GENERAL DISCUSSION

Moderators

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K. CHIAPPA: Dr. Stockard, have you had a chance to evaluate the Cleveland Clinic data, and explain why they could get such a high abnormality rate? Are they using different measures of interpretation?

J. STOCKARD: They used seven criteria for abnormality, most of which were nonquantitative. Only three of the seven measures really allow even the possibility of interlaboratory comparison and they consist of a 0.2 msec prolongation of the peak latency of any of the seven vertex-positive BAEP waves; secondly, an asymmetry of these peak latencies of greater than 0.2 msec between the two ears; and thirdly, a 50% reduction of any wave amplitude compared to the corresponding wave elicited from the other ear. These criteria, as you know, are quite nonspecific with respect to central brainstem dysfunction, and, in fact, when we applied their criteria to 78 normal infants in our own series who were age-matched and sex-matched, 55 of 78, or 71%, of these normal infants met two out of three of the quantitative Cleveland Clinic criteria for brainstem abnormality as revealed by this test. I can assure you that none of those 55 infants were at high risk for anything. They were chosen because they were audiologically and neurologically normal and never had a near-miss episode, or anything else, for that matter. We followed them for up to 4 years now, so I think it was the nonquantitative nature of most of the criteria they used and the nonspecific nature of the quantitative criteria that they did use.

They did not have their own controls either, which does not help. There has been another study recently from the Stanford group which also found no abnormalities in 10 out of 10 near-miss for sudden infant death survivors. In 10 out of 10, they also found normal BAEP results. The Stanford group had slightly different conclusions, though, with respect to the near-miss-for-SIDS group as a population, and that was that they did not differ significantly with respect to their normal controls.

They used a paired *t*-test to match 1 of 10 individual survivors of near-miss episodes against only one control in each comparison. We took a different approach and used group *t*-tests for comparison of population means between our NMSID survivors and age-matched normal controls and the nonparametric Mann-Whitney U test and F-ratios to further compare the two groups, all tests utilizing information about every member of each group being compared. So I think there is a clear explanation for the subtle differences between our findings and those of the Stanford group. There is an even more obvious explanation, I think, for the differences between both of our groups' findings and those of the Cleveland Clinic group.

I. BODIS-WOLLNER: I would like to ask you if you think the anoxia or anoxemia might be the factor for the borderline BAEP anomaly that you can find in some subjects? Wouldn't you think that cortical evoked potentials, maybe in the somatosen-

sory modality, would be a better test to use because, after all, the cortex is more sensitive to anoxia than the brainstem as far as I know of.

STOCKARD: That is true in adults but not in the perinatal period in which the converse obtains. In contrast to the adult hemispheral pattern of anoxic injury, neonates and infants show a different pattern of selective vulnerability to anoxia, which interestingly reveals that the brainstem auditory structures are among the most sensitive to both ischemia and hypoxemia in the entire brain, with the cochlear nucleus and the inferior colliculus being two of the most vulnerable.

I agree with you that somatosensory evoked potentials will probably be more useful than brainstem auditory evoked potential in assessment of these questions but I agree for a different reason. It is not because they are going to evaluate the cortex but because they are going to evaluate a more extensive length of subcortical afferent pathways in this age group.

Dr. Jerger, I just wanted to ask a question about your slide on 500 Hz stimuli compared to the clicks in terms of your estimates. Actually they were a little complex. Were you saying essentially that your 500 Hz thresholds were better predicted by your clicks than your 500 Hz pips?

J. JERGER: No, I am sorry. That slide is a bit confusing. We compared click predictions with thresholds at 2 kHz, and what we wanted to show was that that prediction was essentially unaffected by the audiometric contour, but that accuracy of prediction of the threshold at 500 Hz was accurate as long as the audiogram was rising or flat but that it became progressively too pessimistic as the audiogram began sloping downward from 500. The click data meant to show that the click prediction was not affected.

K. HECOX: Because we are in such desperate need of such comparisons between clicks and tone pips, do you know what the average discrepancies were for click behavioral thresholds versus 500 Hz and 2,000 Hz behavioral thresholds?

JERGER: You mean the distribution between prediction and the actuality? In these children, the prediction was quite good; the average error was perhaps on the order of no more than 4 to 5 db for the click and somewhat higher, perhaps 10 or 12 db, for the 500 Hz tone pip.

A. STARR: Dr. Jerger, did you mention whether the behavioral thresholds you did with the children were done with those very short duration pips, or with the usual standard long counts?

JERGER: No, the same stimuli. The behavioral threshold to the pip at a 20 solidus/sec rate.

CHIAPPA: Dr. Jerger, some of us might be a little bit happier if you could show us replications of tracings using the same stimulus parameters on the results. I noticed in your slides that the patients you showed all had abnormalities after wave III in addition; and, if that was the case all of the time, how do you know that its effect is at the level of III and not at the level of V? Occasionally you can find patients, MS patients, who have normal I–V separations and absent wave III. Did you have any patients that showed that effect?

JERGER: We found five in our series of MS patients who showed normal wave III's but absence or delay of IV-V, and in all of those cases MLD was quite normal so that we felt that it was not a question of generalized abnormality of all waves because they specifically had normal III's and a normal MLD but did not have a good IV-V.

M. HITERBOCKER *(Downstate Medical Center, Brooklyn, N.Y.):* Dr. Stockard, I was wondering whether you had an opportunity to consider the time of day of testing or relationship to the sleep or the state of sleep. Perhaps the diurnal rhythms or perhaps cortisol secretion or some other substance is impeding your almost normal results.

STOCKARD: Yes, we tested the infants during REM as well as non-REM sleep, as well as during wakefulness and there was no difference. We did not expect to find one since we had found no difference between those three states in our age-matched normal controls either. As far as time of day is concerned, it has been shown that there is a 0.2 msec per degree Celsius shift in wave V latency as a function of the circadian diurnal core temperature variation in humans. There is also a 0.1 msec per degree Celsius variation in the wave I latency. So you get a ±0.1 msec diurnal variation in I–V interpeak latency as a function of body temperature. We had our infants within 0.05°C at the time they were tested so the control for that variable was rigorous.

Of course, I should point out that the hypothesis, the null hypothesis, that there were no significant differences when individual infants were considered versus our normal age-matched control population, was quite adequately confirmed. It would be much more important to take those factors into account if one were saying that near-miss survivors did differ as individuals from a control population. And that, of course, was the contention of other groups.

R. GALAMBOS: We were shown some ABRs from people with multiple sclerosis that were rather badly smashed. For example, some of Jerger's recordings looked as if they had only wave I, and yet these people were responding to sounds really quite well; and of course Stockard has presented us in the past with a picture of an individual with only wave I who was audiologically normal. Dr. Starr, can you tell us how it can be that a person with virtually normal audiometric behavioral responses can be giving no brainstem response with the exception of wave I. This fact really sounds as if it is giving brainstem audiometry a pretty bad name. If someone with normal hearing can have no brainstem response, then what exactly is it that we are working with here?

STARR: Actually Dr. Galambos knows the answer to that. There are two ways to answer it. One is that all you need is perhaps one eighth-nerve fiber to work, or very few eighth-nerve fibers to be working and very few brainstem fibers to be working for hearing to be preserved, particularly if the changes occur slowly over time. For instance, you have studied cats where you sectioned 99.5% of visual optic nerve fibers, yet you can get very nice visual functions from them. That can be one interpretation.

The other is that the auditory brainstem responses measure a very limited portion of the auditory pathway and actually measure only those parts that depend upon synchrony of firing. To get the potentials into the averaging process, all of the nerve elements have to be going together, but, for hearing, you may be able to get along very well with asynchronous input because we have a time constant in the auditory system that you can take information over time—long tone pips—and integrate them and get a certain amount of hearing. However, those two possibilities are, in my mind, synchrony, and for that you do not need many fibers.

GALAMBOS: Dr. Starr, you left us with the impression, I think, that you believe that it is the synaptic events that are responsible for this brainstem response, and I had hoped that you would have brought out the other theory.

STARR: No, I actually think most of it probably comes from nerve fiber pathway activity because that could mostly account for the latency changes across the scalp. I do not want to leave out synaptic activity, though I think perhaps with some of the components there will be some evidence of synaptic activity, but I think most of the brainstem response is a series of traveling waves in nerve fibers giving us not only these amplitude differences, but also latency differences.

J.J. EGGERMONT: Yes, especially the last case I showed; it was a case of auditory nerve tumor, and on the tumor side there was only a wave V from the 1–2 kHz area, predominantly from the 1 kHz area actually. Although the thresholds for 8 and 4 kHz were not that much lower, there was no way for wave V to go through. That was the point, that even with a small wave I there were some problems. What we *are looking at*

in the brainstem are synchronous responses, just the functional connections for probably short-latency fibers or fast forming fibers, which Dr. Galambos used to call time-keepers. That may be just a small part of the auditory system as well. And I think hearing and the brainstem are intimately related in subjects with normal brainstems and brains, and if you assess that the brain and the brainstem is normal you would only occasionally find no brainstem response and normal hearing. I would suggest that you check the patient again in that case. In normal hearing especially, or even in peripheral hearing loss, we use the high-pass masking technique, the subtraction technique, to derive audiograms, and they are very accurate. If you use tone pips and you have a properly shaped tone pip with good spectral content, then you have as Dr. Suzuki has shown here the capability of arriving at the correct audiogram.

Dr. Jerger had a little bit of a problem with his 500 Hz tone. Maybe it did not have good spectral properties, let's say only one or a little bit more than one period of 500-Hz signal. In that case, actually, a very broad spectrum exists. In fact, in steep audiograms the limiting factor is the slope of the spectrum of the tone pip, so that fits in all quite nicely.

The important point is what Dr. Stockard said, that the statement that the ABR is not necessarily related directly to hearing, is not completely correct. I think if you can rule out brainstem or brain abnormalities, it has a lot to do with hearing. At least it predicts hearing thresholds very accurately.

STOCKARD: I agree with you that the ABR is intimately correlated with hearing if you have a normal brainstem. Dr. Galambo's question which never was really addressed directly, was a case of a patient with multiple sclerosis with lesions intrinsic to the brainstem, and I do not think that the specific example that he gave has yet been addressed. It is intriguing and not explained by anything that anyone has said thus far really: a patient with multiple sclerosis who would have an eighth nerve action potential only—when we know that only oligodendriglia making central myelin are involved and not peripheral nerve or distal eighth nerve myelin. Thus why would the abnormality begin with wave II? Why would there be no central components, assuming that most of the portion of myelin covering the most proximal eighth nerve and all the distal nerve was not involved by MS?

I think the lesion to answer your question, in our three cases, was in the most proximal portion of the projections from the cochlear nuclei intrinsic to the brainstem, those projections which are involved in subserving this synchrony and phase comparison between the two ears that Dr. Starr alluded to. That would account for the presence of wave I only and no wave II, or of the subsequent components.

ALLEN LUGGET *(Einstein Medical College, Bronx, N.Y.)*: I would like to echo Dr. Starr's comments about the ultimate nerve physiologic source of the brainstem response in studies in the monkey. While we can record peaks of many millisecond duration, I think potential within the structures of the brainstem auditory pathways, especially within those that have a degree of organization in laminar structures, namely, the inferior colliculus and the superior olivary complex and cochlear nucleus, we think specifically of the dorsal cochlear nucleus. These potentials are not recordable more than a few millimeters away from these structures, and it is the shorter duration potentials recorded within the fiber pathways that can be traced into the far field.

I would also like to carry the multiple generator identification back to the monkey equivalent of the human wave II, which in some cases can be distinguished as having two sources on surface recordings. One of these is the cochlear nucleus and the other one turns out to be the N2 component of the eighth nerve action potential, and one of the published cases—well most of the published cases of humans with acoustic neuronomas—only display a wave I. There is one case in the Starr-Hamilton paper,

which displays both wave I and wave II, and several cases reported by Stockard *et al.* that show this. This may reflect the N1 and N2 components in that case, and this, in fact, was what Stockard *et al.* and, independently, Moller *et al.* postulated in recent publications.

STOCKARD: That is a good point. In addition to the Starr and Hamilton case, Drs. Chiappa and Goldie and we also have cases of complete brain death in which there is preservation of wave II, and we found that this wave II differs from the wave II seen in routine BAER testing and that it corresponds exactly with N2 of the compound auditory nerve action potential recorded simultaneously with electrocochleography. It is only seen at higher intensities and has a different field distribution from that of that wave II, obtained at lower intensities, which also has a slightly longer latency.

HECOX: One of my pet peeves is going on here, and I am astonished that Dr. Jerger is tolerating it, given his long-standing record of looking at the auditory system in manners other than those characterized as the audiogram. We are being told that it is astonishing that we are not predicting hearing by these tests—hearing, of course, being equivalent to an audiogram. I think that is a dangerous supposition that when we are trying to characterize complexities of hearing in the pathologic patient, particularly those with central auditory disorders, that we should have any hope or be at all surprised that there is a lack of congruity between audiometric thresholds and super-threshold behavioral measures, super-threshold BAER measures, and super-threshold any measures. That is a long-standing principle in animal work, and I think that is an error we need to stop making.

The other thing is that the brainstem response has a lot to do with hearing; but again, if you have evidence of brain disease, then all bets are off because many, many very important inner ear phenomena are very closely paralleled by BER activity traveling wave and frequency specific activity. Tuning curves have now been done, very nicely matched auditory nerve tuning curves, cochlear nucleus tuning curves which correlate with the BER, and it does have a lot to do with hearing. As always with clinical measures, one has to be a little bit cautious about what one says and what one tries to do with that particular window on the auditory system.

JERGER: Dr. Hecox makes a very good point, but while patients with multiple sclerosis typically have normal audiograms, they typically have far from normal auditory function, and I attempted to show one example of this in the masking level difference effect, which can be quite abnormal in the presence of normal audiogram.

EGGERMONT: Another example of a hearing threshold problem is that in a series of 43 tumors we found subjective hearing thresholds estimated with the tone pips and the electrocochleogram correlated very accurately with the hearing threshold. But if you looked at wave V, there was no correspondence at all. The absence of wave V, or the problems that you are having correlating wave V thresholds or the presence of wave V, is eliminated by looking at electrocochleographic thresholds.

If you looked at mere speech discrimination, and so on, and included these things, then you can be sure that if there are problems in finding or identifying wave V, you have a complex problem which is quite different. There are more problems with the higher functions, so I think threshold is mainly, at least in these cases, a peripheral phenomenon, and all the other things are probably at the brainstem level or maybe above that level dominantly. Then the brainstem response would not be a good estimate.

D. KURTZBERG: Dr. Jerger mentioned some lingering problems in his introductory remarks. If I am not wrong he mentioned false-positive results, do you care to elaborate about this?

JERGER: Yes, there is quite a variation in the reported prevalence of false-positive results in identifying acoustic tumors, for example, ranging from as low as 1% or 2% to

as high as 30% in the work of Clemis and Magee. It is a muddy problem because the criteria for what constitute abnormality are not uniform across most of these studies, compounded by the fact that when the degree of peripheral sensitivity loss exceeds the limiting value, then the results can be noncontributory in the sense that absence of the response could be due to the severity of the peripheral hearing loss, and it is that constellation of findings that I refer to as the false-positive problem.

It was reamplified in a recent publication *Scandinavian Audiology,* which was a report of a symposium in Scandiavian countries summarizing their experience, and it was their uniform conclusion as well.

M. KLEIN: Dr. Eggermont pointed out that the brainstem response differed depending on what temporal frequency was the dominant stimulus. Could some of the other speakers comment on how the brainstem responses differ so according to the different temporal frequencies? I would be especially interested in Starr commenting on that. The importance of this fact is that it seems to wipe out the simplicity of the source story.

STARR: By temporal frequency I assume you mean different spectral components. The brainstem response in normals is dominated by the high frequency input so that the thing that Dr. Eggermont was referring to and Jerger was showing, those longer latency waves V from the apical parts of the cochlea, usually occur out of phase with each other and they cancel. The problem comes in though when you have significant cochlear damage or implied lesions of the eighth nerve; for instance, a tumor that selectively affects the high frequency portions of the cochlea. Then you are going to get problems in interpreting your evoked potentials, and that is one of the major issues really in the use of auditory brainstem potentials in neurological or central applications. The interpretation is confounded if you do not know very much about what is happening at the periphery.

WIEDERHOLT: Dr. Starr, you told us rather convincingly that in the identification of the generator sources that none of the experimental methods reveal very acceptable anatomical correlations. What would you suggest to do to precisely localize or identify these generators if you could set up the ideal experiment? Also, you said you felt that most of the activity recorded on the surface is probably generated in pathways. What is your evidence for that?

And, Dr. Stockard, in regard to the four or five adult patients you showed with the central nervous system apnea syndromes, from what I gather they were pretty sick and had rather serious brainstem pathology. What is the clinical value in those patients getting the BAERs?

STOCKARD: In two of the patients, there was no other evidence, not even corroborating clinical evidence, for brainstem pathology. The patients just suddenly presented with a central sleep apnea syndrome. The BAERs indicated that structural brainstem pathology was the basis for their syndromes and only up to a year later did they develop other signs of a brainstem lesion.

In contrast, our patients with central sleep apnea syndromes who have normal BAERs have up to five years of follow-up now and never have shown any evidence for neurologic lesions. It is a useful diagnostic screening test for patients whth central sleep apnea of later onset in life as it clearly and reliably differentiates those who have central sleep apnea on the basis of progressive, structural brainstem lesions from those who do not.

STARR: Each of the techniques we use has limitations. Initially when we used the technique, I was very enthusiastic about recording techniques in the deaf. I thought *that* would give the answer and there are limitations, of course, just like the new enthusiasm for the current density source that Dr. Vaughan talked about. I do not

think that that is going to tell us what is really happening at the scalp, but it will tell what is happening in the layers beneath perhaps.

Each of the techniques has had limitations. If we put them all together, they would build up a set of arguments which all point to the fiber tracts. The ideal experiment would be to make a lesion that would have no remote effects and that would affect only the particular structure. Right now we are toying with demyelinating lesions in experimental animals in a way that we can control and which will affect the axons but not affect the cell bodies. But I think we are going to have problems with that too.

The evidence for fiber tracts is really a deductive one. I do not have any such evidence. If I did, I would have shown you the experiment. It is all deductive, and the evidence tilts toward the fiber tracts. But I am holding it back because the nasopharyngeal data showing that interesting polarity switch across the brainstem that cannot be accounted for by a fiber tract. It has to be a synaptic potential, but the issue is: Is that thing that I am recording in the nasopharynx being reflected up on the surface or not?

BODIS-WOLLNER: Returning to the paradox that Dr. Galambos so happily defined for this discussion, I have a feeling that we should take out data more seriously and trust them. And what I mean by that is that maybe we should ask questions as he did and go one step further and ask about the pathophysiology of the disease. My reasoning was summarized yesterday for visual evoked potentials where I tried to muster the arguments which point to the fact that in demyelination, a conduction velocity decrement in multiple sclerosis does not account for all the observed and well-documented phenomena in visual evoked potentials as a result of multiple sclerosis.

That does not mean that the explanations are all in, but I wanted to suggest first that we use our evoked potentials in a constructive way in terms of research and trust them. If we trust them without noise, we know that it is a fact. Then we should dare to ask the question: Is it really this pathophysiology which we thought was there? Therefore, I refer to the question from Dr. Stockard: What is the actual evidence for what you said about a single oligodendrocyte being involved in the MS patient who has this type of audiogram and auditory brainstem response?

STOCKARD: I did not say that. I indicated that by virtue of the known involvement of oligodendrocytes (versus Schwann cells) by the disease and therefore central instead of peripheral myelin by the disease, that a plaque of demyelination intrinsic to the brainstem would have to be held accountable for the loss of all waves after wave I in the three cases we reported with MS and with only wave I present. The other possibility is that the small amount of central myelin, supplied by oligodendrocytes, that covers the proximal part of the eighth nerve was involved. This cannot be ruled out in these cases. But the absence of *any* evidence of auditory nerve dysfunction on extensive audiologic testing makes this alternative explanation unlikely. That evidence pertains to what is already well known about the disease, not to a subset of MS patients who have BAER abnormalities.

BODIS-WOLLNER: There have been several other demonstrations, for instance, from Mary Bornstein, who is at Albert Einstein, showing changes at the dendrites. At that time the vogue was to pin the disease to autoimmune processes, but the demonstration of dendrite abnormalities is a fact.

JOSEPH DANTACITY: *(Medical College of New York, New York, N.Y.)*: Even our super-threshold tests are not always sensitive to eighth nerve or brainstem involvement. Even the tests that we do using normal speech discrimination testing are insensitive in many cases to eighth nerve lesions that are fairly large and do, in fact, affect brainstem evoked response measures. Dr. Starr, in regard to your mapping

work, what effect would the plane of this potential have on the localization of those data rather than purely the specific proximity to the electrode with a plane of that potential?

STARR: By plane I assume you mean the vector, which is the most important thing. For instance, if you record between the ears in a horizontal plane, waves IV and V seem to disappear and are replaced by a component of lower amplitude that occurs intermediate between IV and V. Wave III becomes extremely broadened and we end up there with wave III of a dipole, and you think of it as a dipole. The dipole is in a horizontal and a vertical direction, and so the plane is the most important thing. This is the standard plane that we now use, the vertex to the ipsilateral mastoid.

If I had to do it all over again I would record vertex against the back of the neck, but I do not have to. I am going to stick with this technique. Clinically it works very nicely, but we are sampling only a limited portion of the vectors that way.

DANTACITY: The question I was specifically concerned with regards the mapping that you presented in trying to localize specific areas for the locus of potentials. Could the fact be that you generated a larger potential perhaps at the forehead even when you were using the back as a reference? Could that not be because you were checking electrodes for the neurons that were firing in that plane? And had you measured two potentials simultaneously you might be able to vector in on the source that way?

STARR: The sagittal array is very poor because the electrodes have a different relationship to the back of the neck, but on the coronal plane they are all equidistant. But I do not know the answer to your question. We use two electrodes, and I am sure we can do better.

CHIAPPA: Dr. Stockard mentioned one fact about central myelin going out onto the eighth nerve into the canal, and, in fact, Dr. Letterman of the Cleveland Clinic is studying a series of patients who have currently large multiple sclerosis plaques in the eighth nerve. I do not think we should be surprised at the difference between the brainstem auditory evoked abnormalities and conventional behavioral audiometry. As Dr. Jerger has shown in one technique, if you continue and test behavioral hearing in other ways—for example, Housler and Levine used interaural time discrimination—you can find behavioral abnormalities in all of the patients with multiple sclerosis who show central brainstem auditory evoked response abnormalities.

So I do not think that this divergence really exists when you use better tests. The false-positives in acoustic neuromas are largely a factor of not using interwave separation criteria. The studies that have used interwave separation criteria have had very low incidences of false-positives and very low incidences of false-negatives. There really is not a high incidence of false-positives with acoustic neuromas with this test.

Dr. Starr, I was very surprised to hear you say that midbrain lesions knock out waves IV and V, since one of the very few cases published in the literature in humans of midbrain lesions was published by you, and in fact the point you made in the case was that this midbrain lesion had not affected waves IV and V. Perhaps you have some new human, clinical pathological correlation data that you would like to share with us.

Also, I would disagree with your formulation of ipsilateral versus contralateral recordings showing different wave forms in a patient with a brainstem lesion and saying that this is evidence for different generators of the wave recorded in those two different derivations. Why could the explanation not be that the lesion has changed the generators in such a way that the potential field distribution is changed?

The question that Dr. Stockard and Dr. Desmedt raised of short-latency somatosensory evoked potentials in near-miss for SIDS infants has been investigated by us, and we have not found any abnormalities in the short-latency somatosensory evoked potentials in those infants.

Finally, I would like to take a difference of opinion with Dr. Jerger's initial comment with respect to the fact that you have to be an audiologist to interpret these things. As a neurologist I could say that you have to be a neurologist to interpret these things in diseases of the central nervous system. I do not think that either statement is necessarily true and both fields can interpret these brainstem auditory evoked responses.

STOCKARD: I think you have to be an otoneurologist actually to interpret them.

STARR: I think Dr. Chiappa is quite correct that another interpretation for that shift is that you have a shifting vector. When I was brought up, I thought of generators as a point source, but when I think of generators as a vector, then the different planes will record different vectors and in fact different generators. And you are quite correct that in the case that I reported of a midbrain lesion, if the midbrain lesion is restricted to the tectum, there will be no change in the IV-V complex; but if the midbrain lesion extends down into the tegmentum and gets into those fiber tracts, then you will get a change.

M. COHEN: *(City University of New York, New York, N.Y.)*: Dr. Stockard, do you have any information on the use of vitamin therapy in SIDS. I refer to a report by Orlowski.

STOCKARD: Lonsdale and Orlowski reported, in two cases, reversal of putative brainstem auditory evoked potential abnormalities in near-miss survivors by large doses of thiamine. Perusal of those two cases reveal that they were not abnormal centrally to begin with; that is, the BAEP findings did not reflect retrocochlear auditory dysfunction. The sorts of abnormalities that those patients had were much more likely to be attributable—just on the basis of the data presented itself—to technical and/or peripheral hearing problems. So I suspect that, given that was the most likely etiology for the so-called abnormalities to begin with, the correction of technical and/or peripheral factors was also the most likely etiology for their so-called reversal.

The two patients of Lonsdale who responded to thiamine (B_1) therapy had known disorders of thiamine metabolism–Leigh's disease in at least one case–and so even well-documented BAEP improvement would not have surprised me in these patients. Possible alterations in metabolism or deficiency of B_1 in other infantile apnea syndromes is also quite plausible, and needs to be systemically evaluated.

We have studied patients with Wernicke's encephalopathy both during the acute phase in which they were ophthalmoplegic and demented and ataxic, and after high-dose vitamin B_1 therapy and found in those cases who showed dramatic clinical improvement, absolutely no BAEP change in response to thiamine treatment.

COHEN: Dr. Eggermont, the brainstem potential has been described many times by several authors as a series of fat, short wavelets superimposed on the slow positive upswing of the baseline that peaks at wave V. There is some recent information as to a differential effect in MS patients on the slow-wave component as opposed to the earlier preceding pathways. Have you looked into this question with regard to deriving evoked potentials from narrow bands along the cochlea? And is it different from the slow-wave component as opposed to the short waves?

EGGERMONT: I did not look specifically for these effects. We use a filter setting of 100 Hz to 3 kHz, so I think most of the slow wave was missing. And I do not know if they behaved differently.

QUESTION: Dr. Suzuki, do you have any pathologic data to support the inference that your electrophysiologic changes are due to peripheral involvement of the auditory system in kernicterus or to hyperbilirubin encephalopathy?

Our studies in the newborn in the intensive care nursery population have, in a small group of patients, pointed towards a peripheral involvement with delays only

being found in wave I, and then subsequent components. But I am wondering whether it is the cochlear or the auditory nerve that is being affected by hyperbilirubinemia?

I would like to ask Dr. Stockard if he has evaluated that particular risk factor.

SUZUKI: Well, we have no pathological data, but I think I made a conclusion that at least some of the cases had a peripheral lesion. We cannot exclude brainstem lesions, however: so this is a restriction on this test. But mostly, I think, people believe the hearing impairment in kernicterus must be from the brainstem lesions. The point of my report is that there are cases with lesions in the peripheral end organs.

STOCKARD: We have seen both peripheral-type and so-called central-type abnormalities separately in patients with kernicterus, a few of which had autopsies. In the cases in which the abnormalities were of the retrochochlear type they began with wave II, and the two patients had very heavy staining of the cochlear nuclei, which are thought to be selectively vulnerable to hyperbilirubinemia.

HECOX: This is a hard problem primarily because it occurs in the context, at least in the United States, of two entities, one of which is the asphyxiated acidotic infant, and we well know that the distribution of pathology in those cases is very much in the cochlear nucleus, inferior colliculus, and so on, and paralleling the metabolic rates in those areas. Thus it is very difficult to disentangle the effects of asphyxia from the effect of hyperbilirubinemia.

My own feeling about that is that it is probably only in those infants who have hemolytic syndromes who are term babies and have enormous elevations in their bilirubin, out of the context of any asphyxia, that we are going to answer the question.

I have seen a number of kernicteric babies, almost all of whom had some degree of peripheral loss with recruitment implying a cochlear disease not a nerve disease, the presence of recruitment there being helpful. Some of those babies had central auditory problems but almost all of them have had significant asphyxia at the same time. We have three children with hemolytic syndromes where the bilirubin level was greater than 30 and none of those have had any abnormalities centrally but have had marked abnormalities in the periphery, so our suspicion is that it is a cochlear impairment even though staining is surely demonstrable along the central auditory pathway.

S. JONES (*Medical Research Council, London*): I would like to bring up something that nobody else has mentioned very much so far, and that is a question of the polarity of the wide band click. We have not done very many brainstem responses but we were very impressed by the waveform difference betweeen a compression and a rarefaction click, and yet obviously, the click contains compression and rarefaction phases no matter which way it is, according to the manual.

But do you see waveform differences that are consistent in the individual latency shifts to the early components, although quite often wave V is of the same latency for the two polarities. These changes do not seem to be very consistent between individuals. I am wondering if any of the speakers has any information on that?

STOCKARD: We studied this extensively, so extensively in fact that I do not even know if I want to get into it. You may not have seen our article on this complex subject, which I shall send you in lieu of bogging down the discussion in this particular Pandora's box we opened several years ago.

CHIAPPA: That is true; you studied it before we did. We studied 600 neurologic 598patis of whom we found 20 patients with neurological diseases, mostly multiple sclerosis, who had the unusual finding of having completely normal brainstem evoked responses through wave V with one click polarity and having absolutely no wave V with the other click polarity. I am going to show some of these in the Roundtable Sessions later. We never saw this effect in 45 normals and I guess you have done more normals. The normals show subtle but statistically significant latency shifts and amplitude shifts but nothing as dramatic as this and, in fact, we also found in those

patients that if you then reduced stimulus intensity, the previously absent wave V would suddenly appear. I am sure that Dr. Eggermont will have something to say about that. But it turned out that, of those 20 patients culled from a series of 600, 17 showed that effect such that the wave V was missing with rarefaction clicks but present and normal with condensation clicks, and the other 3, of course, were *vice versa.*

We have been trying to develop ways of determining whether this is a central or peripheral effect. Some of the patients who showed this effect had perfectly normal conventional audiometry, and beyond waiting for a patient who has a focal lesion, the only other way we can think of is perhaps using the binaural interaction waveform, which appears to be clearly a centrally produced effect only. If anybody has any other suggestions on this problem or we can bring it up again in the Roundtable Sessions.

STOCKARD: In those patients with MS or whatever in whom wave V disappeared as a function of acoustic phase, how can you be sure that wave V did not merely fuse with wave IV? This is a very characteristic change in waveform morphology as a function of click phase from condensation to rarefaction, which is the direction of change that resulted in disappearance of wave V in 17 of your 20 cases of phase-related "abnormality."

CHIAPPA: Because IV was present at both click polarities with absolutely the same latency and shape. When you see the figures, it is clear to see that what has happened is simply that wave V has reappeared. I do not think there is any question of that being the problem.

STOCKARD: What I am saying is that is what happens in normal subjects. In about 6% of normals you can get complete merger of wave V with wave IV, simply as a function of changing the click phase.

CHIAPPA: Yes, but what I am saying is that with one click polarity we have four peaks and the fourth peak has a latency of 5 msec; with the other click polarity we have five peaks, and the fourth one is still at 5 msec, and the fifth one is at 6 msec.

When I show you the figures and I think you will see how the problem is resolved.

M. ROCOL: *(Cleveland)*: Dr. Starr, in regards to your patient with a tectal lesion, does that mean that waves IV and V are generated entirely caudal to the colliculus? And would you care to comment on the generation of waves VI and VII as to where they might arise from?

STARR: I only have that one human case and I have not heard of any others. The only reason we knew the lesion was restricted to the tectum was because the surgeon went in and he actually took a biopsy of the inferior colliculus and there was an astrocytoma, and when the patient died it still had not spread down.

So I think that the wave IV/V comes from below the tectum. But I still think that they both come from the midbrain and probably from the lateral lemniscal fibers.

Waves VI and VII are very variable. That is the whole problem of trying to do the pathophysiology of it. I have some personal thoughts about VI and VII, but I think, regarding what Dr. Eggermont has said, they are another volley coming through the auditory system and not from an anatomically higher site.

JANET CAMP *(New York)*: Dr. Stockard, I am interested in your hypothesis that the slight prolongation of latency in the SIDS infants is a result of the hypoxic episode that they had experienced. I wondered if you had any chance to follow these infants up later to see whether this is a permanent or a transient effect and also whether you have had any opportunity to examine infants who have had an hypoxic birth, low Apgar scores, or whatever?

STOCKARD: That is a good question. We have followed the near-miss-for-SIDS survivors and infants who have recurrent apneic episodes. The latter will continue to diverge from a normal age latency function for I–V interpeak latency. Those NMSID

survivors who do not have recurrent near-miss episodes will no longer diverge. We have not followed them long enough to see if they converge ultimately with the mean and reach normal values. On limited follow-up, they usually stay parallel with the normal latency–age function while 1–6 months of age and then begin to converge with normal age IPL functions; that convergence usually correlates with disappearance of apneic tendencies and abnormal periodic breathing during sleep.

As for your second question, there are people here who have studied that much more intensively than I. The question is, what are the effects of perinatal asphyxia in general? I think I would like to ask Dr. Hecox to comment on this. I could give you just one caveat. Unlike in the adult age group in which—in the clinical context of anoxic encephalopathy—these abnormalities have fairly straightforward and often unfavorable prognostic and diagnostic significance, all bets are really off in the perinatal age group. This is probably for a variety of reasons: differing ability to withstand the insult, greater plasticity, and larger neuronal reserve. Dr. Hecox, and I think Dr. Starr also, have seen cases such as we have seen in which patients have, as the result of acute hypoxemia, lost all brainstem auditory potentials transiently. Subsequently, they regained not only normal BAEPs but had normal neurologic outcome.

HECOX: I am going to discuss actually this afternoon some of the recovery function phenomena that you can encounter in that group so maybe we can defer that. Maybe Dr. Galambos has some other comments because he has as much experience as anybody in that area.

GALAMBOS: Yes, there is developing a very interesting and knowledgeable literature on the question you asked. There are several aspects to you question. In the study that we published a year and a half ago in *Pediatric Research* we had a hundred youngsters of whom 22 had really very low Apgar scores, and out of this 22 only 11, if you want to say only 11, had permanent damage, as measured by their brainstem response. They all had sensorineural hearing losses, and none of them had neurological disorder as evidenced by an increased I–V interval.

So here you could split two groups of asphyxic babies, approximately equal in external measures. What is the reason that half of them had abnormal ABRs and the other half did not? The answer, the best correlation we could get by going through their clinical histories, was that those babies with troubles were exactly the ones who had repeated bouts of acidosis during their postnatal history.

That is to say, they were roughly equally acidotic and asphyxic at birth, but then if they had other troubles like RDS syndrome, and so on, and were clinically very badly in trouble afterwards, then they were likely to be in our group of damaged people by ABR.

EGGERMONT: I would like to join the few comments about wave VI. There really is a wave VI. About 60% of wave VI, in a normal click response, comes from the basal portion of the cochlea and is actually wave V. If it shifted a little bit it might in fact reduce the whole thing because then you do not have a sharp peak anymore but just a broad thing filling up that negative area of the wave V.

I would ask everybody to be very careful about any statement about wave VI in just a normal click response because you do not know what you looking at, definitely not.

The next thing is about rarefaction and condensation phases in the narrow band responses. We have studied rarefaction and condensation phases and their effect. We should expect especially at the low central frequencies about a half period shift in latency for the rarefaction click and the condensation click because only one phase excites the nerve fibers. Now you do not find it, not in wave I, and not in wave V. The only thing that happens is that there are unexplained amplitude variations across the narrow bands. And these are more or less consistent in normal subjects. We do not find

too much change that might be due to some unexplainable latency difference between I and V because I–V for rarefaction and I–V for condensation in the narrow bands are always the same. So it is definitely not. It must be some interacting effect due to different contributions from different parts of the cochlea. But to be conclusive about it, you would have to do about 50 normals to get out of this problem.