

Guam Seaweed Poisoning: Questions, Answers and Comments Session

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DR. SCHROEDER: Dr. Yasumoto, have you established the dose response for this toxin and was there enough toxin present in the samples that you tested to explain the symptoms?

DR. YASUMOTO: The samples we obtained were collected several weeks after the incident so we cannot directly correlate the toxin level of the suspect seaweed with the human cases. However, in the first sample we received we detected a level of 800 mouse units (MU-1 MU is enough toxin to kill 1 mouse) and three or four weeks later a second sample contained only half that amount, 400 MU, so we can extrapolate from these results that at the time of the poisoning incident the seaweed may have contained 1,000 MU or more.

DR. KALLINGAL: [Dr. Kallingal is a Clinical Psychologist-Ed.] I was impressed by the presentation of the Guam Environmental Protection Agency (EPA), although I do have some serious concerns about it. As we look at more variables we may actually stifle the process of finding an answer to this problem. At this point I think it may be better to utilize the rifle rather than the shotgun approach and to investigate one variable in much more depth before we bring in many other variables even though they may be related. The examination of secondary variables should be reserved for future research.

With reference to clinical practice, one of the patients who survived would not be alive today had I not intervened because he had requested a DNR (do not resuscitate)—that heroic measures not be used to resuscitate him. His girlfriend had died of the seaweed poisoning and he wanted to die. I happened to be in the hospital at midnight and I was called to talk to him because he happened to be my patient. I was able to get the patient to withdraw his DNR request and he agreed to be treated and, sure enough, the treatment was successful and he is alive today. The point is that there are many other clinical variables that you may want to consider too.

DR. STADLER: Thank you Dr. Kallingal. Would anyone like to comment, especially on the first part of Dr. Kallingal's comments, on the rifle versus shotgun approach?

DR. PAUL: With regard to Dr. Kallingal's comments, Dr. Yasumoto has shown us already that in Japan there is a seasonal component to this problem

and I think that is the most obvious thing to look at first. We thought from the beginning that tying in the reproductive seasonality of the plant was an obvious first step. Whether other factors may have an effect as well remains to be seen.

DR. LOERZEL: There is some evidence that the toxin involved in these cases is very resistant. Dr. Yasumoto mentioned something about toxin being inactivated by ash or sodium carbonate treatment. Is the Guam seaweed toxin inactivated in an alkaline medium?

DR. YASUMOTO: Yes, the Guam toxin is vulnerable to alkaline treatment.

DR. LOERZEL: How alkaline does it have to be? Does this offer a potential for treatment, perhaps by lavage of the stomach with some alkaline compound?

DR. YASUMOTO: Well, we have not had sufficient quantities of toxin to conduct tests so I couldn't say with certainty but in the traditional Japanese way of preparing this seaweed we boil it with sodium carbonate. The toxin isolated from algae loses toxicity in ten minutes in alkaline solution.

DR. LOERZEL: Could this information be used in treating people?

DR. YASUMOTO: The one practical way to avoid incidents is to treat the algae with an alkaline solution before eating as we do in Japan.

DR. ROOS: Well, it is news to me that we might be able to inactivate toxin with an alkaline solution because it was obvious that everything else that we tried had no apparent effect: the seaweed had been frozen, it had been boiled, it had been dipped in acetic acid, it had been desiccated; all kinds of things had been done to it but nothing seemed to destroy it, it's just about indestructible. If you could inactivate it by simply making it alkaline before it was cooked, obviously that would be a preventative measure. I doubt, however, that giving someone gastric lavage with sodium bicarbonate would be useful because once the toxin is absorbed the range of blood pH that people can live with is so narrow that I couldn't imagine that you could make a person alkaline enough to really do anything to the toxin without killing the patient. The most effective approach may be prevention.

DR. LOERZEL: Do we know how rapidly the toxin is absorbed?

DR. ROOS: Well, we know that symptoms begin about four hours after the seaweed is eaten so presumably the toxin has been absorbed by then.

DR. HOUSER: If an alkaline medium inactivates the toxin then we can use a public health approach to control this problem and educate people as to how to prepare the seaweed.

DR. STADLER: Is the sodium carbonate Dr. Yasumoto mentioned what we call sodium bicarbonate or baking soda?

DR. YASUMOTO: Baking powder I think.

DR. PARK: I mentioned earlier that all three patients who died presented with severe vascular dilatation as manifested by marked swelling of the brain, swelling of the lung with edema and so forth. I would like to know if the toxicological manifestations of palytoxin or the other toxins mentioned by Dr. Yasumoto are consistent with the pathological finding I presented. Also, could only one type of toxin have been responsible for all of these findings?

DR. YASUMOTO: I'm sorry to say that I don't know the details of the clinical picture in the Japanese incidents because no medical case records are available. I am quite convinced, however, that palytoxin was not involved in the Guam cases. When I called the physician who took care of one of the patients he said the death was not associated with hyperpotassemia. In palytoxin poisoning the main finding is excessive potassium in the blood due to hemolysis. That's the first indication that palytoxin was not involved in this incident. In the Japanese cases there are no reports of hypersalivation or other signs that we see in mice exposed to the aqueous phase hemolytic toxin derived from the Guam seaweed. So we cannot compare Japanese cases with those we see here on Guam and we cannot say how many toxins are involved. From the *Gracilaria* of Guam we obtained polycavernoside A and B and since both of these give the same symptoms there could be at least two toxins involved.

DR. PARK: So you believe that those two toxins can explain all the symptoms and pathological findings, in these cases?

DR. YASUMOTO: No, I'm not sure I can explain all the symptoms with only two toxins. The only reason I believe these toxins are responsible, or at least a major cause, for the human fatalities in Guam is that they were apparently present at high levels at the time of the incident and were later present in smaller quantities. The aqueous phase hemolytic toxin was always there. If this toxin was involved in the fatal cases, we would expect many more outbreaks to have occurred because *Gracilaria* is eaten in many places by many people.

DR. PARK: I have been here on Guam almost twenty years and this is the first time I ever encountered an outbreak of seaweed poisoning but now I am wondering whether it may happen again. I'm pretty sure that the flea market vendors sometimes get their seaweed not only from Tanguisson Beach but other areas as well so why did it happen only this time?

DR. ROZYCKI: I have a related question for Mr. Borja. How long do you expect to have Tanguisson Beach closed to the Public and what criteria would you use to decide to open it up again?

MR. BORJA: Initially it was the consensus of the Guam Environmental Protection Agency (GEPA), Public Health and the Marine Laboratory to maintain closure of the beach because very little was known about the cause of the incident. I think after this conference we'll still maintain that posture because we still know very little about the cause of the poisonings. Personally, my opinion was to maintain closure for the factors that I've outlined. I thought that, to quote a proverb, "A blessing in disguise" was in effect here because, while we justified our action on the basis of the poisonous nature of the seaweed, closure was something that I would have preferred to have instituted a long time ago because of the other environmental problems.

DR. ROZYCKI: One other question. You were talking about an oil lens that has several hundred thousand gallons in it. Is it possible for somebody to drill down and pump that out?

MR. BORJA: Yes, that is possible, however there are both monetary and technical considerations. The GEPA has agreed with the Guam Power Authority

to discontinue pumping for the present. When you pump an area saturated with oil on top of a layer of seawater you expect to withdraw a good amount of seawater, perhaps in a ratio of five or ten parts of water to one of oil, depending on the pumping efficiency of your rig. Unfortunately GEPA does not have an efficient mechanism to separate the oil from the water. This was the subject of a legislative hearing where a senator asked, "Why don't we just put in an oil rig, suck it all up and get rid of it." Easier said than done.

DR. PEREZ: So far we have looked at what can neutralize this toxin but have we looked at what may make the toxin more lethal? I'm sure that the investigators have looked at the preparation of the seaweed from the time of harvest to the time of consumption but I'm not sure if we've really looked into the environmental factors. Why was the Tanguisson area affected? Why after so many years of a great forensic pathologist practicing here has he seen it only this one time. Japan probably consumes more seaweed per capita than any other country in the world and we have only two known fatalities. It is unsettling for me, because the potential exists for there to still be a big problem out there. It may not be Tanguisson the next time but maybe another ship will go by and dump something out there that potentiates this "toxin" which we haven't really identified. We might again have the same public health problem that we have now and we might have to close all our beaches instead of just Tanguisson.

MR. BORJA: My presentation detailed various environmental factors that exist in Tanguisson Point; they're no secret. While I am empathetic with the position that we should examine the organism instead of the site and although I don't consider myself an alarmist I want to point out to Dr. Kallingal that your own patient stated to me that when he began to wash a bowl of the seaweed he noticed an oily sheen. He poured out the rinse water and repeated the washings several times still noticing a sheen each time. He thought this was perhaps not unusual because he had never prepared or eaten this seaweed before. So he added vinegar, soy sauce, chili pepper and onion to the seaweed and consumed it. Now an oil sheen could mean anything, it could be insignificant or it could be greatly significant. But I think we need to be sensitive to the changes that have occurred in our marine waters over the years. I too have never heard of an incident like this before although I was born and raised here. I think the environmental problems in the Tanguisson area are so blatant that even if you choose to ignore them they will not go away. We discussed the similarity of the situation at Ypao Park where picnickers caused bird poisonings by the inappropriate use of contact pesticides; is it conceivable that picnickers could have dumped some substance into the water at Tanguisson and that poisons could have been absorbed by the algae? We at GEPA thought of all kinds of different hypotheses and we tested them exhaustively. Dr. Yasumoto has stated that he is not sure what mechanism, whether environmental, biological or other, apparently caused a non-toxic compound to become toxic. That's the thought that I want to leave with you.

DR. ROOS: There's an aspect of this incident that's particularly perplexing to me and that is the apparent extreme localness of the phenomena that we are dealing with. I presume *Gracilaria* is harvested from that beach on a regular basis

and sold essentially every week that it's available. It was harvested from more than one location at the same beach on the same day and also sold the same day yet one batch was lethal and another was apparently harmless. To try to blame a generalized agent such as an effluent from a power plant, a passing ship or something else that is unlikely to contaminate one local spot and leave the rest of the area unaffected is hard for me to understand. This makes me suspect that the cause must have been something very, very, local; I don't mean local to that beach, I mean local to a few square feet, perhaps. There are a lot of underwater seepages along our beaches on that side of the island and perhaps one of these vents was contaminated with some substance that in and of itself may not be a toxin but may be a stimulant to the growth of whatever it is that produces the toxin.

In my own mind I'm convinced that Dr. Yasumoto is right that it was an organically produced toxin that killed these people. But what stimulated the production of such a high level of that toxin in a localized area? Rather than looking for diffuse cases that would have been affecting the entire bay, I would look more locally as to what might have been present in very local areas. To my mind it must have been a local stimulating effect that led to a high level of toxicity in the algae, perhaps related to an algal bloom.

MS. CLAUDIA TAITANO: Mr. Borja explained that shortly before the incident ethylenedinitrotetraacetic acid (EDTA¹) had been used in the power plant oil treatment system. Can you explain how the methyl groups of a possible toxin precursor might have been affected? Could that have converted the precursor to a more active compound?

DR. PAUL: Perhaps I can clarify this a little bit. Dr. Yasumoto has described a methanol soluble toxin that he calls the XAD2 toxin. He believes this could be a precursor-type compound that is converted to polycavernoside A or B but we don't know this for a fact yet. It is known, however, that inducible defenses are very common among terrestrial plant systems. If a tree, for instance, is grazed by insects or attacked by fungi it can rapidly produce very large quantities of more toxic or bioactive compounds. That sort of conversion from a less toxic compound to a more toxic compound is certainly not unprecedented, it is very common and well documented. Now we know much less about the same phenomenon in marine systems in general and in seaweeds in particular. If Dr. Yasumoto's compounds are closely related as he suggests they may be, a simple enzymatic reaction might convert one to the other. We just need to determine what factor causes that enzyme to become activated; it could be stimulated by hormones in the plant or environmental factors or grazing history or pathogenic influence on the plant or any number of other factors. We certainly don't have a handle on that at this time but this type of conversion is certainly not uncommon at all. Whether EDTA could do it or not, who knows.

¹ This is not the same EDTA commonly used in seaweed cultures—that is ethylenediamine-tetraacetic acid.—Ed.

DR. YASUMOTO: Well, I think we can also suspect that EDTA could have some effect on the toxin because it has four oxygen molecules making a pore to contain a sodium or potassium ion. When this compound exerts its toxic effects, it may contain either a sodium or potassium ion in this cavity. It is still speculation, but it is possible to link EDTA to this effect.

Another thing I'd like to mention is that one research group studying the *Gracilaria* poisoning incidents in Japan has attributed the cause to prostaglandins. When you wash *Gracilaria* in tap water and leave it in tap water overnight, one enzyme is destroyed but another which converts arachidonic acid to prostaglandin is activated. One Japanese commercial company is taking advantage of this conversion effect by harvesting *Gracilaria*, washing it with fresh water and adding precursor arachidonic acid. It is much easier to produce prostaglandins by this method than by synthesis. Because we are aware of this kind of reaction I am concerned about *Gracilaria* cooking methods; this might be a factor that stimulates the production of toxin.

Another factor that I am concerned about is localized variation in toxicity as typified by studies of *Palythoa*. One patch of *Palythoa* may be highly toxic while *Palythoa* from another site just a few meters away can be practically non-toxic. Some variation in toxicity is known to depend on the sexual stage of the *Palythoa*. When *Palythoa* has eggs it is known to accumulate a large amount of palytoxin. Among corals and algae, when one patch starts spawning other patches of the same species growing nearby may also release sperm or eggs at the same time. That kind of phenomenon could have taken place at Tanguisson Beach because it's so localized. While I suppose that it is possible that detergent, oil or some other pollutant could have caused the damage that initiated the production of this toxin, it is quite difficult for me to accept this line of reasoning. If these effects were due to oil or some other pollutant I would expect the damage to affect all of the bay, not just small patches. There are still many possible mechanisms that we have to test to solve this problem but similar phenomenon are already known in marine ecosystems.

DR. KALLINGAL: I would like to make a recommendation for further research on this weed. It was pointed out that at the time you tested this seaweed you found the toxicity to be high and at a later time it was lower, right? Now when a plant is ready to be harvested obviously there may be less toxicity as opposed to a time the plant is not ready for harvesting. If you break a branch at the wrong time, you've got a lot more pus coming out versus when it's ripe. I certainly would encourage study of different times of harvesting the weed, to see if there's significant variabilities in the level of toxicity. If I may also add to Mr. Borja's statement: I saw a little cartoon somewhere, "don't breathe, don't drink, don't eat, everything is poisonous." While it is true that the environment is becoming terribly poisonous, that is a different issue. We have a definitive issue here: this seaweed has killed three people so we should exhaust study of the weed itself before we look at the global issue.

DR. ROOS: The next time I'm called to the Emergency Room and they tell me there is a patient there that is complaining of tingling around their mouth

and burning in their hands and feet and vomiting and sweating and salivating, what should I do? We threw everything we had at these patients with little effect. Mr. Bignami has said that he uses calcium to enhance the effect of palytoxin so I don't think calcium gluconate was a good idea but I'd like to know what else we should try. Our poisoning incident was similar to the description that I read of mackerel poisoning in Hawaii due to palytoxin and what those people actually died of was an ischemia due to intense vasoconstriction. The logical treatment would therefore be a vasodilator and I'm wondering if anybody has any thoughts about that. What do we do the next time a victim of this poisoning comes in other than say, "We're real sorry, you may die or you may not but there's nothing we can do about it either way."

MR. BIGNAMI: I'd like to comment that we didn't see any evidence that palytoxin was present in the Guam cases nor did Dr. Yasumoto. Administering calcium may or may not have had any effect on the clinical course of your patients. Another consideration is that what stimulates activity *in-vitro* may or may not translate to the *in vivo* situation. I don't have an answer for you in terms of what you can do, but I would just comment that the palytoxin issue is probably not what should be focused on.

DR. O. CRUZ: I would like to know if these seaweeds are found all around the island or are they only found in the areas where sewage or waste products are draining? I heard one of the girls in the Emergency Room say that they have them now in Agat where they never had them before. I've never seen them in East Agaña, but I'm not one of those people who go real deep out into the ocean. If these seaweeds are localized in certain areas only, perhaps studying their lives and how they're distributed in Guam will be helpful.

My next comment is that I've seen many patients before with fish poisoning that we labeled Ciguatera if they had neurological findings but we don't really know what they have because we never test the patients or the fish that they ate. Fortunately, although I have been here for a long time I have never lost a patient to ciguatera poisoning and that is why I didn't get too alarmed when these patients began coming in with paresthesias. I figured I could let my peers sleep a little bit longer and wake them up when it's time for them to come and take over care of the patients. So now should Dr. Haddock revise the fish poisoning and food poisoning questionnaires so that we routinely ask what kind of seaweeds have been eaten and should we have samples of seaweeds in the emergency room so that we can ask patients to point to the one that they ate? When we see a case of numbness associated with eating seaweed should the patient be admitted immediately? That could affect quite a number of patients because many people with just nervousness come in complaining of numbness. The development of toxin-specific diagnostic tests would be very helpful in preventing deaths and this should be a priority of researchers. It was shocking to learn that these patients had died after leaving the ER. It is a nightmare for the physician who must treat these cases because we don't know if we should lavage them or give them cathartics, admit them or send them home. If you look at the number of people who come into the emergency with numbness and paresthesias, it is really quite

large. It is essential that we have some criteria on how we should deal with these cases, specifically how we can make an accurate diagnosis and how we should proceed with treatment.

As far as Doctor Kallingal's patient is concerned, I think he told Dr. Haddock that he gagged himself and he told his girlfriend to gag herself as well in an attempt to get rid of the poison. Although he had only eaten a very little seaweed, Dr. Kallingal had to be called in because he became very emotional when he found out that his girlfriend had died. Maybe we have to consider that patient separately from all the others. But all of us would like some help because we certainly don't want to have another nightmare of this type. Even though we did our best to treat these patients it still eats away a part of us because we would like to have a better outcome.

MR. BORJA: One result I would like to see from this conference is an outright ban on the collection or sale of this seaweed. I recently had the opportunity to sit down with Dr. Hokama of the John Burns School of Medicine at the University of Hawaii—some of you may know that he developed the stick-test assay for ciguatera. I was trying to get his impression of how we could prevent Ciguatera poisoning on Guam; could we use the stick test on Red Snapper, the species here on Guam that is most frequently toxic? Dr. Hokama said, "Forget the stick test, just ban the fish." So I hope that you don't see any more seaweed poisoning patient simply because nobody is eating *Gracilaria* on Guam. I would really like to embark on a high visibility public education and outreach program that includes photographs of the seaweed in its raw and cooked forms so that nobody consumes it.

DR. LOERZEL: One more question of the clinicians who see these patients in the emergency room and have made a diagnosis of Ciguatera fish poisoning: how firm is this diagnosis and is it possible that some Ciguatera diagnoses in the past were really seaweed poisoning?

DR. ROOS: That's possible although I think these cases typically presented and evolved in a different way than the Ciguatera cases we are used to. In answer to the question of Dr. Olivia Cruz, I think we clearly are not going to have a blood test we can order to find out if our patient has this new poisoning, at least not in the near future. Two things are evident from our clinical experience. The only useful test that we saw was the arterial blood gases; when these patients show hypoxia and especially hypercarbia, this should be an immediate tipoff that this is not typical Ciguatera. The other thing that's useful is that their clinical course was very rapid. If a person comes in with typical Ciguatera symptoms, simply observing the patient for a few hours may resolve this question because all of the patients that died deteriorated very rapidly. Within a few hours our cases were obviously sick, even if they looked good when they first came in. I think the only way we can now separate the two conditions is to observe the patients over a period of hours although this may be only separating those that will die from those who won't. I can't imagine anything else we can do with people that come in complaining of numbness and tingling to rule out seaweed poisoning, at least on the basis of the data that we have so far.

DR. NATARAJAN: Dr. Paul has reported that low levels of toxin have been found in algae collected in areas of Guam other than Tanguisson, including remote and presumably unpolluted sites such as Cetti Bay. From a policy development point of view, by closing just one beach we may be giving a false impression to the public that algae collected from other beaches is safe. If somebody gets sick tomorrow from eating algae which was harvested at Agat Bay, for instance, I'm sure I will be in trouble. So I would like to see all the beaches on the island closed to seaweed harvesting rather than Tanguisson Beach only.

DR. STADLER: Thank you. It sounds like there is enough stimulus now to get the appropriate agencies to meet promptly and issue some guidelines for all of us. Since it is now past five o'clock, I would like to thank all of you for attending this conference and for contributing to its success.

The conference is adjourned.