permeability to monovalent cations[4-6] and with the changes in Ca-binding of cell membranes[8] reported. These initial differences between SHR and NWR might also be understood as a manifestation of compensating mechanisms in SHR, which at this stage are still effective. The alterations in SHR are of interest because they already appear in the prehypertensive stage and may reflect biochemical processes whose failure contributes to the development of hypertension.

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Trace metal requirements in total parenteral nutrition: A theoretical approach by mathematical modeling

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Summary. A new computer-based approach has been developed to assess the optimal doses of essential trace metal ions which should be included in nutritive mixtures, used in human total parenteral nutrition, to compensate for the ligand-induced losses of these metal ions. An example of application is given for zinc, copper and manganese.

Although the need for supplementation of trace elements, especially zinc, during total parenteral nutrition (TPN) is well recognized, the quantitative requirements are not precisely known. They are difficult to estimate because they depend on the clinical setting and because urinary excretion of transition metals in promoted by the administration of naturally occurring ligands[1-4]. Accordingly, the doses of trace elements which have thus far been included in TPN fluids range widely between limits established by experimental trial and error[5-7]. We thus decided to investigate the effect of TPN on the metal-ligand equilibria in human blood plasma and to attempt to estimate ideal quantities of zinc, copper and manganese ions which ought to be routinely added to TPN solutions. However, there are no experimental methods available which could accomplish this; the very small amounts of transition metals that occur in biofluids and the labile nature of the equilibria involved would thwart most known analytical techniques. So a theoretical approach, based on computer simulation of the relevant chemical interactions was adopted. Computer models of 9000 complexing species formed by about 60 components have been developed for blood plasma[8-10]. These were used directly to look at the effect of infused ligands in vivo and were adapted to provide information about metal binding in the infusate[11].

The concentrations of aminoacids in the blood plasma of 4 patients on prolonged TPN were measured using column liquid chromatography. The subjects were all suffering from severe digestive disorders: 2 had Crohn's disease of the small bowel, and 2 had chronic radiation enteropathy. The concentrations of the main ligands in the nutritive solution (aminoacids were from Bellon Laboratories, Neuilly, France) commonly used in the TPN unit of one of us (C.M.) were (mmole/l): histidine 6.25, cysteine 1.67, glycine 23.23, valine 20.68, leucine 20.53, proline 13.47, lysine 18.32, phenylalanine 14.66. Our computer simulation studies revealed that cysteine and histidine are the predominant low-molecular-weight ligands bound to zinc in blood plasma[11]. Furthermore, the computer models predicted that although the size of the low-molecular-weight zinc fraction would be directly related to the concentrations of both ligands, it would be most sensitive to the level of cysteine because of an important biscysteinato zinc complex. As the concentrations of cysteine are, on average, more than doubled by the TPN infusions, it seems very likely that this TPN component is the chief cause of the zinc losses. On the assumption that TPN solutions should contain metal ion supplements which cause the smallest possible effect on the metal binding in normal blood plasma, we have also calculated the amounts of calcium, magnesium, zinc, copper and manganese which need to be included in the nutritive mixture most commonly used in the TPN unit of one of us (C.M.) These values, shown in the table, all lie

Total concentrations and predicted doses for zinc, copper, manganese, calcium and magnesium to be added in the TPN aminoacid solution[a] used at $-\log[H^+]=7.4$

Metal	Total concentration[b] (mole · dl^{-1})	Predicted dose[b] (mg/day)
Zn(II)	1.914×10^{-5}	32[c]
Cu(II)	7.857×10^{-7}	1.3
Mn(II)	5.537×10^{-13}	10^{-6}
Ca(II)	4.903×10^{-4}	507
Mg(II)	4.070×10^{-4}	257

[a] Identical to that indicated in the text. [b] The calculations are based on a mean value of the calculated free metal ion concentrations[8] and on the measured aminoacid ligand concentrations in the nutritive mixture. The predicted dose is the calculated amount of each metal in 2.5 l of nutritive mixture, this being the usual volume administered daily. [c] Partly calculated from statistically estimated equilibrium constants; the experimental determination of these constants (to be performed by one of us (GB.)) should result in a lower dose.

within the ranges which have been used hitherto[5,7]. The calculations depend on current estimates of the free metal ion concentrations in plasma. Such estimates can be obtained for the transition metal ions from a knowledge of the dissociation constants of the predominant metal protein complexes in the biofluid. The value for calcium can be measured directly using ion sensitive electrodes. The excellent agreement between the theoretical and practical values for this metal ion reflects this. On the other hand, the greatest uncertainty is associated with magnesium because neither the free ion concentration in plasma nor the relevant metal binding constants are well characterized.

These findings imply that the noxious effect of TPN on trace element metabolism can be minimized by a suitable choice of fluid composition, and suggest that transition metal supplements can be calculated to suit the particular mixture being administered.

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Cardiac hypertrophy accelerated by left cervical sympathectomy in spontaneously hypertensive rats[1]

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Summary. Cardiac hypertrophy in spontaneously hypertensive rats was accelerated by denervation of the left cervical sympathetic ganglia. Supersensitivity due to denervation may also exist in cardiac muscles.

Cardiac hypertrophy is usually the consequence of an increased circulatory resistance. Myogenic and neurogenic factors may participate in cardiac hypertrophy. With regard to the neurogenic factor, it is a relevant question how the nervous control of heart muscle may influence cardiac hypertrophy. In 1939, Cannon[3] reviewed a law of denervation. According to this review, a supersensitivity to chemical and physical stimuli is developed in the denervated muscles. The present experiments were performed to elucidate whether cardiac hypertrophy was accelerated by denervation.

Male spontaneously hypertensive rats (SHR) from the Okamoto strain, kept in our laboratory for more than 25 generations, were used for these experiments. 10 male SHR, weighing 210–300 g, were used at the age of 3.5 months, and 11 male age-matched Wistar-Kyoto (WKR), weighing 225–280 g, were employed at the age of 3.5 months. In 6 of the SHRs and 6 of the WKRs, the left superior and middle cervical ganglia including the sympathetic trunk were removed under ether anesthesia. Other SHRs and WKRs as control groups underwent sham operations. 8 weeks after denervation, the heart was removed under ether anesthesia. The tissue was immediately fixed by the vascular perfusion method for electron microscopic examination, using cold 2.5% glutaraldehyde buffered with 2% paraformaldehyde at a pH of 7.4. Some pieces of the tissue were refixed with 10% formalin for light microscopic examination. Electrocardiograms and blood pressure were measured every 2 weeks.

Although blood pressure in the non-denervated SHR was significantly elevated, an appreciable elevation of blood pressure was not seen in the denervated SHR and both groups of WKR. 8 weeks after denervation the electrocardiogram was markedly changed: A leftward deviation of the electrical axis was observed in all denervated SHR and 3 of the denervated WKR. The leftward deviation was not necessarily related to the elevation of blood pressure. The QRS duration in lead II became wide only in the denervated SHR ($p < 0.02$). The PQ interval was prolonged in denervated groups of SHR and WKR, an effect which was statistically significant ($p < 0.01$). The amplitude of the QRS wave in $R_I + S_{III}$ and R_{aVL} decreased 8 weeks after the

Cell diameters at various portions of left and right ventricles

	Left ventricle Anterior	Lateral	Posterior	Septum	Right ventricle
Spontaneously hypertensive rats (SHR)					
Denervation	12.58±2.46* (n:80)	13.02±2.72* (n:80)	12.83±2.22** (n:80)	12.28±2.08* (n:80)	9.61±2.35 (n:80)
Sham-operated	11.75±2.21 (n:60)	12.06±2.25 (n:60)	11.77±2.13 (n:60)	11.49±1.85 (n:60)	9.50±1.70 (n:60)
Wistar-Kyoto rat (WKR)					
Denervation	9.79±1.90 (n:90)	10.26±1.81 (n:90)	10.15±1.66 (n:90)	9.93±1.85 (n:90)	9.10±1.70 (n:90)
Sham-operated	9.52±2.00 (n:60)	9.74±2.10 (n:60)	9.99±1.91 (n:59)	9.53±1.53 (n:60)	8.78±1.62 (n:60)

The values are mean±SD (μm); * $p < 0.05$ by t-test; ** $p < 0.005$ by t-test.