Abstract
There are very rare instances of severe reactions or even death following the usual infant inoculations. Although such events are rare, we need to do all we can to prevent them. Animal observations have shown that the blood histamine concentration is increased following the injection of vaccines or toxoids and this is most likely responsible for the problems. Vitamin C supplementation is now known to reduce the blood histamine levels; it also reduces the mortality rates following inoculations, both in animals and in man.

It is suggested that inoculations should not be given to severely debilitated infants and that supplementary vitamin C should be given in orange juice, before inoculation, to any infant with coryza, and also to any infant or adult who is to receive an unduly large number of inoculations at one time. Moreover, vitamin C should be given by injection whenever convulsions or other untoward events occur within a day or two after vaccination or inoculation.

Introduction
Elevated blood histamine levels occur following the injection of vaccines or toxoids in guinea pigs. Blood histamine levels are also increased by other stresses such as heat or cold, by infections and by several drugs in guinea pigs and even by sleep-deprivation and by early ascorbate depletion in man.

We are all familiar with the effects of increased tissue histamine levels, including asthma, hayfever or allergic rhinitis and nettle-rash or urticaria, but the effects of elevated blood histamine levels are not evident until they cause convulsions, coma or death, so we must be judicious concerning the number of inoculations that we give at one time.

It was the work of Parrot and Richet in guinea pigs which revealed that ascorbate depletion increases histamine sensitivity; they found that the dose of histamine causing death in half the animals (LD50) was reduced from 8 mg/kg to 2.5 mg/kg after 15 days on a vitamin C-deficient diet.

We now know that even sub-optimal plasma ascorbate levels are associated with increased blood histamine levels, both in guinea pigs and in man. Thanks to the work of Chatterjee et al., we have learned that optimal blood ascorbate levels are needed for the detoxification of histamine by converting it to hydantoin-5-acetic acid and then to the simple amino acid, aspartic acid. Actually the observation that borderline ascorbic acid deficiency increases the morbidity and mortality from diphtheria toxin in guinea pigs goes back to the work of King and Menten in 1935, not long after the isolation of ascorbic acid by Svirbely and Szent-Györgyi; and by King and Waugh in 1932.

Nowadays the number of inoculations recommended for infants and for soldiers going overseas, seems to be rising all the time, so we must pause to consider the cumulative affect of all these insults, and other factors, on the blood histamine concentration. It is therefore very important to appreciate that blood histamine levels and histamine sensitivity can be increased or decreased by depletion or supplementation with ascorbic acid, both in animals and in man. We must be judicious in the number of inoculations that we give at any one time, and we should try to avoid inoculation of any infant whose health is severely compromised in any way.

Search of the world literature reveals that supplementation with vitamin C protects against the morbidity and mortality resulting from typhoid, diphtheria, tetanus and four varieties of gas gangrene toxins, even in rats, mice and rabbits which make...
their own ascorbic acid in the liver.

**Relevant Human Studies**

There is evidence that infants with sub-optimal vitamin C status have decreased resistance to vaccinations and inoculations. This was first pointed out by Kalokerinos in 1971 and by Dettman in 1973. In his book “Every Second Child” Kalokerinos described his experience working with Aborigine and Caucasian children in Australia; he observed so many deaths following the usual inoculations with DPT for diphtheria, whooping cough and tetanus, that he was ready to give up medicine, until he discovered the cause of the problem. Kalokerinos was giving these injections to infants attending his clinic for other problems, such as upper respiratory infections, because he thought he might not have another opportunity of seeing them; the infants were vitamin C deficient because their illnesses had further decreased their vitamin C status, which was already low, and they could not tolerate the toxicity of the inoculations; he found that vitamin C was a simple solution to the problem and the infant deaths ceased, but very few physicians seem to be aware of this important work.

Inadequate vitamin C intake is rare today; breast milk contains about four times as much vitamin C as the mother’s blood, and bottle-fed infants usually get supplementary vitamin C from fruit juice in addition to the variable amount of vitamin C supplied by their infant formulas. However, many factors besides vitamin C intake affect the vitamin C status of an individual.

Even minor infections such as the common cold can cause a 50 percent reduction in the leukocyte ascorbic acid level within 24 hours, as shown by Hume and Weyers; moreover copper-tainted water and even iron supplements can cause losses of ascorbic acid by oxidation and subsequent hydrolysis.

Nowadays it is the fashion to give apple juice to infants, instead of orange juice, but apples are a poor source of vitamin C. One hundred grams of fresh orange juice (3 1/4 fluid ounces) contain about 49 mg of vitamin C, compared with 16 mg in 100 grams of canned tomato juice and only 1 mg in the same amount of fresh canned apple juice; so unless the parent knows to purchase the apple juice with added vitamin C, there could be a risk of vitamin C deficiency.

This problem of infant death or brain-damage following inoculation is not confined to Australia, as some would like to believe, but still occurs occasionally in Britain, the United States and elsewhere. In fact, there are so many concerned parents of affected children that they have formed a group to collect information under the name of the National Vaccine Information Center, and the U.S. government has formed the National Vaccine Injury Compensation Program which assists the parents of injured children. A book has been written by Coulter and Fisher giving details of large numbers of infants believed to have been brain damaged by DPT, DPTH or other inoculations.

Although much work has been done to determine the relative toxicity of various components of the inoculants, it may be more the cumulative insult of all the toxins that is important. Infants are often given DPT, MMR and OPV as a first inoculation, to protect them against diphtheria, whooping cough, tetanus, measles, mumps, german measles, and polio all on the same day. More consideration should be given to the variable resistance of the infants and to the question as to whether children should ever be immunized when they are already ill. The writer does not dispute the need for these inoculations, but suggests that the inoculation of debilitated infants should either be postponed, or they should be given the benefit of a sizeable vitamin C boost (500 mg), at the same time, or some time before these inoculations, to protect them against these bacterial toxins.
Animal Studies

Although Kalokerinos was one of the first to draw attention to this problem in human infants, the scientific literature on the relationship between vitamin C status and resistance to bacterial toxins goes back a long way. Work on guinea pigs by Harde, by King and Menten, by Jungblut and Zwemer, and by Kligler has shown that vitamin C deficiency increases the susceptibility of these animals to diphtheria toxin. Moreover, these workers found that vitamin C has a direct detoxifying effect on diphtheria toxin, both in vivo and in vitro. King and Menten observed that there is a wide zone of vitamin C deficiency, without the appearance of scurvy, where physiological processes are subnormal and the animal is more sensitive to bacterial toxin. Any infection, even the common cold, causes a sharp drop in the blood leukocyte ascorbic acid concentration, so Kalokerinos’ advice to avoid inoculation of children when they are ill for any reason would seem to have been entirely correct.

In addition to providing protection against diphtheria toxin, vitamin C is also protective against the toxins of four different varieties of gas gangrene bacteria in mice, as shown by Büller, Souto and Lima (Table 1, p.140) and against tetanus toxin in rats, as shown by Dey (Table 2, p.141). These findings are remarkable in that both rats and mice, unlike humans, have the ability to synthesize ascorbic acid in their livers; clearly sometimes even they do not make enough ascorbic acid to provide maximal protection from these bacterial toxins.

Fukada and Koyama demonstrated that pretreatment with ascorbic acid (500 mg/day), mixed in their soybean curd diet, protected rabbits against the toxic effects of Salmonella typhi endotoxin. Ascorbic acid saturation markedly ameliorated the depletion of liver glycogen after endotoxin, both in intact and in adrenalectomized rabbits, and completely prevented the attendant hypoglycemia.

Not only does vitamin C deficiency reduce the bodily resistance to bacterial toxins, we now know from the work of Aleo and Padh in 1985 that the endotoxin of Escherichia coli bacteria inhibits the uptake of vitamin C by mouse fibroblasts in tissue culture, so a vicious cycle can develop wherein vitamin C deficiency permits the development of infection and infection causes further depletion of tissue vitamin C levels. This undoubtedly accounts for the very rapid onset of vitamin C deficiency in the presence of infection.

Rationale

Until recently it was believed that we need only enough vitamin C to prevent scurvy, but it is now known that significant metabolic abnormalities occur whenever the plasma ascorbic acid concentration is suboptimal. Chatterjee et al. studying guinea pigs, found that a vitamin C-deficient diet caused a rapid rise in the blood histamine concentration when the plasma ascorbic acid concentration fell below the normal level of 1 mg/100 mL (or 56.9 μmol/L); scurvy does not occur until the ascorbic acid concentration falls to one tenth of that value. These workers also found that the blood histamine concentration of these animals was increased when they were exposed to heat, cold, vaccines, toxins or drugs. Moreover, they demonstrated that such histamine elevations could be prevented by vitamin C. They discovered that ascorbic acid promotes the detoxification of histamine by converting it to hydantoin-5-acetic acid and then on to a simple amino acid, aspartic acid.

Clemetson made similar observations of histaminemia in people with suboptimal plasma vitamin C status. The blood histamine rose when the plasma ascorbic acid concentration fell below 1.0 mg/100 mL and was significantly elevated when it fell below 0.7 mg/100 mL (or 39.8 μmol/L) (p<0.001); this included blood samples from 150 out of 437 ambulant people, indeed 34 per cent of
those studied in New York City had suboptimal plasma vitamin C and elevated blood histamine concentrations.

This relationship has recently been confirmed by Johnston et al., who found that 22 out of 135, or 16 per cent, of volunteers on the Arizona State University campus at Tempe, Arizona, had a subnormal plasma vitamin C status (< 28 μmol/L or < 0.5 mg/100 mL), associated with elevated blood histamine concentrations, which were significantly reduced by supplementation with vitamin C.

Addendum

The vitamin C status of the general population is much poorer than is generally appreciated, as shown by Johnston and Thompson, who found plasma vitamin C deficiency (less than 0.2mg/100mL) in 6 per cent and vitamin C depletion (less than 0.5mg/100mL) in 30 per cent of people attending a Health Maintenance Organization (HMO) clinic in Tempe, Arizona.

Likewise the National Health and Nutrition Examination Survey (NHANES III) for the years 1988-94 revealed plasma ascorbic acid deficiency (< 0.2 mg/100mL) in 12% of Caucasians, 15% of Blacks and 9% of Mexican Americans.

The only reason that this is not generally known is that hospital laboratories do not usually measure vitamin C.

The concerned citizens of the National Vaccine Information Center believe that many instances of infant death or brain damage have been caused by inoculations. However, the U.S. National Vaccine Advisory Committee believes that there is almost never such a causal relationship.

Conclusions

It is suggested that any infant with coryza, or any infant or adult receiving an unduly large number of inoculations at one time, should receive supplementary vita-

Table 1. Protective activity of L-ascorbic acid 10 mg daily, given intramuscularly to mice for 3 days preceding a single or a double LD50 dose of four different gas gangrene toxins. Note the surprisingly good protective activity by ascorbic acid, even in mice which make their own ascorbic acid.

<table>
<thead>
<tr>
<th>1 LD50 dose of toxin of Clostridium</th>
<th>AA treated dead at 48 hrs. n</th>
<th>Controls dead at 48 hrs. n</th>
<th>Percentage Survival of controls</th>
<th>Percentage Survival of AA treated mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>welchii</td>
<td>55</td>
<td>14</td>
<td>26</td>
<td>50%</td>
</tr>
<tr>
<td>septicum</td>
<td>30</td>
<td>7</td>
<td>10</td>
<td>50%</td>
</tr>
<tr>
<td>cedematius</td>
<td>22</td>
<td>3</td>
<td>11</td>
<td>55%</td>
</tr>
<tr>
<td>histolyticum</td>
<td>18</td>
<td>3</td>
<td>15</td>
<td>60%</td>
</tr>
</tbody>
</table>

| 2 LD50 dose                         |                             |                             |                                |                                     |
| welchii                             | 57                          | 38                          | 30                             | 0%                                  | 33%                                 |
| septicum                            | 31                          | 15                          | 12                             | 17%                                 | 52%                                 |
| cedematius                          | 24                          | 9                           | 11                             | 27%                                 | 63%                                 |
| histolyticum                        | 18                          | 16                          | 15                             | 0%                                  | 11%                                 |

From A. Büller Souto and C. Lima, Translated and summarized by C.A.B. Clemetson. AA=L-ascorbic acid; n = number of animals. An LD50 dose of toxin is that previously found to kill 50 percent of the animals. 2LD50 is twice that dose.
min C in orange juice, before or at the time of the inoculation. Vitamin C should also be given by injection to any infant who convulses or shows any other untoward reaction within a day or two after inoculation. Moreover, inoculation should be postponed in any infant whose health is seriously compromised.

References
8. Kalokerinos A: The aboriginal infant mortality

### Table 2. Efficiency of vitamin C in counteracting the toxicity of tetanus antigen in adult rats

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Rats</th>
<th>Symptoms</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>2MLD tetanus toxin i.m.</td>
<td>5</td>
<td>All convulsed and died within 47-65hrs.</td>
<td>None</td>
</tr>
<tr>
<td>2MLD tetanus toxin i.m. with 1g AA (per kg body weight) i.p. and 1g AA/kg b.i.d. for 3 days i.p.</td>
<td>5</td>
<td>Only very mild local tetanus after 48 hrs.</td>
<td>All</td>
</tr>
<tr>
<td>AA 1g/kg b.i.d. for 3 days then 2 MLD tetanus toxin + AA 1g/kg b.i.d. for 3 days</td>
<td>5</td>
<td>No signs of toxicity</td>
<td>All</td>
</tr>
<tr>
<td>2 MLD tetanus toxin. AA1 g/kg i.p. only when convulsions began after 16 to 26 hrs. and continued b.i.d. for 3 days</td>
<td>5</td>
<td>Convulsions arrested</td>
<td>All</td>
</tr>
<tr>
<td>2 MLD tetanus toxin. Animals anesthetized after 40 to 47 hours when general tetanic convolution occurred-then AA 300 mg. given IV</td>
<td>10</td>
<td></td>
<td>All</td>
</tr>
</tbody>
</table>

From P.K. Dey19

AA = L-ascorbic acid; MLD=minimum lethal dose.; 2 MLD=twice minimum lethal dose; i.m.=intramuscular injection; i.p=intraperitoneal injection.
12. National Vaccine Information Center at 512 West Maple Avenue, No. 206, Vienna, VA 22180. Phone (703) 938-0342