The role of immunocompetent cell renal infiltration in the pathogenesis of arterial hypertension

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«… the small red kidney (interstitial nephritis), the salient clinical feature of which is arterial hypertension…»
C. Jiménez Díaz, A. del Cañizo. In: Manual de Medicina Interna. L. Hernando and G. Marañón, eds.
Ruiz Hermanos Editores, Madrid, 1934.

INTRODUCTION

Human evolution has been intimately related to diet. One and a half million years ago, the consumption of animal protein with a high energy content was possibly one of the reasons allowing progressive brain development among our ancestors and their separation from *Australopithecus*, which continued to consume a plant diet.[1] In the Paleolithic period 45,000-50,000 years ago, the salt content of the human diet was about 0.7 grams per day,[2,3] and increased considerably 10,000 years ago when the agricultural revolution resorted to salt for the preservation of foods. The location of the best known prehistoric caves, relatively close to the sea or to the salt mines of the time (fig. 1), offers indirect evidence of the importance of salt for the development of these human communities.

While different animal species ingest an excess of salt only in response to body salt deficiency, humans have a taste for the substance,[4,5] and throughout history have found additional applications for salt apart from mere food preservation. The Old Testament considered salt an essential part of offerings (*You shall present salt in all your offerings*. Leviticus 2:13), and medical authorities of the time recommended its use as an expectorant (Hippocrates, 400 BC), laxative (Dioscorides 100 AD), anti-infectious agent (Galen, 120-129 AD) and diuretic (Paracelsus 1493-1541 AD). The word salt has served to define health (*salus, salubritas*), retribution for work done (*salarium*), wisdom («*… a good man, but scant of salt in the head*» Don Quixote, Miguel de Cervantes), and discrimination or doubt (taking an affirmation *cum grano salis*). Salt has been attributed with amatory powers (*Venus saligena*) and sexual vigor («*les femme sallent leurs maris pour du doux le rendre gueris*», a poem from 1157 in the National Library in Paris). It has been responsible for rebellions (Mahatma Gandhi against salt taxes in India), and has given names to cities (Saltzburg, Hallein). At present, 200 million tons of salt are produced each year throughout the world; of this amount, 1/3 is obtained from salt pans or mines, while the remaining 2/3 are obtained from surface or underground rock salt deposits. The modern human diet contains 10 grams of salt a day on average.

The relationship between blood pressure and dietary salt content has been examined and confirmed by many studies, which in turn have been the subject of a recent and extensive review.[6] Globally, these studies indicate that mean blood pressure is higher, and the increase in blood pressure between 20 and 69 years of age is more significant in populations with a high dietary presence of salt[6,7]. In contrast, Oliver reported that in Aboriginal communities that still consume no salt or only very little salt in their diets, blood pressure does not increase with age, and a common feature is the absence of arterial hypertension in such individuals[8] (fig. 2).

The benefits of moderate dietary salt restriction in relation to the prevention or improvement of arterial hypertension is universally accepted, with some exceptions.[9] The existing evidence has been examined by He et al.[10] who concluded that a reduction in dietary salt from 10 to 5 grams a day for four weeks results in a 5 mmHg reduction in systolic pressure and a 2.7 mmHg reduction in diastolic pressure in hypertensive individuals. In addition, this reduction in salt intake applied to the general population would result in a significant decrease in the incidence of heart attacks and stroke.[10]

Dietary salt increments and reductions give rise to corresponding changes in blood pressure among both hypertensive and normotensive individuals.[11,12] In this context, the term «salt sensitivity» refers to a subgroup of individuals in which changes in dietary salt content are associated with exaggerated changes in blood pressure that possibly pose an added risk of cardiovascular complications.[13-17]

The pathogenesis of salt-sensitive or salt-dependent arterial hypertension is fundamented upon a tendency towards sodium retention by the kidneys.[7] Guyton et al.[17,18] suggested that the rise in arterial pressure constitutes a compensatory

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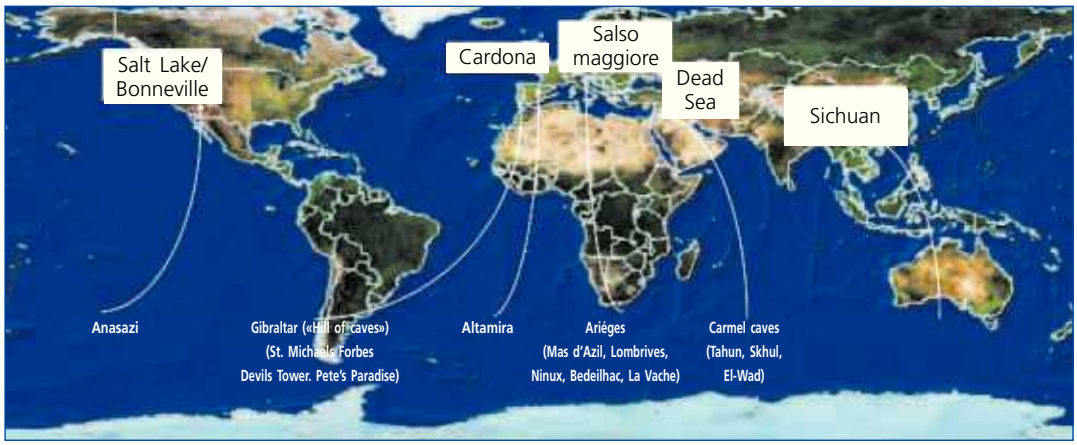

Figure 1. Caves with evidence of prehistoric human communities and salt mines exploited in ancient times. The relative proximity of the caves to the sea or to salt mines suggests an association to human development.

response to deficient sodium elimination by the kidneys. In this sense, hypertension would be a hemodynamic response destined to increase salt excretion through pressure-mediated natriuresis. The renal disorder limiting sodium excretion is responsible for shifting of the pressure-natriuresis curve to the right, in order to restore the point of sodium balance (fig. 3). Arterial hypertension thus would allow the maintenance of sodium balance.

Genetic defects (genetic variants and mutations of channels and transporters), systemic disorders (excessive sympathetic tone, insufficient suppression of the renin-angiotensin system, reduction of atrial natriuretic peptide activity and/or of melanocyte stimulating hormone, hyperuricemia, metabolic syndrome), and specific (endothelin receptor dysfunction, reduction of dopamine activity) and nonspecific renal defects (reduction of the number of nephrons, lowered kallikrein-quinine system activity, reduction of 20-HETE and of epoxygenase levels, increased intrarenal angiotensin II (AII) activity, oxidative stress, intrarenal inflammation) have all been implicated in the pathogenesis of salt-sensitive hypertension, and have been the subject of a recent review.[7] The present article is limited to examination of the evidence that immunocompetent cell infiltration of the renal interstitial compartment is a common feature of experimental arterial hypertension of any etiology, and that the induction of local oxidative stress with increased AII activity in the kidney represent a common end-pathway responsible for alterations in the physiological mechanisms of sodium excretion. In this context, tubulointerstitial inflammation constitutes a key element in the shift of the pressure-natriuresis curve to the right, and hence in the etiology of arterial hypertension.

THE RENAL TUBULAR INTERSTICE IN EXPERIMENTAL ARTERIAL HYPERTENSION

Models of salt-sensitive hypertension are characterized by a number of conditions that promote a tendency towards sodium retention and the hindering of pressure natriuresis (table I). It is important to stress that the conditions specified in table I are inter-related and stimulate each other – thereby reinforcing their tendency to induce defective functioning of the physiological mechanisms of natriuresis.

Lymphocyte and macrophage infiltration in the tubulointerstitial regions of the kidney has been demonstrated in all

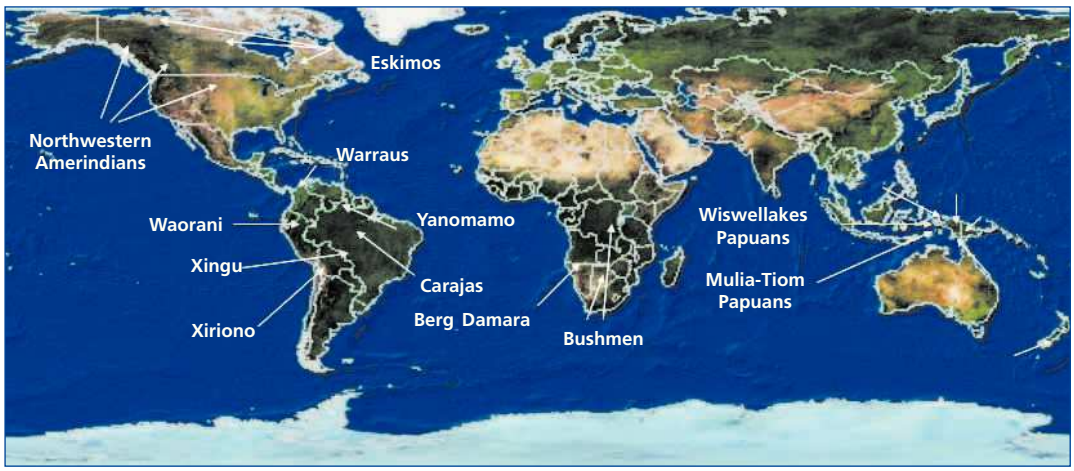

Figure 2. Aboriginal tribes that consume little or no salt according to studies of diet composition or urinary sodium excretion, or both. Figure reproduced from Oliver WJ. *Primitive people without salt: a perspective from industrialized societies.* Ann Arbor MI, Quality Books Inc. 1925, page 181.

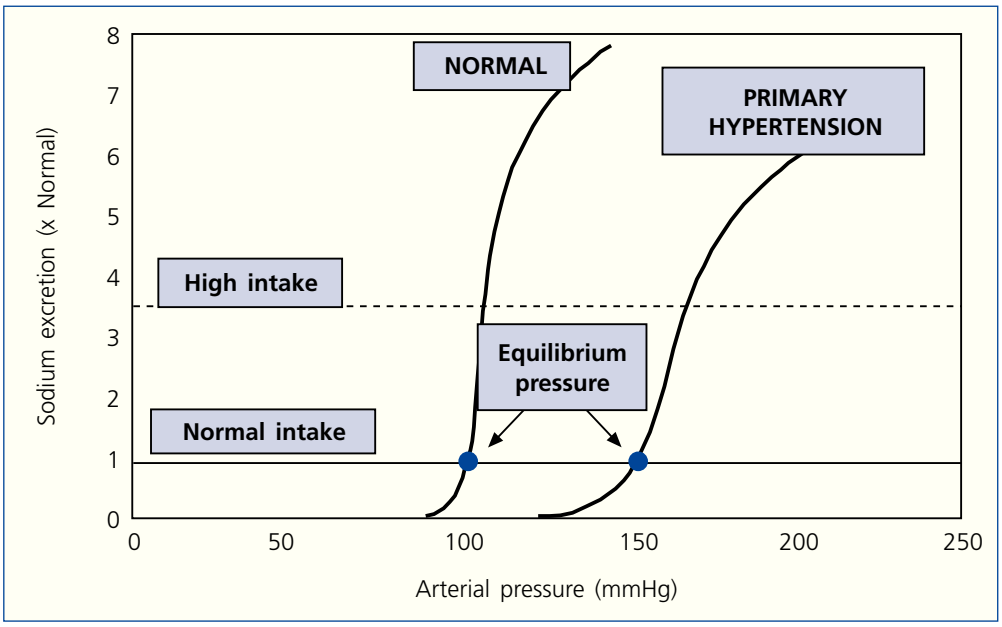

Figure 3. The pressure-natriuresis curve shifts to the right in the hypertensive patient, to compensate sodium excretion defects and restore the point of sodium balance[17,18].

the experimental hypertension models. Far from constituting an epiphenomenon, the functional importance of such infiltration has been demonstrated by the fact that a number of experimental treatments designed to reduce inflammatory infiltration are able to correct or improve arterial hypertension. Our group has carried out studies administering mycophenolate mofetil (MMF) during the period of salt-sensitive hypertension induction, prior to the administration of a high-sodium diet,[19-21] and has also used MMF or nuclear transcription factor kappa B (NFκB) in spontaneously hypertensive rats[22,23] or rats made hypertensive through chronic intoxication with low doses of lead,[24] or be enveloping the kidney in cellophane (Page hypertension model).[25] Other research groups have carried out studies with different immunosuppressive strategies that will be mentioned further below.

The loss of peritubular capillary integrity (table I) and its potential impact upon natriuresis and the development of hypertension was initially postulated by Johnson and Schreiner,[26] and posteriorly associated to inflammation and tubulointerstitial damage in the pathogenesis of salt-dependent hypertension.[27-29] Interstitial inflammation clearly reduces the useful area of the peritubular capillaries, thereby leading to pressure natriuresis malfunction.

The increase in activity of the renin-angiotensin system (RAS) is not necessarily related, and sometimes may even be opposed to the plasma levels of AII. It is important to stress that all components of the RAS, including angiotensin-converting enzyme (ACE), may be evaluated through determination of the interstitial concentration of AII.[30,31] In contrast to plasma AII, the interstitial concentrations of angiotensin I and II are not suppressed by extracellular volume expansion – thus demonstrating that the intrarenal RAS does not respond to the physiological modulation of systemic RAS activity.[32] Salt-dependent hypertension, associated to extracellular volume expansion, is a «low renin» form of hypertension,[33] and is characterized by suppressed plasma AII levels, while intrarenal AII is increased.[34] This contrasting physiopathology has been evidenced by the simultaneous determination of plasma and renal interstitial fluid levels of AII. As can be seen in figure 4, in the model of salt-sensitive hypertension induced by a short infusion of AII in rats treated and not treated with MMF, and in rats administered high and normal sodium diets, an inverse correlation is observed between the concentration of circulating AII and renal AII.[34] In contrast to this negative correlation, a positive correlation is seen between the intensity of renal inflammatory infiltration, renal AII (expressed as concentration or as cells expressing AII within the interstitial compartment), and the severity of hypertension in the models of salt-sensitive hypertension.[19-22,34]

There is abundant experimental evidence of the association of *oxidative stress* to arterial hypertension, with a reduction of the latter in response to lowered oxidative stress. Such evidence has been the subjects of a number of

Table I. Conditions found in the renal tubular interstice in the models of arterial hypertension

- Inflammatory infiltrate composed of lymphocytes and macrophages.
- Loss of peritubular capillary integrity.
- Increase in local angiotensin II activity.
- Oxidative stress.
- Vasoconstriction and remodeling of the afferent arteriole.
- Reduction of the number of functioning nephrons (in the presence of advanced renal damage).

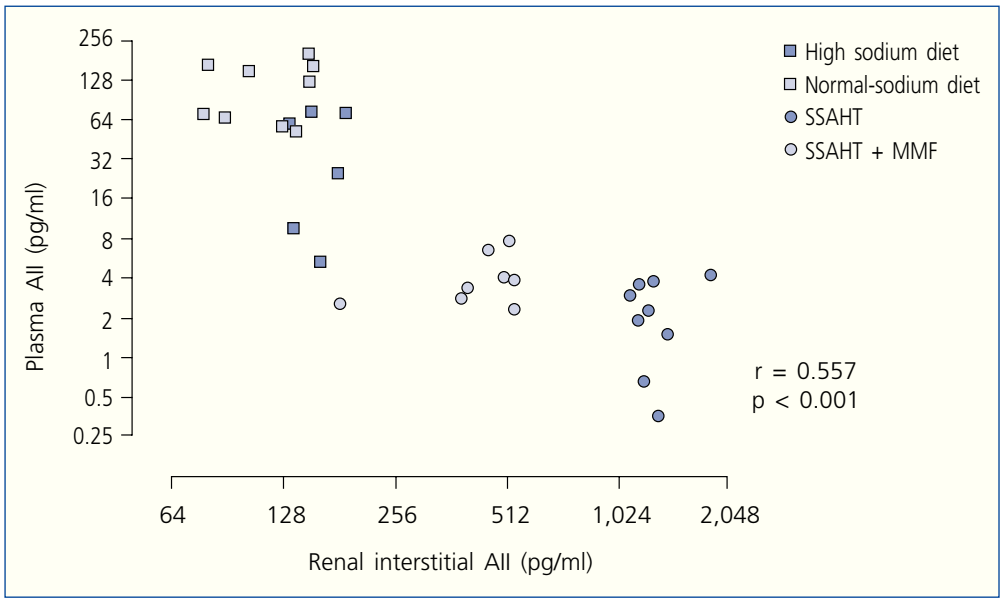

Figure 4. Hypertension induced by high-sodium diets (salt-sensitive arterial hypertension, SSAHT) is characterized by extracellular volume expansion and the suppression of circulating angiotensin II (AII)(low-renin hypertension), though intrarenal AII may be increased in association to intrarenal inflammation. The figure shows the inverse correlation between plasma AII concentration and AII within the renal interstice in rats with SSAHT induced by a short subcutaneous infusion of angiotensin II, treated and not treated with mycophenolate mofetil (MMF), and in normal rats administered a normal- or high-sodium diet. The study from which the data are obtained has been published recently (data taken from reference 34).

recent reviews.[35-38] Our laboratories have examined the antihypertensive and antiinflammatory effects of diets containing abundant antioxidants,[39] and of the administration of pharmacological doses of the endogenous antioxidant melatonin.[40] In these studies it has been seen that a reduction of oxidative stress in turn lessens intrarenal inflammation. However, antioxidant treatment of hypertensive patients has failed to improve arterial hypertension.[41-44] A number of explanations have been suggested for the therapeutic failure of antioxidants in the different clinical series.[38] As an example, antioxidant treatments are varied, and some of them may be unable to reach the intracellular compartment where oxidative stress originates. In this context, water- and lipid-soluble vitamins would have only limited effects in the respective compartments. On the other hand, the rate of reactive oxygen species reactivity may exceed the capacity of the antioxidant treatment to prevent such reactions. This characteristic, which is essential for the antimicrobial actions of white blood cells, constitutes a barrier against the therapeutic use of antioxidants. An added problem is represented by definition of the adequate dose of a given antioxidant treatment, since the clinical doses and administration routes of antioxidants have not been established. A very low dose is ineffective, while too high a dose may exert the opposite effect – intensifying oxidative stress, because the subproducts of antioxidant metabolism are reactive in themselves and must be inactivated by the endogenous biological systems, which may prove insufficient if an antioxidant overdose generates too many reactive metabolites.[38]

The close relationship between oxidative stress, intrarenal AII and intrarenal inflammation has been examined in recent reviews.[35-37] These conditions form a vicious circle in which each component can be stimulated by the rest, ensuring their persistence within the kidney, and thus giving rise to the cause and effect of the tendency towards sodium retention and arterial hypertension. Figure 5 shows this inter-relationship using as example the cellophane kidney-wrapping model of hypertension (Page model). In this model, the administration of MMF improves inflammation in the kidney and the hypertension, and a direct relationship is observed among macrophage infiltration, oxidative stress and intrarenal (non-plasmatic) AII activity.

In the context of an experimental model it is probably not possible to establish the triggering factor behind sodium retention physiopathology. However, it is reasonable to assume that the initial triggering factor may vary according to the experimental model used. As an example, in hypertension associated with congenital mitochondrial superoxide dismutase (SOD) deficiency[45] and in chronic lead poisoning[46], oxidative stress is probably the primary factor, while in spontaneously hypertensive rats immunocompetent cell infiltration of the kidney precedes arterial hypertension.[47]

Vasoconstriction and remodeling of the afferent renal arteriole (table I) reduces glomerular filtration, and thus serves to promote hypertension. Tubulointerstitial inflammation is one of the factors potentially responsible for the alterations in glomerular hemodynamics, since micropuncture studies have shown that the reduction of isolated nephron filtration and increased afferent arteriole resistance are corrected by the administration of MMF.[48] In fact, Ruiz-Ortega et al. have suggested that part of the pro-hypertensive effect of AII is related to its action as a proinflammatory cytokine.[49] An additional effect of inflammation and arteriolar remodeling is the induction of increased rigidity of the glomerular afferent arteriole; despite the fact that the arteriolar lumen is reduced under such conditions, the loss of elasticity prevents the normal auto-regulatory responses and exposes the glomerule to the hemodynamic impact of

Table II. Effects of high-sodium diet on inflammation, oxidative stress and renin-angiotensin system (RAS) activity

Proinflammatory effects of the high-sodium diet
- Activation of NFkB and up-regulation of TNF-alpha, indicating its proinflammatory potential.[55]

Pro-oxidant effects of the high-sodium diet
- Increased superoxide generation at renal medullary and cortical level, mediated by NAD(P) oxidase.[58,59]
- Reduction in l-arginine reuptake capacity (reduction of cationic amino acid transporter).[61]
- Generalized supression of the nitric oxide synthetase isotypes.[62]

Increased renal renin-angiotensin system activity
- Up-regulation of expression of the genes encoding for the AT1 receptor of angiotensin, with the corresponding changes in renal arteriolar reactivity to AII.[57]
- Increases in renal interstitial AII in models of salt-sensitive hypertension.[34]

Table III. Experimental models and clinical conditions showing improvement or prevention of hypertension with a reduction of renal inflammatory infiltrate*

	References
Hypertensive rat strains	
SHR	22,23,39,40,66,67
Transgenic rats dTGF	74
Salt-sensitive Dahl rats	75, 76
Lyon hypertensive rats	77
New Zealand black rat (NZB)	78
Programmed hypertension in the prenatal period	79
Models of acquired hypertension	
Hypertension secondary to renal infarction	80
Cellophane-wrapped kidney (Page model)	25
Chronic poisoning with low doses of lead	46
Prevention of salt-dependant hypertension	
DOCA model	69, 81
Subcutaneous infusion of AII	19, 82
Inhibition of nitric oxide synthetase	20
Overload proteinuria	21
Grade I hypertension in humans	83

*Data modified from reference 7 and updated.

systemic hypertension – thereby facilitating glomerular sclerosis and degeneration.[50]

INFLAMMATION, RENIN-ANGIOTENSIN SYSTEM, OXIDATIVE STRESS AND THE TENDENCY TOWARDS SODIUM RETENTION: EFFECTS OF HIGH SALT INTAKE

Figure 6 provides a schematic representation of the inter-relationship among these three conditions, and shows how a high-salt diet stimulates each of them. The triad composed of renal tubulointerstitial inflammation, oxidative stress and increased intrarenal RAS activity leads to a reduction in glomerular filtration, and thus to a drop in sodium elimination. More distal within the nephron, RAS hyperactivity stimulates the tubular reabsorption of sodium, and pressure natriuresis becomes less effective, since the alteration of tubulointerstitial structure reduces the available area of peritubular capillaries, and because the presence of an inflammatory edema increases compliance of the interstitial space.[51] On the other hand, recent observations published by Guzik et al. have shown T lymphocytes to be implicated in the vascular dysfunction seen in hypertension induced by AII.[52] The tendency towards sodium retention is counteracted by the increase in arterial perfusion pressure, which in turn increases pressure natriuresis. However, arterial hypertension directly stimulates oxidative stress,[53] which in turn tends to perpetuate the physiopathological process.

A high-salt diet stimulates each of the pro-hypertensive triad components operating upon the kidney, thereby conditioning defective functioning of the mechanisms in charge of physiological natriuresis. Table III specifies the proinflammatory, pro-oxidant and intrarenal RAS stimulant effects of salt intake. These effects include up-regulation of the genes implicated in the synthesis of TGF-beta and its feedback circuit, which has repercussions upon kidney damage as a target organ.[54] High-salt diets induce the activation of NFkB and the up-regulation of TNF-alpha[55] – with the capacity to induce microangiopathy when associated to genetic susceptibility.[56] Regarding the RAS, the chronic changes associated with salt intake induce parallel changes in the expression of the genes encoding for the AT1 receptors of angiotensin, with corresponding changes in the reactivity of the renal arterioles to AII.[57] As has been commented, a high-salt diet induces increases in renal interstitial AII in models of salt-sensitive arterial hypertension.[34]

Regarding the direct influence of a high salt intake upon oxidative stress, superoxide production in the renal medulla and cortex increases in hypertensive Dahl rats administered a high-salt diet. This effect is suppressed by the superoxide dismutase-mimetic agent, tempol.[58] NAD(P)H oxidase is the most important originating factor underlying this increase in superoxide produced by a high-sodium diet [59], and is associated with an expanded expression of gp91 (phox) and p47 (phox), and with a reduction of manganese (Mn)-superoxide dismutase.[60] These effects add to the fact that a high-salt diet reduces the amino acid cationic transporter —resulting in a lessened l-arginine uptake capacity—[61] and that such a diet moreover induces generalized suppression of the nitric oxide synthetase isotypes, with consequent reinforcement of the effects of oxidative stress upon nitric oxide and arterial hypertension.[62]

From the above comments it is clear that a high-salt diet exerts direct effects upon the pro-hypertensive triad components, which in the kidney condition diminished sodium excretion capacity.

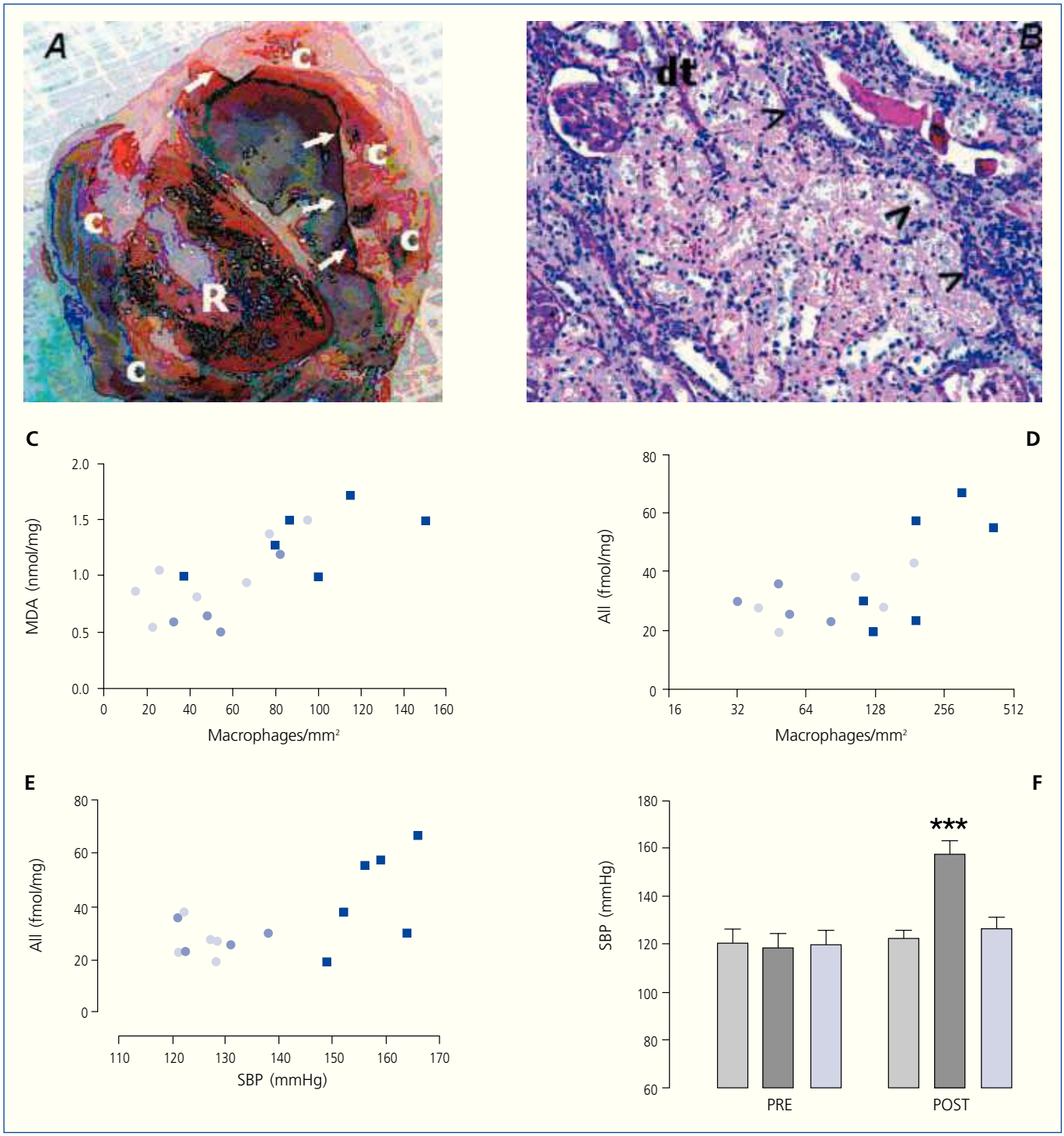

Figure 5. Hypertension induced by wrapping the kidney in cellophane («Page kidney»). Panel A: The macroscopic preparation through the kidney *(R)* shows the presence of a fibrous capsule *(C)* surrounding the cellophane (arrows) after 5-7 weeks. Panel B: Light microscopy showing a focal inflammatory infiltrate of variable intensity (arrowheads), with areas of tubular dilatation (dt). The results of treatment in this experimental model using mycophenolate mofetil (MMF) (black circles in panels C-E and striped columns in panel F) are compared with the results obtained in animals administered placebo (black squares in panels C-E and black columns in panel F) and in the controls (sham-operated animals: clear circles in panels C-E and empty columns in panel F). The direct relationship between the macrophage infiltrations and renal malondialdehyde (MDA, as an indicator of oxidative stress) and the renal interstitial concentration of AII is shown in panels C and D, respectively. Panel E: Direct relationship between interstitial AII concentration and systolic blood pressure (SBP). Panel F: Baseline SBP (PRE) is similar in the experimental groups, while at the end of the study the rats belonging to the Page kidney model treated with MMF present SBP values similar to those of the control rats, and significantly lower than those of the untreated Page model rats.

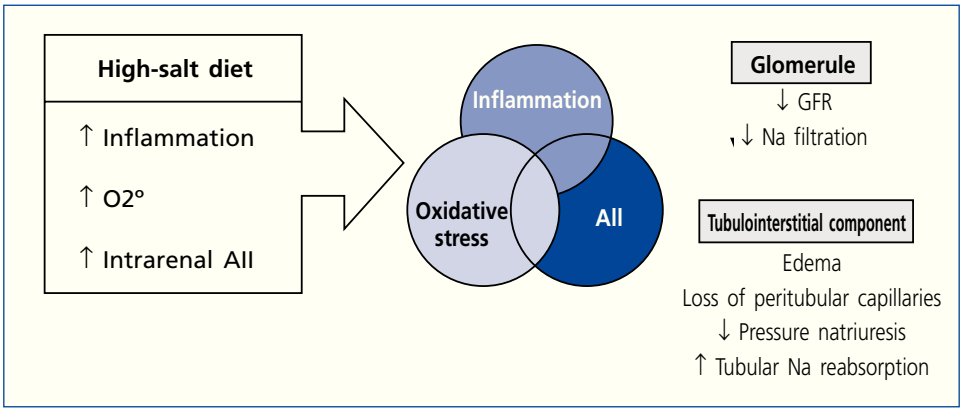

Figure 6. Intrarenal inflammation, oxidative stress and intrarenal angiotensin II (AII) constitute three critical influencing factors that mutually stimulate each other and maintain the tendency towards sodium retention in hypertension. The high-salt diet stimulates all of these conditions (see text).

IMMUNE MECHANISMS IN THE RENAL INTERSTITIAL INFLAMMATION OF ARTERIAL HYPERTENSION

Three decades ago, Svendsen[63] found that the salt-dependent phase of hypertension induced by deoxycorticosterone (DOCA) was not seen in athymic mice (nude mice), and that thymus gland grafts restored salt-dependent hypertension. Posteriorly, in the 1980s and early 1990s, a series of experiments suggested the existence of immune dysfunction in spontaneously hypertensive rat (SHR) strains. Some experiments pointed towards an immune deficiency, with the observation of improvement in arterial pressure with IL-2 injections Il-2,[64] the demonstration of poor blastogenic and cellular immune responses,[65] and the observation that anti-thymocyte serum treatment induced a transient reduction in blood pressure in SHRs.[66] These findings were interpreted as being due to an adaptive response tending to minimize the potentially fatal effects of severe hypertension.[66] Other investigators reported that immune suppression with cyclophosphamide and anti-thymocyte serum improves arterial pressure in SHRs,[67,68] and that immune suppression improves hypertension in the black New Zealand rat[69] and avoids the development of hypertension induced by kidney infarction.[70] However, these observations were sporadic, and in 1990 an editorial pointed out that immune dysfunction was only rarely cited in discussions of arterial hypertension.[71]

Table III summarizes the studies of a number of laboratories, including our own, in which the introduction of immunosuppressive measures reduced renal interstitial inflammation and improved or prevented arterial hypertension. Special mention should be made of a study made in 8 hypertensive patients administered MMF as part of their treatment due to the presence of rheumatoid arthritis or psoriasis. During administration of this drug, the patients experienced improvement of their grade I arterial hypertension, and in the urinary inflammation markers.[83]

Based on the existing evidence, we have postulated that the long-term maintenance of an inflammatory infiltrate in the hypertensive kidney could be the result of low-intensity autoimmune reactivity, and have suggested the possibility that stress or heat-shock proteins (HSPs) could be responsible for causing or conditioning the development and maintenance of autoimmune reactivity in the hypertensive kidney.[38,72,73] HSPs are highly preserved chaperone molecules that participate in the immune response to infectious microorganisms, and which under certain circumstances may participate in autoimmune processes such as those found in arthritis, multiple sclerosis, diabetes and arteriosclerosis.[84,85] The data supporting this hypothesis are still only circumstantial, however. Increased HSP expression is observed in models of salt-sensitive hypertension.[86,87] Preliminary results indicate the presence of circulating antibodies targeted to HSP70 in both experimental[88] and human hypertension.[89] In this same line, T cells (splenocytes) in experimental models of salt-sensitive hypertension exhibit a proliferative response indicative of cellular hypersensitivity, upon being treated with HSP70.[90]

In addition, conclusive evidence has been gained that renal infiltration on the part of immunocompetent cells is a common factor in experimental arterial hypertension, and is of pathogenic relevance in salt-dependent hypertension. The results of many studies offer a reasonable explanation for observations such as that contained in the epigraph to this review,[91] which since the beginning of the last century have related hypertension to renal inflammation. The studies currently underway point to the possible participation of autoimmunity in the development and maintenance of low-intensity reactivity in the kidneys of hypertensive patients. Confirmation of this hypothesis would pave the way towards new treatment options for a disease that causes 7.1 million deaths and the loss of 64 million disease adjusted life years (DALYs) in the world today.[92]

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