EFFICACY OF CHELATED MINERALS; REVIEW OF LITERATURE

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The recent report (Leach and Patton, 1997) of an assay procedure for chelated minerals removes an obstacle that has long hindered consideration of chelates by the animal feed industry. In the absence of a reliable assay, it is understandable that some would hesitate to embrace a technology that's existence could not be proven empirically. Nonetheless, circumstantial evidence kept most minds open to the issue, as there was no ready explanation for such things as the classic experiment of Neathery et al. (1972) at the University of Georgia. These workers grew corn supplemented with radiolabeled zinc, and in this manner obtained intrinsically labeled corn. When this corn was fed to animals, it was possible to measure zinc uptake by tissues and vital organs. As a control, an identical dose of radiolabeled zinc was fed as an inorganic mineral supplement. The zinc from the corn plant grown with radiolabeled zinc was 40% more effective than the inorganic supplement at increasing tissue levels. Open minds also pondered the fact that inorganic iron supplements are better absorbed if fed with vitamin C, and are less absorbed if fed with phytic acid. However, hemoglobin, a form of chelated iron, is neither increased in absorption by vitamin C nor decreased by phytic acid. While such insights tend to support the theory that minerals may be more effective in organic form, as does the growth of organic sales in the market, unequivocal proof of efficacy still awaits validation.

But as the recent insight regarding the new assay expands, and its utility improves with broader application, interest in chelated minerals can be expected to respond and increase, generating questions on the part of those charged with the technical support of the animal health industry . To assist in addressing these questions, the following literature review was undertaken. At the close of the last decade, a review cited less than a dozen refereed articles (Patton, 1990) but recent years have seen a prolific increase in the number of researchers interested in chelated minerals.

Overview: Of the over 90 references considered in this review, well over half are peer review journal articles describing research in recent years, with abstracts, proceedings and book chapters the balance. As will be seen, in most cases, the experimental results show a benefit, or at least no disadvantage, to feeding chelates. But the exceptions are noteworthy. Giving credit where it is due, much of this work was supported by Zinpro Corporation, but in the same sense of fairness, until recently, it was all too common to use as the control treatment the oxide form of copper or zinc. This unduly favors the chelate in that the oxides are inferior in bioavailibity to the sulfates, as several studies show, and furthermore, sulfates are commonplace in animal nutrition. Eloquent investigations utilizing radiolabeled chelates, lead by Robert Cousins and his colleagues at the University Florida, have brought us to the beginning of an understanding of the exact mechanism of action of chelates. Dr. Hemken and coworkers at Kentucky have been energetic contributors to the field, and Dave Baker and his associates at Illinois have helped define bioavailability in measurable tenns. Various workers underscored the complication of inhibition, such as that due to phytase and excess calcium. It is intriguing to see that the nutritional status of an individual for a given mineral may directly influence the uptake of that mineral. For this reason, Jerry Spears of North Carolina State, a veteran investigator of minerals, always recommends bioavailability evaluations using known suboptimum mineral levels. Site of absorption, it develops, is not a straight forward issue, and some tissues proved to be reliable indicators of nutritional status, while others it would appear are nearly meaningless. An interesting abstract of work in beef cattle (Littledike et al., 1994) that followed dietary treatments for up to five years indicates that body composition alone can alter tissue levels of trace mineral. Montana workers (Swenson et al., 1996) did not observe liver levels of trace minerals paralleled by serum values, and proposed that serum was not a good indicator of mineral status. Stress, especially due to infection, is a common theme in several papers.

Certain topics are not part of the focus of this review. Selenium for one is excluded, because due to electron chemistry, it cannot form a true chelate. Chromium, until only very recently, was verboten in animal agriculture, but as the work of Dave Mowat at Guelph has shown, its role may be critical. Investigations of chromium abound, as well as interest in general, to the point where chromium probably merits a treatment in its own right, so it is not included in this effort. Regarding animal species, it is possible to cite numerous reports in every animal of the food industry, including fish. As a matter of fact, the cat is about the only one missing, with pertinent articles to be found on research in the horse, dog, rat and even mink. The literature on mineral nutrition research has grown beyond what anyone individual can command short of a full time preoccupation, and in this case the foreign language literature was, regrettably, largely igflored. While it was the ambition to include all peer review work to date, oversights, though inadvertent, are inevitable. *Lastly, and quite importantly, it is essential to bear in mind that several companies produce chelates, most claiming a unique status apart from the others, and research results on one company's product may not pertain to other company's products.* Indeed, they frequently do not.

Different chelates: No attempt will be made here to list all manufacturers of chelates. However, some explanation of the difference in approaches is appropriate, allowing for the fact that each product is best described by its own representatives. First of all, a chelate is a mineral bound to nonmetal entity , referred to as the *ligand.* The nature of the bond is fairly well accepted, inasmuch as it is a function of the laws of physics, but exactly what constitutes the ligand is the source of all the territoriality on the part of the various players. Reiterating the caveat again, that each company is best suited to explain its own products, the matter can be reduced to the following main points. Depending on the product, the ligand is one of three things; 1) a specific amino acid, 2) a small number of amino acids, more than 800 and less than 1200 molecular weight, or 3) an unspecified group of amino acids. As far as this reviewer is concerned, this constitutes the whole of the basic differentiation required of a nutritionist or buyer. There is the one infrequent exception, that of metals in combination with carbohydrates or polysaccharides, but little research presents itself to guide us on this matter (Lowe et al., 1994b; Hussein et al., 1993; Kennedy et al., 1993; Stansbury et al., 1990).

Deficiency sensitizes absorption: Or more correctly, it would appear that nutritional status ofa given mineral can directly alter the uptake of that mineral. To fairly evaluate the evidence that follows, preliminary comments are in order. One needs to keep in mind that in trace mineral metabolism, just as in all biology , variation is the rule, along with mystery. For example, recently Kornegay et al. (1996) reported that the major site of Zn absorption in the pig was a function of level of Zn in the diet. At 32 ppm, the colon predominated ($p<.001$) while at 132 ppm, the intestine and stomach absorbed more Zn. This implies that there may be a site-by-dose interaction, and this should inform our evaluations. Another axiom essential to bear in mind is that nutritional status itself alters bioavailability, and the body's need influences absorption. Hallmans et al. (1987), working with radiolabeled Zn in rats, can be quoted directly. "It is quite evident that values for Zn absorption from food obtained under conditions in which the body's need for Zn is not increased can hardly be used as measures of the availability of Zn in these foods." Mejborn (1990) proved the same principle at work in mink, and cited other work proving it in humans. Valberg et al. (1985) showed a difference in ^{65}Zn uptake in people depended on delivery carrier, water or minced turkey, and Sandstrom (1992) showed the same for a liquid meal versus a solid meal. Rojas et al. (1994a) stated that the difference in bioavailability of Zn sources may not be evident until Zn becomes limited in the diet. Menard and Cousins (1983) offered the most succinct insight to date. Under conditions of normal dietary zinc, uptake by the brush border membrane of the mucosal cell depends on transfer by a membrane associated carrier; this system has been shown to increase significantly in Zn depletion. This concept, that plane of nutrition or status for a given mineral alters its uptake was proven more rigorously just recently, at the mRNA level (Sullivan and Cousins, 1997).

Oxide versus sulfate: The availability of copper from copper oxide is rated essentially zero for the chick (Baker et al.,1991) and very low for the weanling pig (Cromwell et al., 1989). This evidence was pervasive enough to provoke the observation by Baker's group that feed producers should be discouraged from using either CuO or Cu_2O. Hahn and Baker (1993) reported that zinc from ZnO was 46% as available as zinc from ZnSO4 for the weanling pig (P<.05). Wedekind and Baker (1990) found quite similar results in the chick, observing a relative bioavailability of ZnO of 40% if tibia zinc content was the end point. Kegley and Spears (1994a) concluded that copper oxide was essentially unavailable for growing cattle. Lowe et al. (1994b) showed that zinc from a zinc chelate was not affected by calcium antagonism, and that ZnO was not able to overcome a calcium antagonism. (The issue of chelates and dietary antagonists is a recurring theme and probably central to the entire concept of chelates. It is treated separately below.) Feed grade oxides are of poor bioavailability compared to sulfates, and any study contrasting chelates with oxides is biasing the results in favor of chelates. Too many earlier reports (ca 1980 to 1992) used this approach, but recent investigations tend to use a more rigorous control. Some insight as to the problem with oxides is hinted at by Aoyagi and Baker (1992) who observed a bioavailability of the more pure *analytical grade* CuO of 97.3% of CuSO4. The swine industry seems to be well aware that the purity of a dical source effects performance, and perhaps we see here an analogy with feed grade oxides and their lack of purity .

Inhibition: Normal ingredients of a diet, as well as inadvertent components of the ingredients, can inhibit trace mineral absorption. Inhibition of trace mineral absorption is not difficult to document, though it can be quite species dependent. The copper-molybdenum interaction is common knowledge. Phytate decreases zinc absorption (Hempe and Cousins, 1989). Calcium decreases the absorption of copper (Kirchgessner and Grassmann, 1970) and zinc (Lowe et al., 1994b; Wedekind et al., 1994). Molybdenum and sulfur decrease rumen soluble copper (Ward and Spears, 1993) and plasma copper (Ward et al., 1993). In a ponderous yet logical discussion, Miller et al. (1996) postulate that the adverse effects of excess iron can be overcome with zinc, and draw evidence from the literature to support this hypothesis: Heifers and cows deliberately overfed iron showed 65% less retained placentas and 16% less edema when fed supplemental zinc as a combination of $ZnSO_4$ and Zn methionine. While this reveals nothing regarding the relative effectiveness of the two zinc sources, the point is that excess iron has deleterious effects and supplemental Zn appears to ameliorate these problems. Sandstrom (1992) points out that the chemical similarity of manganese and iron could result in competition for absorptive mechanisms, and relates that the addition of manganese to an iron containing solution depresses iron uptake. But lest we carry insight in one species too far, keep in mind the report by Spencer et a1. (1965) that the calcium antagonism for zinc in animals could not be demonstrated in man.

Review of literature; Ruminants: The point of the foregoing discussion was to delineate parameters invoked in evaluating the body of literature on this topic. Unfortunately, a systematic approach to the literature does not present itself, as any of the convenient categories, e.g., species, year, mineral, laboratory, are invariably overlapped with the others. Spears (1996a) offers an excellent review organized by form of chelate or type of ligand, and a second review (Spears, 1996b) by mineral element. This article is organized as much as possible by species. As indicated, a common failing, especially of older work, was poor (often pathetic) control treatments. One study (Brazle, 1994) had 24 times more zinc in the experimental diet compared to the control. Studies that did not at least attempt to design iso-zinc diets (or copper, etc.) were de-emphasized in consideration as input for answering basic questions relating to science. However, no judgment is held out regarding their usefulness for marketing purposes. Inasmuch as oxides are proven to be of low bioavailability, especially in monogastrics, studies that compared sulfates to chelates deserve consideration as more valid. Brazle and Stokka (1995) reported that newly arrived feedyard calves fed Fourplex (a feed additive from Zinpro Corporation that contains copper lysine, zinc methionine, manganese methionine and cobalt glucoheptonate) required fewer ($p<.05$) medication days, but Fourplex did not improve average daily gain or feed intake, or reduce mortality. Kegley and Spears (1994a) reported that copper lysine and copper sulfate performed the same. According to Chirase et al. (1991) in the first of three experiments, feed intake tended to drop less in zinc methionine fed calves challenged with Infectious Bovine Rhinotracheitis (IBR) compared to ZnO fed calves. In the second experiment, control calves fed 30 ppm zinc had lower ($p<.05$) feed intake compared to zinc methionine fed calves receiving 90 ppm zinc, while in experiment three, recovery from depressed feed intake due to IBR fever was slower for ZnO fed calves compared to calves fed zinc methionine. In this third experiment, the control was the lowly zinc oxide, but at least the same level of zinc was used for treatment and control. In a subsequent two part study with IBR stressed cattle (Chirase et al., 1994) investigating the interaction of high and low copper diets on oxides and chelates of Zn and Mn, the treatment and control groups had identical levels of these minerals, and there was no effect on plasma Mn or Zn on days 0, 7, or 14 post infection, though the trend favored the chelates, and rectal temperature did ($p<.05$) favor chelates. Injection of copper in this trial consistently lowered feed intake. The second part of this research showed increased ($p<.05$) feed intake for chelates compared to oxides, but differences in body weight were not significant. Galyean et al. (1995) found a trend in favor of zinc methionine in beef cattle, but the results were not significant. They point out that several minerals can affect zinc absorption, including cadmium and chromium, and suggests an idea that is recurring in the literature, that requirements may be multilevel, e.g., maintenance may be different from maintenance during stress. Green et al. (1988) saw no effect on feed efficiency in cattle but did note that carcass quality and internal fat were improved ($P<.05$) by feeding zinc methionine compared to zinc oxide. Graham et al. (1992) considered dairy cow health as affected by Zn, but treatment had 43 ppm more zinc than control. These workers did look at the effect of methionine versus zinc methionine, a question often asked in the field, and found that methionine did not give a response equal to zinc methionine. Others observed the same, and are discussed below.

Reiling et al. (1992) considered hoof strength and elasticity of feedlot heifers fed zinc proteinate, and saw a non significant trend in favor of chelated zinc, but as one might suspect, there was also an effect of age on hoof elasticity. Rojas et al. (1994a) compared zinc methionine, zinc sulfate and zinc oxide in 32 yearling cattle and detected no difference on all parameters measured, which included serum, liver, pancreas, kidney, bone, bone marrow, hair, hoof and muscle. Metallothionine levels likewise were not different. Working with calves, Saker et al. (1994a) reported increased ($P<.05$) expression of histocompatability complex class II for copper lysine fed animals compared to controls fed copper sulfate. In a companion study, these same workers (Saker et al. 1994b) related that copper lysine increased ($P<.05$) plasma copper and monocyte phagocytic activity compared to control, but controls received only half as much copper as the copper lysine group (43 v. 104 ppm).

Ward and Spears (1993) in the process of offering a good basic review of molybdenum and sulfur, reported work from their lab that showed there was no difference *in vitro* between copper lysine and copper sulfate, but they did prove that molybdenum and sulfur can decrease rumen copper. These researchers indicated that their work was in contrast to the report of Kincaid et al. (1986) who did detect an increase ($p<.05$) of both plasma and liver copper in ruminating calves fed copper proteinate compared to copper sulfate. In a broader study considering copper, manganese, zinc and cobalt, Ward et al. (1992) found there was no difference between copper sulfate, copper oxide or copper lysine for dry matter intake or gain after 28 days. There was an immune response tending in favor of chelates ($p<.10$). Ward et al. (1993) in a follow-on study of their *in vitro* work, compared copper lysine and copper sulfate in steers challenged with molybdenum and sulfur. No difference in copper source was found when looking at gain, feed conversion, feed intake, plasma copper, ceruloplasma or immune response. Molybdenum plus sulfur decreased blood copper levels. In the most recent work from Dr. Spears lab (Ward et al., 1996), it was demonstrated that chelated copper was no advantage over copper sulfate in diets of low molybdenum content, but if molybdenum was greater than 7ppm in the ration dry matter, the chelate form of copper was indicated as possibly of greater bioavailability .Working on immunity in steers, George et al, (1997) observed an increase ($P<.05$) in humoral and cell-mediated immune response in favor of chelates compared to isoelemental levels of inorganic forms of copper, manganese and zinc.

A few studies have been undertaken in sheep. Those of Spears (1989) and Lardy et al. (1992) corroborated each other in that each found that absorption was essentially identical for inorganic and chelated zinc, being about 40%, but that the chelated form of zinc was retained better ($p<.05$) than the inorganic form of zinc. Hatfield et al. (1993) reported no effect of zinc methionine added to a basal diet when lamb average daily gain was measured. During gestation, zinc methionine fed ewes had higher ($P<.02$) feed intake, but no such effect was seen in lactation. Kegley and Spears (1994b) reported higher ($P<.01$) plasma copper in lambs fed zinc oxide compared to those fed zinc methionine, while plasma zinc, average daily gain or feed conversion were unaffected. Rojas et al. (1994b) compared zinc lysine and zinc sulfate and found no difference in liver zinc levels, but zinc lysine did increase ($P<.05$) the enzyme metallothionein in liver, kidney and pancreas compared to zinc sulfate. Henry et al. (1992) evaluated manganese absorption in lambs fed manganese methionine, manganese sulfate or oxide. Tissue uptake in bone, kidney and liver was significantly increased (P<.0 1) by manganese methionine compared to other sources fed, as well as by amount of manganese.

In dairy cattle, somatic cell count (SCC) is often purported to be lowered by feeding chelates. While this may be true, it can be difficult to prove, as so many other factors interfere. In the author's personal experience, simply moving cows from one pen to another increased SCC significantly, and probiotics that eventually lowered SCC initially increased the level. Whitaker et al. (1997) reported no effect of zinc proteinate on SCC, mastitis, infection rate or recovery rate. Moore and coworkers (1989) observed no effect of zinc methionine on SCC, even with lower zinc intake in the "controls", compared to the treatment cows. Kellogg et al. (1989) reported no difference in SCC between groups of dairy cows fed a basal diet or the same basal diet plus zinc methionine. Spain (1993) reported that cows fed Bioplex Zinc actually had higher (240,000) SCC compared to controls (179,000), but this difference was not significant. There is little hard evidence that chelates improve SCC, and in this area, more work is needed.

Two abstracts come to light on the subject of milk replacer for calves. Jacques and Newman (1993) compared chelates and sulfates in milk replacer provided to Holstein bull calves up to weaning at six weeks of age. Weight gain tended (p<.07) to favor the Bioplex supplemented calves, that also required fewer respiratory disease treatments. Sowinski et al. (1996) in a similar protocol evaluating zinc methionine and copper lysine, saw no treatment effect for the parameters they measured.

Chicken: Deyhim and Teeter (1997) have produced what is perhaps the most recent work with mineral proteinates in chickens that is in the public domain, showing that ascites was reduced (P<.05) from 5% to 2% when chelates were fed. There was also the suggestion in their data that the high vitamin and inorganic mineral supplementation of contemporary diets potentiates ascites. Aoyagi and Baker (1993) studied copper and zinc, showing that these minerals in complex with lysine were 120% and 106% as available as the same mineral in sulfate form. These differences were not statistically significant. In an earlier publication (Aoyagi and Baker, 1992) they saw no difference between copper lysine and analytical grade copper sulfate. In the mounting evidence against oxides, Baker et al. (1991) reported that copper oxide, the cuprous form, CuO, provided no bioavailable copper to chicks, and based on accumulation of copper in the liver, cupric oxide (Cu_2O) and copper lysine were not different from copper sulfate. Dr. Baker's lab also investigated the bioavailability of manganese chelate compared to manganese oxide (Fly et al., 1989). Manganese from the proteinate form was found to be 174% more available than manganese from the oxide, when fed in a diet that was partly corn and soy. Ferket and Qureshi (1992) reported that zinc/manganese methionine enhanced humoral and cell mediated immune function in turkeys, and Ferket et al. (1992) found that the same chelate combination improved feed efficiency (P<.05) and reduced mortality (P<.05) and leg abnormalities (P<.05) in toms when supplemented on otherwise nutritionally adequate inorganic basal diets. In their words, turkey diets containing 80 ppm Zn and 120 ppm Mn as the sulfate supplement were nutritionally adequate, but the addition to these sulfate containing diets of 20 ppm or 40 ppm (but not 0 ppm) Zn/Mn-methionine improved feed to gain ratio and reduced mortality and leg abnormalities.

In a report of layer performance during low calcium stress (Keinholz et al., 1992), hens fed Zinpro gave more eggs (p<.05) than controls, but treatment and control were not identical in zinc levels. Pimentel et al. (1991) studied zinc in chicks and reported that there was no difference in zinc methionine and zinc oxide in the chick for the parameters measured, which included growth, tibia and liver zinc, copper or iron, or immune function. Prior to investigating chelate bioavailability Wedekind and Baker (1990) compared zinc sulfate and zinc oxide in the chick. Zinc oxide, as mentioned above, was only 60% as available as zinc sulfate, if weight gain was the parameter used as the biological end point, and 40% if tibia zinc content was used. When these same workers went on to assess efficacy of chelates (Wedekind et al., 1992), the insights reported were interesting. Apparently, as the level of phytate increases in a diet, the relative value of zinc methionine also increases. With the bioavailability of zinc from zinc sulfate set at 100%, zinc from zinc methionine was 117% in a purified diet, 177% in a soy isolate diet and 206% in a corn-soy diet. This work is implying that the advantages of chelates over inorganic supplements will not necessarily be evident in all circumstances. These authors further suggest that these results also point to a different absorption mechanism for chelates, echoing the retention studies in ruminants mentioned, (Spears, 1989; Lardy et al., 1992) and discussed further below.

Swine: Apgar et al. (1994) evaluated copper lysine and copper sulfate as growth promotants for weanling swine and found no difference, which is in contrast to the results observed by Coffey et al. (1994) who reported that copper lysine was superior ($P<.03$) to copper sulfate in weanling swine. In a study of curiously mixed outcome, Hahn and Baker (1993) observed that zinc lysine and zinc sulfate were not different in affecting plasma zinc levels in one trial, but in another trial, zinc methionine and zinc sulfate increased plasma zinc two fold ($P<.05$) over zinc oxide. In a digression from the trend, zinc oxide fed pigs gained 16% faster ($P<.05$) than all other treatments. Hill et al. (1986) reported that zinc methionine increased feed intake ($P<.05$) compared to zinc sulfate, but there was no difference in feed efficiency. The following year , these same workers (Hill et al., 1987a) used radio labeled zinc to look at absorption in pig and chicken gut *in vitro.* Although not significant, the average uptake of 65Zn into gut tissue was numerically greater from ^{65}Zn methionine in both the pig and the chicken, while zinc uptake from $^{65}ZnCI_2$ was significantly greater ($P<.05$) on the serosal side of the gut sac in both species. According to the authors, this suggests the possibility of different rates of absorption and transport for the two zinc sources. The companion study (Hill et al., 1987b) found no difference in performance between these two zinc sources when daily gain or feed efficiency were evaluated in pigs and rats.

Feeding 44 ppm of manganese from manganese amino acid chelate or manganese oxide to pigs, Kats et al. (1994) found the two sources equal with regard to average daily gain, feed efficiency or carcass quality. In the study mentioned above by Kornegay et al. (1996) more zinc sulfate ($P<.05$) was absorbed in the stomach than zinc lysine, but there was no such difference in the intestine. In this report, the colon proved to be an operative site of zinc uptake on lower levels of dietary zinc. In an experimental design more in keeping with feed industry practice, Mirando et al. (1993) fed sows a control diet identical to the treatment diet with regard to level of zinc, copper and manganese. However, the treatment diet had 25% of these minerals supplied from chelated sources, while 75% were from the same inorganic minerals as the control diet. More sows were pregnant ($P<.05$) on the chelate diet, and chelate fed sows had more live fetuses ($P<.10$) and less dead ($P<.05$) fetuses than the sows fed the all inorganic diet. In a well controlled investigation comparing a blend of copper, manganese and zinc in chelate form to inorganics, Richert et al. (1994) saw better gain ($P<.05$) in weanling pigs fed chelates for days 0 to 7 post weaning, but by day 28, there was no effect due to source of mineral. Although not a chelate technically, Carter and coworkers (1996) conclude that zinc *propionate* increases the availability of zinc compared to zinc sulfate, but one could also say that this is overstating their data. In a Latin square designed retention study with urine collection, pigs fed lOO ppm zinc from zinc sulfate had higher (p<.05) zinc retention than when fed the same zinc level from zinc propionate. Schell and Komegay (1996) basically saw no benefit to zinc fed as a chelate compared to sulfate. Stansbury et al. (1990) studying the weanling pig, compared copper as both an inorganic chelate and an organic chelate, along with copper sulfate. Copper sulfate proved equal to either chelate in their opinion. Swinkels et al. (1996) compared zinc amino acid chelate and zinc sulfate for ability to restore serum and tissue levels in zinc depleted swine and reported zinc source were not different in effectiveness. Kidney copper was increased (P<.0 1) for both zinc treatments in zinc depleted pigs, and iron levels increased in the intestine of pigs fed the chelate treatment. In a different yet logical evaluation of their results, T .L. Ward et al. (1996) concluded that with regard to feed efficiency in swine, zinc methionine providing zinc at 250 ppm was equal to zinc sulfate providing zinc at 160 ppm or zinc oxide at 2000 ppm. Wedekind et al. (1994) fed different zinc sources and concluded that for the growing/finishing pig, zinc from the sulfate and zinc methionine were equal. This study also demonstrated that calcium can decrease zinc absorption, and that plasma zinc is a poor indicator of zinc status in the pig.

Rat: There are actually several studies done using the poor old rat, and useful information has resulted. In a rare study contrasting copper chelates from two different suppliers, Du et al. (1996) observed that copper lysine increased (P<.05) liver and spleen copper more than copper sulfate, and that copper lysine and copper proteinate increased kidney iron and decreased kidney copper more (P<.05) than copper sulfate. In an eloquent study using radio labeled zinc from both inorganic and chelate sources, Powers et al. (1995) compared tissue deposits of zinc for ^{65}Zn derived from either zinc sulfate or zinc chelate. Zinc uptake increased for the chelate vs sulfate in hair (P<.002), kidney (P<.02) and muscle (P<.006).

Probably one of the leading groups in this field is the team at the University of Florida. Employing sophisticated techniques for sub-cellular scrutiny, combined with radio tracer methodology, precise questions are addressed by these investigators. (Cousins and Lee-Ambrose, 1992; Hempe and Cousins, 1989). Of interest for our purposes, in a concise trial with rats, zinc methionine was less (p<.Ol) absorbed than zinc chloride (Hempe et al., 1992) and also less absorbed than zinc chloride and methionine. This work was in vitro, and also revealed much progress in understanding the exact mechanism of action of chelates at the cellular level.

Other species: Without doubt, the most impressive indications of chelate effectiveness over conventional inorganics is seen in fish. Tom Lovell of Auburn University observes that fish seem to be more responsive to chelates than other animals of agriculture. In work reported from Lovell's lab (paripatananont and Lovell, 1995) fish growth was optimized with less zinc if it was from zinc methionine compared to zinc sulfate. In a purified diet, i.e., one not containing phytic acid, maximum growth of young channel catfish was enabled by 5 ppm of zinc from zinc methionine, while 15 to 20 ppm was required to achieve the same growth from zinc sulfate. If a conventional commercial diet was used, with normal levels of the presumed inhibition due to phytate, the effect of zinc methionine was more impressive. Maximum growth on a diet supplemented with zinc sulfate needed 80 ppm of zinc, but if zinc methionine was the zinc source, only 20 ppm yielded maximum growth. Fish challenged immunologically maximized survival rate with half as much zinc from zinc methionine as compared to those supplemented with zinc sulfate. Lovell also reported that bone zinc content of fish was more responsive to zinc methionine. This data from Lovell's lab is contrasted with the report out of Mississippi State by Li and Robinson (1996) that found no difference between zinc methionine, zinc proteinate and zinc sulfate, when fed to catfish.

Lastly, the dog. Lowe and co-workers have also utilized radiotracer labeled chelates in their investigations of zinc amino acid chelates. They reported (Lowe et al., 1994a) that zinc absorption in the chelate form is significantly greater than that of zinc oxide, and that the absorption of the zinc from zinc amino acid approaches that of amino acids alone, about 89%. These workers showed that in the dog, hair was a reliable indicator of zinc uptake (Lowe et al., 1994b) and also reasoned that calcium caused a decline in zinc uptake as evidenced by increased fecal zinc. This effect of lowered zinc uptake due to calcium was less ($P<.05$) when zinc amino acid chelate was fed compared to zinc oxide or zinc polysaccharide.

Reproduction: It is tempting to invoke chelates as helpful in reproduction, and the Mirando et al. (1993) and Manspeaker et al. (1987) studies would appear to supports this, but otherwise, data is rather scarce. A few experiment station reports (Holden et al., 1996) and several field trials certainly lend credence to the idea, but animal numbers are just too few to support their inclusion in this review. Kuhlman and Rompala (1995) reported more pups born to bitches fed zinc, manganese and copper chelates, but treatment and control weaned equal live pups. In evaluating copper, manganese and zinc supplements antagonized by molybdenum, sulfur and iron, Workers at Montana (Swenson et al., 1996a) observed a trend ($P<.10$) for proteinate fed heifers to breed by AI in greater numbers compared to those fed sulfates. In a related study (Swenson et al., 1996b) they observed higher liver levels of zinc ($P<.05$) at calving for chelate fed heifers compared to those fed sulfates, and these levels remained higher ($P<.0$ 1) through breeding. It is not difficult to theorize how chelates could enhance reproduction, given the intensity of animal production and the proof of efficacy otherwise, but at this time, there is not conclusive evidence to this effect in the refereed literature. While this by no means precludes the possibility of enhanced reproduction due to chelates, more work is needed. Olson et al. (1996) actually reported a decline ($P<.0$ 1) in fertility of heifers, attributed to proteinates.

The methionine part of zinc methionine: There has long been interest in the methionine portion of zinc methionine, and several years ago Heinricks and Conrad (1983) determined that the methionine of this proteinate was only of small consequence in the rumen. Several papers (Aoyagi and Baker, 1993: Graham et al., 1992; Henry et al., 1992; Hempe and Cousins, 1989; Komegay et al., 1996) pretty well dispel the notion that the methionine portion of zinc methionine is making any significant contribution to the effect of chelates.

Agreement on retention: Colorado workers (Nockels et al., 1993) performed an ideally controlled study investigating copper and zinc in stressed calves, during repletion. Zinc sulfate was compared to zinc methionine, each providing 36 ppm of zinc, and copper sulfate was compared to copper lysine, each providing 10 ppm of copper. We see here all the essential aspects of a mineral study that can provide useful comparisons; identical mineral supplementation in both treatment and control, good bioavailability of controls, and test animals with a nutritional need for the mineral under question. Calves fed copper lysine had a definite trend of 53% greater apparent copper absorption and increased (P<.05) copper retention during repletion compared with calves fed copper sulfate. Calves fed zinc methionine had a non significant trend of 58% more zinc retention than calves fed zinc sulfate. These workers also showed that urinary copper and zinc decreased during stress, and that urine volume was less (P<.05) for chelate fed calves. The part of this work that is critical is the *retention.* This addresses mineral that has been taken into the body. Absorption has already happened, and in this trial, the chelated copper was retained better, after absorption. In and of itself, this is one isolated point of significance, but the literature provides us with corroborating data. Spears (1989) saw the very same phenomenon in sheep; identical absorption between chelates and inorganics, but greater (P<. 01) retention. Subsequent to the North Carolina State trials of Dr. Spears, Lardy et al., (1992) at Missouri, also working with sheep, observed the very same result of similar absorption, but significantly (P<.05) more retention of chelated zinc. These three investigations are noteworthy in that they suggest that we may need to expand our thinking regarding chelates. Studies that compare dry matter digestibility alone, i.e., simple absorption or uptake across the gut wall, might not be asking the right question. Perhaps we should be asking if chelates, once absorbed, are handled differently metabolically.

These trial results do beg that question, and support the hypothesis that it is so. The work of Webb (1992) certainly shows that our traditional approach to protein absorption requires new thinking. It develops that not all proteins are hydrolyzed to single amino acids before entering the gut cell wall, as there is now proof that short polypeptides are absorbed intact. Do we see here the insight needed to more fully understand chelated mineral uptake?

In the preponderance of earlier work, experimental design was less rigorous and we are perhaps better advised to neither denigrate or extol this portion of the literature. As we have seen, chelates can be rather elusive in showing their effect, and it is certain that many earlier studies would be done differently today. Based on stronger design and more recent investigations, it would appear that there is fairly substantial support for the following hypothesis: Chelated minerals are indicated to help overcome reduced absorption of inoganics due to inhibition of such compounds as excess calcium, iron, molybdenum and phytic acid, to cite the more prevalent ones. In periods of stress, to enhance immunity, chelates are probably further indicated as economic insurance. F or an excellent review of nutrition and immunity, see Cook-Mills and Fraker (1993). Kidd et al. (1997) cover the same topic with specific reference to zinc.

Chelated minerals usually cost more, per unit of metal element, than the same metal in inorganic form. Historically the argument against chelates was that increased use of inorganics was more economic than feeding chelates, and only ongoing scrutiny will eventually answer this concern. However, there is indication that in some situations, chelates can achieve biologic endpoints that inorganics cannot. Lowe et al. (1994b) reported inhibition of inorganic zinc uptake by calcium, and increased inorganic zinc did not overcome this inhibition, but chelated zinc did. Spears and Flowers (1995) investigated reproduction in swine and fed 100% ofNRC for Zn, Fe, Mn and Cu, where the chelate form provided 25% of the level of each mineral. This dietary level was contrasted with a treatment where 125% ofNRC was fed, but all the minerals were in inorganic form. The treatment feeding lower but partially chelated levels showed higher (p<.10) litter weaning weight than the higher but all inorganic level (166.4 vs 148.91b).

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