the hypertension might well suggest a disturbance of adrenal corticoids, yet it is certainly unusual for a patient with these common manifestations to meet the criteria of Cushing’s syndrome. On the other hand, Esanou et al. have described “Cushingoid” patients who fall into a gray zone between normality and true Cushing’s syndrome. In experimental and in spontaneous obesity, the free plasma cortisol and urinary cortisol are within normal range even though the secretory rate is increased. However, insufficient work has been done to rule out possible derangements of pituitary-adrenal function in the hypertensive obese, particularly in those with cushingoid features. In the animal world, Angelin and Kulmar have found that the Koletsky strain of obese hypertensive rats has an increased 18- and 11-β-hydroxylation both of deoxycorticosterone and of corticosterone, the precursor of aldosterone. Rapp and Dahl found the same in rats bred for increased response of arterial pressure to dietary sodium. No similar defect has been reported in humans to date.
Carbohydrate Metabolism, Insulin Resistance, and Hyperinsulinemia

There has been much interest lately in the possibility that in hyperinsulinemic, overweight hypertensive patients, insulin itself may be contributing to the sodium retention and hypertension. There is much evidence that insulin affects transport of sodium in various organs. In 1967, André and Crabbe reported that insulin enhanced sodium transport by frog skin, and later Nizet et al. reported from the same laboratory that insulin affected sodium and potassium excretion by the isolated dog kidney. That insulin can directly affect renal sodium reabsorption in humans was shown by DeFronzo et al. They maintained the concentration of glucose in the blood at a normal level while infusing variable amounts of insulin. Reabsorption of sodium was increased by insulin without change in filtration rate or in the concentration of aldosterone in the serum. This, in addition to the studies of Kolanowski of the renal action of insulin, provides one explanation for the natriuresis of fasting and the antinatriuresis of refeeding. Possible mechanisms have recently been reviewed by DeFronzo. Infusion of insulin curtails the natriuresis that follows an overnight fast. Insulin increases gluconeogenesis in slices of kidney cortex, and isolated renal cortical tubules have specific binding sites for insulin. Insulin also affects sodium flux in muscle, in the frog muscle and in humans.

It remained for Björntorp’s group at Göteborg to suggest several years ago that, since insulin can affect renal sodium reabsorption and sodium transport elsewhere in the body, the insulin resistance and hyperinsulinemia of the obese might directly contribute to hypertension in susceptible individuals. They had demonstrated that a period of physical training for overweight middle-aged persons could strikingly reduce the concentration of insulin relative to glucose even though there was no measurable change in total body fat. More recently, they have studied the effect of physical training in a group of obese women who were also hypertensive. There was a substantial decrease in blood pressure in all, and this was correlated not with change in body fat or initial blood pressure, but with the degree of reduction of the elevated serum insulin and also with reduction of serum triglycerides. It appeared that the metabolic disorder rather than the obese state per se was of importance. They further suggested that the “essential” hypertension of the typical middle-aged man with slight hypertrophic obesity might result from the same mechanism, since these patients have many of the same metabolic rearrangements as the more frankly obese.

These effects of insulin on sodium retention have so far been demonstrated in short-term experiments. The possible contribution of insulin on a long-term basis remains to be determined. As already noted, Tuck et al. found that the decrease in PRA and aldosterone concentration correlated well with the decrease in blood pressure in obese patients losing weight with a diet containing 320 kcal/day and 45 g of protein, 30 g of carbohydrate, and 2 g of essential fatty acids, plus supplements of calcium, phosphorous, magnesium, trace metals, and vitamins. Potassium intake was 40 mmoles per day. No studies to date have included measurements of serum insulin to establish whether there is a similar correlation. In our laboratory, Bogardus et al. have studied the changes in insulin resistance in 18 middle-aged obese patients with glucose intolerance or Type II noninsulin-dependent diabetes before and after a 12- to 14-week period of either dietary therapy alone or dietary therapy combined with an aerobic training program. The basic diet during the period of weight reduction had a mean caloric content of 915 with protein providing 25% of the calories, fat 15%, and carbohydrate 60%, together with 25–30 g of dietary fiber. During a weight-maintaining period of 10 days prior to testing, diets with similar distribution of macronutrients were employed. Physical training was suspended for the period prior to testing. The subjects achieved a 10% decrease in weight during this period. There were significant improvements in glucose tolerance, in total glucose disposal measured by euglycemic clamp technique, and in suppression by insulin of splanchnic glucose production. Measurements of blood pressure were made with suitable cuffs on the subjects upon awakening while supine and while standing on five consecutive mornings during the two admissions to the Clinical Research Center. Serum insulin response to a mixed meal was measured over a period of 3 hours, and the mean of the insulin values was compared. Radioimmunoassay was by the method of Starr et al. None of the patients was hypertensive, although several had a previous history of hypertension. Mean blood pressure of the group was 4 ± 7 SD. Three patients were excluded because of incomplete series of blood pressure measurement, one because of complicating disorders (adrenal hyperplasia), and one because of myocardial infarction several months after completing the study. Both groups had a small but significant decline in standing \( p < 0.05 \) but not in supine blood pressure after the period of treatment, as shown in figure 2. There were no significant differences in the response between groups. Figure 3 shows the relation of the change in standing mean blood pressure (diastolic pressure plus one-third systolic and diastolic pressure) and changes in the mean concentration of insulin during the 30 to 300 minutes following a standard low-fiber meal. Mean concentration was taken in preference to total area above baseline to avoid the difficulties of treating negative values. There was a significant correlation between the two variables \( r = 0.54, p < 0.05 \). There was no significant correlation between the small change in blood pressure in this normotensive group and change in fasting insulin, the insulin response to intravenous glucose or arginine, or the glucose disposal rate during the euglycemic clamp. The findings are thus only partly consistent with the concept that the decrease in insulin resistance is a factor in the hypertensive effect of the weight loss and increased physical activity. A study in which PRA and aldosterone, thyroid hormones, and insulin were measured simulta-
neously in plasma would be useful in clarifying the relative contribution of their changes in concentration to the fall in blood pressure.

**Thyroid Hormones and Sympathetic Nervous Activity**

Another set of mechanisms can contribute to the retention of sodium in the overweight and overfed hypertensive, and this involves an adaptive response to excess caloric intake. Under less affluent conditions, our remote ancestors may have had to eat excess quantities of what then corresponded to "junk" food to obtain enough of an essential nutrient such as protein or salt. An ability to dispose of some of the unneeded energy and thus to minimize accumulation of excess weight would have had survival value. Conversely, in times of actual famine, it would have been advantageous to reduce the resting metabolic rate to enhance survival. We now have evidence that these adaptations do exist and involve the synergistic action of thyroid hormones and catecholamines.35

Danforth et al.36 in our laboratory and others have shown that overeating of protein, carbohydrate, or fat causes an increase in the iodination to the relatively inactive metabolite, reverse T3. The reverse changes take place when intake of food is restricted. One might expect that deprivation of food would stimulate sympathetic activity, but Landsberg and Young37 have shown, by turnover studies of norepinephrine in the heart of rats subjected to dietary manipulation, that at least in chronic deprivation the reverse is true. The increased concentration of T3 resulting from overfeeding increases the reactivity of the tissues to catecholamines. Even though the total caloric intake is not reduced, sharp reduction of the intake of carbohydrate can bring about a reduction in production of T3.36

The catecholamine response to overfeeding may contribute directly to sodium retention and the development of hypertension in susceptible persons following overfeeding.37 Both administration of catecholamines and stimulation of the renal sympathetic nerves causes reabsorption of sodium independently of any induced changes in renal hemodynamics or adrenal steroid secretion.38 Overfeeding sucrose increases norepinephrine turnover in the rat, and in the spontaneously hypertensive rat (SHR) and the normotensive Wistar rat39 blood pressure is increased. A portion of this increase may, of course, be due to increased insulin secretion. Thus, a third mechanism may contribute to the effect of caloric restriction on blood pressure.

**The Relative Importance of Intake of Sodium**

Consideration of nutrition in relation to hypertension is dominated by concern over the effect of increased intake of sodium.40 In the overweight hypertensive, however, this may not be a matter of overriding importance.

Dahl et al.41 suggested that the increased intake of salt along with high caloric intake in the obese contributes to their hypertension, but this presupposes that the obese necessarily have a high caloric intake. They were able to demonstrate reduction of blood pressure...
in a relatively small number of patients whose sodium, but not caloric intake, was restricted, but Reisen et al. in Israel reported that restriction of caloric intake lowers blood pressure even though intake of sodium is liberal. Eliahou et al. have further reported that, of 212 hypertensive patients over 10% in excess of ideal weight, 42% complied with a reducing regimen that included a balanced diet. They were advised to eat salt freely and that they did this was documented by 24-hour analyses of urine sodium. Two thirds of the compliant patients achieved normal blood pressures with a loss of only one-half of their excess body weight. Thus, an effect of intake of sodium could be overridden by the various effects of caloric restriction. This is not to deny, however, that, in certain individuals predisposed to hypertension, restriction of sodium intake may provide an important benefit. In the same way, rats that are susceptible to developing hypertension are sensitive to the effects of increased intake of sodium.

Clinical Trials Comparing Pharmacologic with Nonpharmacologic Management of Hypertension in the Overweight

There are no such trials to date. Major details of some of the prospective studies of drug treatment of hypertension have been reviewed elsewhere. The mean degree of overweight in most of the large-scale studies has been approximately 30%, but the overweight subgroup of patients or those with a family history of diabetes are not identified and considered separately. The only large-scale study in which both dietary modification and increased physical activity were emphasized is the Chicago Prevention Evaluation Program, which comprised 519 subjects, including 115 hypertensives and 110 marginally hypertensive subjects. Each participant was urged to take "modest" light exercise at least three times a week and to reduce caloric intake from 2500 to approximately 1750 kcal. There was a sustained mean weight loss of 5.3 kg, and, with this moderate loss, systolic blood pressure was reduced by 13.3 mm Hg and diastolic by 9.7 mm Hg. There was no control group, but the results of this attempt at using nonpharmacologic measures to reduce risk factors compares favorably with those of pharmacologic intervention. It also suggests that, with sufficient governmental support, a controlled clinical trial would be feasible.

Initial Management of Hypertension in the Overweight and Underactive

A sharp reduction of caloric intake, as in the various types of supplemented fasts, can achieve a rapid decrease in blood pressure in overweight patients. For a patient who is obese, or for one whose ratio of adipose tissue mass to lean body mass is high, the first step of treatment of newly discovered mild-to-moderate hypertension could well be aggressive caloric restriction under careful monitoring rather than immediate treatment with drugs. In the experience of our group, the long-term success rate of this measure alone is not high and it is best preceded by a period of controlled and mildly restricted intake during a period of reeducation and instruction in monitoring both intake of food and physical activity. We have also noted relief of severe angina by institution under close observation of a protein-supplemented fast in an obese patient. This remission was presumably brought about by the decrease in sympathetic activity from caloric restriction.

Chronic Management of Hypertension in the Overweight and Underactive

There are a number of published studies concerning weight reduction, increased physical training, and their effect on hypertension in the overweight, but none to date provides long-term follow-up. This is in contrast of the number of costly national trials throughout the world of the efficacy of various drugs. We do not know whether a formerly hypertensive patient who has successfully reduced weight and modified life style can achieve a relatively permanent control of the hypertension. It is important that trials be designed to provide the answer. Some of the interventions proposed to date are shown in figure 4.

There is a widespread and quite understandable belief that obese patients simply cannot be induced to lose weight and to maintain the loss. The study of Stunkard 23 years ago is frequently cited in support of this belief. However, there are more encouraging
recent reports. The experience of the Chicago Program is one such. So is the experience of J.K. Davidson (personal communication) in treating the insulin resistance of Type II diabetic patients. He has found that, of 433 patients for whom therapy with hypoglycemic oral agents was discontinued in 1970, 87% of those given diet therapy and 72% of those given insulin achieved a sustained loss of weight of 20.3 and 11.3 lbs respectively by the time of follow-up 9 years later. This represents a notable achievement, especially in a general clinic population. However, since 787 patients were lost to follow-up, the overall success cannot be evaluated. There is increasing interest in developing techniques of nonpharmacologic intervention for hypertension and diabetes. To say that it cannot be done successfully becomes a self-fulfilling prophecy.

Oliver has recently emphasized that there has been “insufficient concern about the development and incidence of unexpected adverse reactions to drugs given prophylactically over many years in attempts to reduce risks of cardiovascular disease in predisposed but otherwise healthy persons.” A good portion of the hypertensive population is not healthy from a metabolic point of view. The commonly used agents have undesirable side effects in the form of increased serum lipids, impaired glucose tolerance, hyperuricemia, impotence, and increased peripheral circulatory disorders.

These may be of crucial importance for the obese hypertensive with early or latent diabetes or other metabolic disorders. We have no means of knowing or of evaluating possible long-term effects in a population that may be taking drugs for a matter of decades. In contrast, the nonpharmacologic measures have the added advantage of reducing insulin sensitivity, improving glucose tolerance, reducing hypertriglyceridemia, and, perhaps most important, restoring a sense of well-being.

The formal consensus of those attending the 1980 Florence meeting on obesity and hypertension was that the conventional “stepped care” program of management of mild-to-moderate essential hypertension should be revised to the following form:

**Step 1.** Characterization of the subtype of obesity and of possible metabolic disorders.

**Step 2.** Provision of caloric intake below maintenance requirements with diets high in fiber and complex carbohydrates and moderately restricted in salt, together with:

**Step 3.** Increased physical activity leading to an improved state of training, reduction of hyperinsulinemia, insulin resistance, and sympathetic activity.

**Step 4.** Maximal behavioral support.

Only after the four steps above have been given fair trial should one consider:

**Step 5.** Conventional “stepped care” pharmacologic treatment.

It was also the consensus of those attending the 1980 Florence meeting that priorities for research in hypertension in the overweight and physically inactive should include the following:

1. To further develop methods of characterization of overweight and hypertensive patients, including metabolic parameters and estimation of body composition.
2. To continue to evaluate methods of acute and chronic weight reduction and their effect upon hypertension.
3. To evaluate further the value of increased physical activity as an adjunct to the treatment of hypertension.
4. To develop more satisfactory methods of sustaining change in weight and increased physical activity.
5. To carry out long-term controlled studies of the efficacy of nonpharmacologic vs pharmacologic measures in the treatment of mild and moderate hypertension.
HYPERTENSION IN THE OVERWEIGHT/Sims


Mechanisms of hypertension in the overweight.
E A Sims

Hypertension. 1982;4:III43
doi: 10.1161/01.HYP.4.5_Pt_2.III43

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/4/5_Pt_2/III43.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/