Environmental Health Perspectives
Vol. 81, pp. 241-242, 1989

Letters to the Editors

The Role of Aluminum and Age-Dependent Decline

Dear Editors:

You are to be congratulated on publishing the very thought-provoking article by P. O. Ganrot, entitled "Metabolism and Possible Health Effects of Aluminum" (*1*).

After reviewing a substantial part of the extensive literature, Ganrot analyzes it carefully and shows that an element of the properties of aluminum will indeed prejudice normal function if it reaches sensitive parts of the organism. His Table 1 points to the conclusion that only aluminum has all the qualifications for long-term destructive action. Only aluminum and beryllium have an ionic diameter small enough to ensure easy access and penetration. Although beryllium is a fast-acting poison, it could not at all cause the long-term chronic effects of aluminum. A world in which beryllium, instead of aluminum, constituted 8.4% of its surface, could only sustain bacteria, and at the very most some exceptionally fast-breeding fleas might have evolved.

Chromium is the only metal listed by Ganrot, which is nearly, but not quite, as versatile a cross-linking agent as is aluminum, with zirconium a runner up. However, the chromium atom has too large a radius to occupy a calcium site, and above all, the cell metabolism can escape chromium by changing the ambient so as to reduce trivalent chromium to its innocuous bivalent form. Aluminum is the only one of the metals mentioned that is *always trivalent*. None of the metals with multiple valences needs to be considered as a stand-in for aluminum. They can all escape an awkward metabolic situation by being switched to a lower valence.

That this escape option is actually used is evidence in the case of chromium by the findings of Markesbery et al. (*2*). Chromium increases slowly but steadily up to the persons that died in the range of 40 to 60 years, but then makes a sharp dip, as if a corrective or escape measure had been taken. Aluminum shows no such dip (Fig. 1). This same course is evidenced by Zinsser et al. (*3*). This paper shows the aluminum levels of 14 aortas from necropsies in the age group up to 40 years and 13 aortas in the age group 41 to 50. The latter group shows an increase in aluminum of 2.72 times. Chromium analyses were made from analogous age groups, 10 aortas from a group up to 40 and 6 from 41 to 50. These analyses showed a decrease of 29.9% in the chromium content at death. After age 50, the sharply increasing mortality rate from cancer, heart disease, and other causes obscured the results. The analyses were made by emission spectrography at Columbia University, New York, NY, where the late H. H. Zinsser, Jr., was professor of urology.

On page 400 of Ganrot's article, he concludes, "In summary, Al^{3+} clearly has caused DOM [dialysis osteomalacia], but on a molecular level, the pathogenic mechanisms are completely unknown." This surprising statement become understandable when I recalled that Ganrot's bibliography with 959 references did not go back far enough to include Staudinger and Heuer (*4*) and Staudinger and Husemann (*5*). The basic papers proved that as little as 0.01% of a typical cross-linking agent could change a soluble linear polymer to a 99% insoluble aggregate. (Staudinger received the 1953 Nobel Prize in chemistry.) Cross-linking is the process by which the smallest input can cause the greatest possible change.

Ganrot's estimate of the lethal quantities of aluminum is incorrect. In the tanning industry, to which Ganrot refers, the quantities of aluminum used are thousands of times larger than what would be fatal in a human brain because a) industry required speed in interest of economy. Therefore, it uses large excesses of tanning (cross-

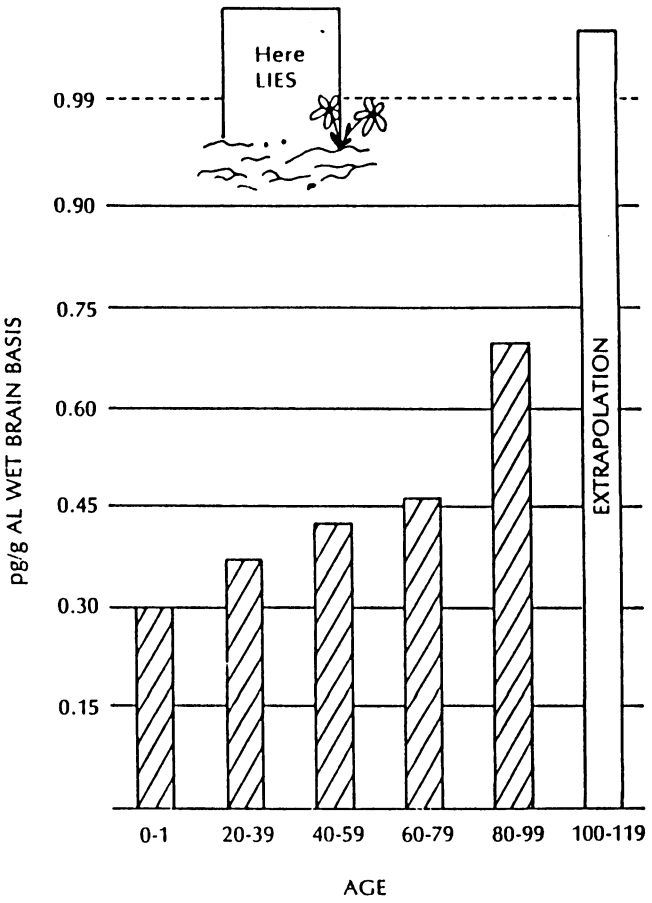

FIGURE 1. Brain aluminum concentrations as a function of age. Shaded columns after Markesbery et al. (*2*); unshaded column extrapolation by Bjorksten.

linking) agents to accomplish in a few hours or minutes a degree of tanning found in humans at the end of a normal life, and b) in tanning, by far the largest percentage of cross-linking agents is bound and thus neutralized by low molecular peptides and amino acids (*6*).

Cross-linking efficiency is one of the most crucial properties in life chemistry. A few words of elucidation appear appropriate at this point: We may think of a large ship tied to a pier. The ship is an ocean liner weighing 40,000 tons. The pier might weigh 110,000 tons. The ropes that bind together ship and pier might weigh only a few hundred pounds, yet, they prevent the ship from sailing on the seas and further prevent the pier from loading or discharging new cargos. In this example the ropes are the cross-linking agents. We can easily understand that it is not important to know the exact chemical identity of the ropes—they could be steel wires or nylon or hemp or polypropylene; their composition means very little as long as they are strong enough.

Thus, we do not need to know the exact chemical compositions of the ropes, what matters is how many ropes there are and where they are attached. Similarly, it is futile to spend time on identifying cross-linking agents as long as the resultant bonds are strong enough and sensibly arranged.

To think of aluminum as the one and only accumulating, life-limiting substance would be an error. There are many others. Aluminum is merely the most evident, most available, and above all, the analytically most easily followed member of a much larger group: the cross-linking agents. While other metallic cross-linkers are relatively unimportant in the big picture, there are numerous organic substances that qualify very well. Any organic substance that has at least two hooks is a cross-linker, including some free radicals. Since Staudinger showed that the quantity of cross-linker will bear about the same relation to a cross-linked aggregate, as the ropes are a part of the ship-pier system, it is evident that trying to identify a particular organic cross-linker is like searching for a needle in the proverbial haystack. Aluminum is the one exception, for there we can burn the haystack and find the aluminum needle in the ashes. The indications at present are that of the lifespan-limiting cross-linking agents, aluminum constitutes 80 to 90%. The remaining organic cross-linkers are many. When I took a count of those identified in human blood, I found in 1963 17 substances (*7*), today the list would be longer. However, first things first: Aluminum is a barrier to longevity now in plain sight (*8*).

This letter should not be construed as critical of Ganrot, who has given us an impressive study of a field that deserves not only attention, but action, with a firm resolve to succeed.

Summary. The cross-linking agents correspond to the ropes connecting a ship to a pier. Of all known types of chemical reactions, cross-linking is among those of which the smallest possible quantity of a reagent has the largest possible insolubilizing effect. A cross-linking agent is anything that has at least two reactive sites at some distance from each other. The aluminum ion is one of the most effective cross-linking agents and has for a century been used as such (*6*). More recent implications of these effects were covered in Bjorksten et al. (*8,9*).

JOHAN BJORKSTEN
Bjorksten Research Foundation
Madison, WI 53233

REFERENCES

1. Ganrot, P. O. Metabolism and possible health effects of aluminum. Environ. Health Perspect. 65: 363–441 (1986).
2. Markesbery, W. R., Ehmann, W. D., Alauddin, M., and Nossain, T. I. M. Brain trace element concentrations in aging. Neurobiol. Aging 5: 19–28 (1984).
3. Zinsser, H., Bjorksten, Jr., Brucck, E. M., Baker, R. F., Kaeburn, L, Kinnear, J., Cohen, A., Andrews, E., Sarfati, L., and Light, I. The freezing pool: A unified sequence of the aging process. In: Medical and Clinical Aspects of Aging (H. T. Blumenthal, Ed.), Proceedings of the 5th Congress of the International Association of Gerontology, 1962. Columbia University Press, New York, 1962, pp. 460–482.
4. Staudinger, H., and Heuer, W. Über hochpolymere Verbindungen, 94. Mitteilung: Über ein unlösliches Poly-Styrol. Ber. Dtsch. Chem. Ges. 67: 1164–1172 (1934).
5. Staudinger, H., and Husemann, E. Über hochpolymere Verbindungen, 116. Mitteilung: Über das begrentzt quellbare Poly-Styrol. Ber. Dtsch. Chem. Ges. 68: 1618–1634 (1935).
6. Bjorksten, J. Crosslinkages in protein chemistry. In: Advances in Protein Chemistry, Vol. 6 (M. L. Anson, J. T. Edsall, and K. Bailey, Eds.), Academic Press, New York, 1951, pp. 343–381.
7. Bjorksten, J. Aging, primary mechanism. Gerontologia 8: 179–192 (1963).
8. Bjorksten, J. Longevity: Past, Present and Future (M. Buis-Dulin and D. Nieto, Eds.), JAB Publishing Co., Charleston, SC, 1987, pp. 50–84.
9. Bjorksten, J., Sundholm, E., and Tenhu, H. Aging, crosslinking and Alzheimer's disease. Rejuvenation XII, No. 3–4: 43–46 (1984).