I seriously read the Special Article by Dr Carlisle [1]. As is well known, Dr. Carlisle is interested in the area of peri-operative medicine [2]. Similarly, I am interested in this area and have made efforts to improve the postoperative outcomes of surgical patients. Additionally, we have provided information on diaphragm muscle dysfunction and its improvement in animal studies. However, this article by Carlisle can obviously be very damaging to me and I want to answer it seriously, but I am not a statistician. I can only offer a few elements of rebuttal at this point.

Postoperative nausea and vomiting (PONV) remains a common complication for surgical patients. In addition to patients’ discomfort, the physical act of vomiting may increase the risk of aspiration, wound dehiscence, and delayed recovery and discharge times [3]. For the management of PONV in high-risk patients, we have evaluated the efficacy and safety of antiemetics, including serotonin receptor antagonists, droperidol, metoclopramide and others, as first reported by us in 1994 [4]. Factors affecting PONV include patients’ characteristics, surgical procedure, anaesthetic technique and postoperative care [3]. Patient-related factors associated with increased PONV include age, female sex, obesity, a history of motion sickness and/or previous PONV, and menstruation. Increasing age during adulthood is associated with a decreased incidence of PONV. Considering these factors, most reports by us have excluded patients aged over 60 years, those who were obese, those with a history of motion sickness and/or previous PONV, and those who were menstruating. Being different from European and American nations, most Japanese people are middle-sized. Consequently, patients’ characteristics would be comparable in our series of clinical investigations. In addition, middle-aged Japanese women suffer from specific diseases, such as uterine myoma, breast cancer and goitre. Difference in diet, level of stress, etc can certainly produce a bizarre distribution of data specific to Japanese people. We cannot select the patients of our studies as broadly as we would want to.

As described in Kranke et al.’s letter and my response [5], granisetron, classified as a serotonin receptor antagonist, lacks the sedative, dysphoric and extrapyramidal symptoms associated with non-serotonin receptor antagonists. It is known that mild headache is one of the adverse effects in patients receiving granisetron. As mentioned in our published articles, trained nurses asked the patients about their conditions postoperatively. According to these results, in our manuscripts, its incidence was verified as approximately 10%. The researchers asked the patients if they experienced headache, dizziness and drowsiness, with only two possible answers (yes/no). This assessment might have caused the identical results regarding the incidence of postoperative adverse events. When analysing the degree of headache in detail, different results may have been obtained.

The diaphragm is the most important muscle in the respiratory pump. Since publishing our first laboratory report [6], we have studied the effects of several drugs, such as phosphodiesterase-3 inhibitors, calcium channel blockades, benzodiazepines, and others, on diaphragmatic contractility in animals. All measure-
ments (including haemodynamics, blood gas tensions, trans-diaphragmatic pressure and integrated activity of the diaphragm) and analyses of data obtained from the experiments were performed by myself and colleagues (co-authors), and this can be proved by them.

I understand that the tests by Dr. Carlisle are designed to uncover statistical anomalies based on very few assumptions about the data. I am not qualified to counter specific allegations concerning the ‘central limit theorem’ and its applicability in our case. As I said, our data sample is very special, but I do not have the skills to examine in detail if it has an impact on Carlisle’s analyses.

Finally, since the critical report against me by Krank et al. was published in 2000, I have greatly suffered. Nevertheless, I have continued my clinical and laboratory studies with great care. In addition, there has been confusion concerning the ethical procedures at Ushiku Aiwa General Hospital where I did clinical research. This hospital did not have a formal institutional ethics committee, and therefore I sought and obtained the approval of the Vice-Chairman. Later, while at Toho University School of Medicine, I was unfairly blamed for Ushiku’s informal procedures. As a result of a lack of ethical approval, I received the advice of the university authorities and left Toho University.

The only thing I can say is that we performed the tests over years with full honesty and integrity. Additionally, I did not write these articles alone, and some of data were collected by others as well.

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A reply

We thank Dr Fujii for his letter which, unfortunately, does not address the fundamental basis of the analysis of his work [1]. As has been explained [2], the distribution of means sampled from any population of continuous measurements, no matter how bizarre the original distribution of measurements, is always normal/Gaussian (see Fig. 4, reference [2]). Furthermore, the alleles that contribute to individual characteristics behave according to fundamental laws of nature and thus apply to all populations – including the Japanese - however distinct they may be [2, 3].

The statistical principles underlying the analysis [1] are literally universal. Apart from genetics, they apply to the behaviour of tiny particles (e.g. mass-velocity of atoms) and galaxies (e.g. Doppler shifts), and to analyses of the extremes of time (e.g. the speed of light and the slowest radioactive decay). An exception to these mathematical principles would shake the basis of most of modern scientific knowledge and understanding.

Access to Dr Fujii’s original data would help us confirm the veracity or otherwise of his claims.

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