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## **Changes in the Vascular Wall and Sodium Chloride**

**By C. D. de Langen, Utrecht**

Much has been said, and even more has been written, in the last few years about the influence of nutrition on the development of changes in the arterial wall. The atheromatous vascular affections came in for special interest, chiefly because they are pathologically most important. Many interesting publications have appeared in the last few years, especially in the United States. However, it should be remembered that much of what is offered at present as new, has already been reported in 1934 at the International Congress on geographical pathology in Utrecht, which was devoted entirely to the important problem of arterio- and atherosclerosis. On that occasion, a picture was given of the distribution of these vascular affections throughout the world, in man as well as in animals.

Widely differing vascular changes observed in animal experiments can be effected in various ways. Rabbits, rats, and young chicks were the test animals of choice. One of the first facts to be established more than 50 years ago was that in rabbits a diet rich in cholesterol caused typical atheromatous vascular changes within a brief period of time. This finding was corroborated in many researches which eventually led to the assumption that certain protein-lipoid fractions possess to a high degree the property to penetrate into the vascular wall and to precipitate therein. Other lipoid fractions of animal and human sera were stated not to act in this way, or only to a minor degree.

Thus, an increasing amount of experimental work came to support the conception that the diet is of great importance in the development of various, pathologically important, vascular changes.

It was also found that an important increase of fats and lipoids in the serum of test animals could be effected not only by a certain diet, but also by other means, after application of which a more frequent occurrence of the vascular changes was observed. However, all this did not hold true as regards the sclerotic vascular changes without precipitation of lipoids or the true calcification of the vessels. It could not be proved -

either in animal experiments or clinically — that a certain diet plays a special part in the development of the latter changes. The only nutrient known to stimulate calcification of the blood vessels is vitamin D.

The various experimental data agree essentially with those of geographical pathology. Atheroma of the vessels is indeed rare in countries where the diet is poor in fats and lipoids, and the frequency of this affection is highest in countries with a high standard of living, with a large consumption of fats and lipoids. The other arteriosclerotic vascular changes have an altogether different geographical distribution; therefore they must be due to other causes.

A study of the occurrence of the various vascular changes in the animal kingdom is most enlightening in this respect. On one hand, it confirms the great importance of the diet and, on the other, it shows that other factors are also involved.

There is a remarkable, many-years-old, experiment to which too little attention has been paid in the present tendency to give pride of place to the diet as the principal cause of atheromatosis. This experiment was not even mentioned in the latest symposia on the atherosclerosis problem.

If, during a certain period of time, adrenalin is injected into rabbits, very particular vascular changes develop, chiefly in the tunica media. The latter atrophies and often calcifies and, in addition, many lipoid granules precipitate in it. Moreover, typical accumulations of lipoid, identical to those found in true atheromatosis, are found along the margin of these patches caused by adrenalin. When the test animals are, at the same time, fed on a diet rich in fats and lipoids, combination pictures develop.

The point of attack of adrenalin probably lies in its influence on the capillaries, *i.e.*, on the *vasa vasorum* of the adventitia. Changes in pressure in the *vasa vasorum* have a marked influence on the pressure gradient within the vascular wall, from which the media suffers most.

As regards the significance of sodium chloride in the development of the various vascular changes, the following was shown experimentally.

Relatively large quantities of cholesterol and fat are needed to cause atheromatous changes in the experimental animal, especially the rabbit, much larger than it ever ingests spontaneously. However, when an extra quantity of NaCl is added to the food, much smaller quantities of cholesterol and fat are required than when NaCl is omitted. Moreover, the vascular changes develop much more rapidly when extra NaCl is administered; a salt-free diet, on the other hand, even when rich in fat and lipoids, has the opposite result, *i.e.*, few typical vascular changes develop

after a much longer period of time than when a normal or large quantity of NaCl is mixed with the food.

*Heintz und Pollmann* stated that, like DOCA, a diet rich in NaCl is sufficient in itself to stimulate the development of arteritis after non-specific stimuli. They mentioned many experimental proofs that non-suppurative, inflammatory reactions in the arterial wall are enhanced by abundant—sometimes also by normal—ingestion of NaCl. However, the mode of the sodium action—for it is probably the sodium ion which counts—is unknown. In their experiments the concentrations of Na, Ka and Ca in the serum of all test animals remained normal.

Furthermore, typical vascular changes occur regularly in test animals under the influence of factors which heighten the blood pressure. It is well known in human pathology that an increase of pressure within the vessels favours the development of changes in the vascular wall. DOCA alone fails to cause an increase of blood pressure or typical vascular changes; in test animals, however, administration of a large quantity of NaCl simultaneously with DOCA, causes these changes to develop, the development being earlier and more extensive as the quantity of NaCl in the diet is increased.

Substances like renine and angiotonine are also able to induce vascular changes, but only when the diet of the test animal contains a fair amount of sodium chloride.

All tests showed that the intensity of the changes in the vascular wall and the increase of blood pressure are not directly correlated, but that such a relationship exists between the extension of the vascular changes, the rate at which they develop, and the quantity of NaCl in the diet.

Sodium chloride appears to influence the peripheral vascular system and the *milieu intérieur* in such a way that conditions leading to hypertension and vascular changes develop more easily; in a way, however, that the latter does not depend primarily on the former, but that they develop simultaneously and partly independently from each other. The greater or lesser sensitivity of test animals to hypertension and vascular changes under the influence of a surplus of NaCl appears to be related to their functional capacity to remove the surplus of electrolytes from their organism as rapidly as possible. Chicks are unable to get rid of NaCl quickly and react very rapidly; even a diet containing only 1% NaCl gives a prompt result. The rat, on the contrary, does not—or only weakly—react to this concentration; vascular changes develop, however, as soon as a hypertonic NaCl solution is administered. So far, the dog has been found to be able to assimilate particularly large quantities of NaCl without untoward effect on the vascular walls.

One is inclined to assume that hypertension and changes in the vascular walls developing under the influence of sodium chloride are based essentially on the same principle as those caused by the retention of NaCl which may develop under the influence of DOCA.

Hypertension and changes in the vascular wall may develop after ingestion of large amounts of NaCl, alone or in combination with DOCA. The following observations in albino rats proved that different factors for the development of atheroma are brought into action by NaCl.

Two groups of animals were fed on a mixed diet, one group receiving an extra supply of NaCl, whereas the control group did not get additional salt. Atheromatous vascular changes developed much more frequently and much more rapidly in the NaCl group than in the controls. However, another symptom was observed in this experiment. In animals fed on a diet rich in NaCl, the serum became markedly richer in fats and lipoids than in the controls. This is an indirect indication of the importance of the fat and lipoid factor.

The finding of the varying sensitivity of different animals to NaCl is also of importance in human pathology. I think we may assume that this sensitivity is connected with the functional capacity to eliminate the surplus NaCl from the body as quickly as possible.

The questions which occupied me were: At what rate is the human body able to get rid of surplus NaCl? Do individual differences exist in this respect, and which are the factors governing the rate of excretion? Are there certain factors which retard the elimination and others which stimulate it?

I was unable to find detailed studies on this subject in the literature. Our personal observations are too few to warrant definite conclusions. However, they justify a few preliminary conclusions, and from these I would deduce a few possibilities.

There are in fact very marked individual differences:

1. Some people are capable of eliminating large quantities of NaCl very rapidly, whereas others need a much longer time to effect the same.

2. The elimination process is influenced by the composition of the diet. When large quantities of protein are ingested simultaneously with NaCl, the excretion time is lengthened.

3. The quantity of fluid ingested simultaneously with NaCl is another factor. There is no complete parallelism in this respect; fluid and NaCl excretion are not coupled together.

4. Various hormones, especially those of the hypophysis and adrenals, exert an influence.

5. Psychical factors effect changes.
6. The excretion process is distinctly lengthened in some patients with essential hypertension.
7. Therefore, restriction of NaCl in hypertensive patients serves a double purpose; apart from its importance as regards the blood pressure, it may prevent—or at least retard—the development of changes in the vascular wall which are very liable to occur in these patients.
8. Determination of the specific weight of the urine alone does not suffice, though it provides an important insight into the functional capacity of the kidneys. It is also necessary to know the period of time required by the body to free itself of too large amounts of NaCl.
9. The elaboration of a simple method of examination to establish the excretion time is highly desirable.
10. The most valuable data will probably be obtained by checking the time required to remove the ingested Cl ions from the body, and controlling concentration of urine after extra NaCl and pitressine.

The influence of sodium chloride on blood pressure and changes in the vascular wall indicates that the internal functioning of the vascular wall merits as much attention as the composition of the blood. More attention should be paid to the *milieu intérieur* of the vascular wall, the flow of fluid therein, and the factors regulating the latter. The vascular wall is fed by two flows of fluid. One starts from the lumen of the vessels; it moves in accordance with the direction and the force of the pressure gradient within the vascular wall which, in the arteries, runs from the inside to the outside; in the veins this gradient runs in the opposite direction, viz., from the outside to the lumen. The second fluid flow leaves the arterial side of the capillaries in the adventitia. The two flows unite finally in the efferent venules and lymph vessels of the adventitia.

Another fact to be kept in mind in the study of the vascular wall is that, although the vegetative nerve tracks end in the adventitia, there is also a peripheral autonomous system which, with its network of fibres and Cajal cells, reaches into the intima. This peripheral nervous system exerts a great influence on the *milieu intérieur* of the vascular wall.

As yet little is known about the factors which influence the flow of fluids and the composition of the milieu. We do know, however, that sodium chloride influences both this flow and this composition by its Na, as well as its Cl component.

These considerations make it understandable that sodium chloride may exert an influence on changes which develop in the vascular wall.

### Summary

The author discusses the possible influence of sodium chloride on the development of changes in the vascular wall. Researches on the experimental induction of these changes have all shown that the amount of sodium chloride in the food is an important factor in the development—or non-development—of various vascular changes. The significance is discussed of the rate at which men and animals are capable of getting rid of the surplus of sodium chloride via the kidneys.

### Zusammenfassung

Der Autor behandelt den möglichen Einfluß von Natriumchlorid auf die Entwicklung von Veränderungen in der Gefäßwand. Untersuchungen über die experimentelle Erzeugung dieser Veränderungen haben alle gezeigt, daß der Gehalt an Natriumchlorid in der Nahrung ein wesentlicher Faktor bei der Erzeugung oder dem Ausbleiben von Gefäßveränderungen ist.

Es wird die Bedeutung des Anteils von Natriumchlorid erörtert, den Menschen und Tiere als Überschuß durch die Nieren auszuscheiden imstande sind.

### Résumé

L'auteur discute de l'influence possible du chlorure de sodium sur les modifications de la paroi vasculaire. Les recherches par provocation de modifications expérimentales ont toutes démontré que la quantité de chlorure de sodium dans la nourriture est un facteur important dans le développement — ou l'absence de développement — des différentes altérations vasculaires. L'auteur discute du degré de vitesse à laquelle l'homme et l'animal sont capables d'éliminer l'excédent de chlorure de sodium par l'intermédiaire de leurs reins.

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