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AT THE HOUR OF OUR DEATH, THERE IS A DECLINE IN OUR LYMPHOCYTE COUNT THAT EMULATES THE BEHAVIOR OF PARASITES.

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ABSTRACT

In the terminal phase of a wide variety of human diseases, the daily total lymphocyte count declines hand in hand, with the approach of the actual time of death of the patient.

This raises some fundamental questions: How do the lymphocytes know the patient is dying, and the exact time of death? And how is the reduction of the lymphocyte population organized; some lymphocytes undergoing apoptosis while some stay behind, and yet other lymphocytes seem to be trying to escape entombment in their erstwhile host?

The similarities between these behavior patterns and those of protozoan parasites, further instantiates the concept, that, under certain critical conditions, such as the impending death of the host, lymphocytes are, to some extent, capable of atavistic reversion to their postulated primordial parasitic modus operandi.

Keywords: Human Death. Lymphocyte Behavior. Mimics Parasites. Proteomic Signals.

INTRODUCTION:

Being able to make a reasonable estimate of the time of death of a chronically sick patient is important in at least two ways, it impacts the degree of aggressiveness regarding the treatment of complications as they arise, and it helps patients and families with terminal planning. To this end tools such as the Palliative Prognostic Index (Morita et al, 1999) have been developed.

In this context, it has been noted that a decline in the daily total lymphocyte count is also an ominous finding as in a wide variety of terminal human diseases, this also presages the approach of the end of the patient's life. This is a mark of distinction between the behavior of the lymphocyte population, and that of all the other cells of a host, since none of the latter cells display any behavior pattern even vaguely resembling this reduction in numbers.

This finding lends a measure of support to the hypothesis that lymphocytes are somehow different from the other cells of the body. Indeed these actions are closer to the behavior of a protozoan parasite, in the sense that when there are too many parasites in the host's body, this hyperparasitemic burden is sensed as contributing to the premature demise of the host. Then, in order to prevent the death of the host, there is often a voluntary reduction in parasite numbers, a form of "auto culling", by apoptosis.

This unique lymphocyte behavior pattern in turn, also supports the concept that lymphocytes may have actually originated as protozoan parasites in fish, and over time, by dint of being useful "guard dogs",they evolved into endosymbionts in fish, (Coulson, 2013), and persisted in this role in modern vertebrates,

CLINICAL OBSERVATIONS:

Shah et al, (2016), studied the low eosinophil and low lymphocyte counts in 771,231 individuals, of whom 55,004 presented with cardiovascular disease, for a median follow-up of 3.8 years. Over the first 6 months there was a strong association of low lymphocyte counts with unheralded coronary death, and ventricular arrhythmia leading to sudden cardiac death.

This finding holds true for diseases of other organs, both benign and malignant. In the case of renal failure, Carvounis et al (2000), found that the total lymphocyte count appeared to be an index of mortality for patients on chronic ambulatory peritoneal dialysis. Renal cell carcinoma patients similarly displayed a clear relationship between low lymphocyte counts and a poor prognosis, (Saroha et al, 2013).

In neonates there is an association between a lower lymphocyte count and adverse outcomes. The report from Christensen et al, (2012), found that among 120 babies meeting criteria for birth asphyxia, those with a low lymphocyte count had a higher mortality, as well as more transfusions more neurology referrals.

Following their findings with recurrent ovarian cancer patients, Nakamura et al, (2016 a), were able to correlate patient survival with the ratios of neutrophils to lymphocytes, and platelets to lymphocytes.

Subsequently, Nakamura et al, (2016 b), felt they could generalize their working hypothesis to the point where they stated that the "Neutrophil/lymphocyte ratio has a prognostic value for patients with different types of terminal cancer", with a progressive decline in the lymphocyte count as the patient approached death.

PROTOZOAN PARASITES; RELEVANT OBSERVATIONS

Following the classic work of Anderson and May, (1978), and Ebert et al, (2000), Luder et al (2010), noted that Programmed Cell Death (PCD) was a common technique employed by a wide variety of protozoan parasites along with regulation of cell proliferation, to avoid hyper-parasitism which would lead to the untimely death of the host. The authors concluded that "the sensing of population sizes via distinct environmental cues ….support the hypothesis that PCD in protozoa contributes to their density regulation." The precise nature of the cues remains unknown at this time.

Similarly the work of Reece et al (2011) showed that if host or vector survival was negatively related to infection "the best strategy was for enough parasites to undergo apoptosis to maintain a sub-lethal density.".Curves from Fig 3 in their paper demonstrates how altruistic suicide by apoptosis reduces the number of malaria ookinetes transforming into oocysts to maximize the chances of successful transmission of the parasite, accompanied by the authors' model assumptions and the mathematical equations. Recent related work has shown the ability of protozoan parasites to undertake quorum sensing and to detect genetic diversity (Pollitt et al, 2011).

This brings us to the bigger question: how do the parasites sense that their host is dying? Work on addressing this question is still in its very early stages. At the cellular level the paper by Moudy et al (2001) , indicates that Toxoplasma gondii can sense a reduction in potassium concentration, which in turn activates phospholipase C activity that facilitates egress of the parasite. However at the "whole body" level, there is a dearth of information.

PATIENT'S AWARENESS THAT DEATH IS NEAR, SOMEHOW SENDS SIGNAL TO LYMPHOCYTES

According to a study by Pearson (2015), many patients are aware that they are going to die 72 hours before the event. This coincides with the terminal plateau lymphocyte count. During this time the patients start talking about "going on a journey home", and they develop physical exhaustion, and a much reduced appetite.

Since awareness of death is a brain function, we can only surmise that this most probably involves a brain signaling system, probably involving proteins which have yet to be described, cerebroterminins, for want of a better term. Similarly, and again at this stage, this is is pure speculation, lymphocyte detection of small amounts of this protein class or its precursor would be the alarm responsible for the initiation of the subsequent decline in lymphocyte numbers.. Quorum sensing might then determine the total numbers to be sacrificed in an attempt to reduce the incorrectly perceived "hyperparasitic" lymphocyte burden on the host, but work on how the decisions are made about who stays, and who goes, lies in the future; further speculation at this point being limited by Occam's razor.

However, having said that, a study of conjoined twins possibly offers some insight as to the nature of these postulated cerebroterminins. Eng and Chang Bunker died within hours of one another, similarly in the case of Mary and Eliza Chilhurst the interval was 6 hours. In the case of Gibb twins who died in 1967 at the age of 55, the second twin died within minutes of the first,

(http://www.twinstuff.com/conjoined-twins/). So, whatever the proteomic signal proves to be, it is quite lethal and relatively fast acting, although one can envisage molecular amounts leaking.out during the 72 hour synthesis period prior to the final biochemical coup de grace, sufficient to alert the patrolling lymphocytes. The protein must also have an extremely short half life, as organs can be transplanted from brain dead patients with no untoward effect on he recipient's brain; although it must be noted that terminally ill cancer patients would rarely be used as organ donors.

In 1870 Chang suffered a stroke and according to the account in Wikipedia, his health declined over a four year period, the terminal event being severe bronchitis; Eng remained in good health. On January 17, 1874, Chang died while the brothers were asleep. Eng awoke to find his bother dead, and said:"Then I am going." He died 3 hours later.

An autopsy on Eng failed to find an obvious cause of death. In the case of Chang, his death was attributed to a cerebral blood clot. It should be noted that the brothers were joined by a small piece of cartilage at the sternum and that although their livers were fused, they were capable of completely independent existences..Because of the smallness of the amount of tissue constituting the tissue bridge, breakdown products from the other twin's tissues probably did not cause Eng's death (Patients can live with dead bowel or gangrenous legs for days.). In addition this case would indicate that the postulated cerebroterminins are blood borne, since their tissue bridge had no nervous tissue.

Kuru provides some further circumstantial evidence,(Kuru.https://en.wikipedia.org/wiki/Kuru_(disease)). It is a neurodegenerative condition that reached epidemic proportions in the late 1950's among the Fore tribe in New Guinea, and is believed to be caused by the transmission of prions during the funerary cannibalism wherein deceased family members were cooked and eaten. Females and children selectively ate the brain, the organ in which the infectious prions were most concentrated, and as a result the disease was more prevalent among this group. To complicate the story, since the women and children also cleaned the relatives after death, and since they often had sores and cuts on their hands, an alternative explanation for the transmission of the disease is obvious, the contamination of the open wounds, which could also be a portal of entry for cerebroterminins or their breakdown products. There is enough variation in the clinical course of kuru that it might encompass more than one condition, all of which have so far been attributed to the classical prion etiology, when in fact the postulated cerebroterminins may play a role in some cases.

DISCUSSION AND CONCLUSION:

In this brief review what we have attempted is to provide another piece of evidence to support the possibility that lymphocytes evolved from protozoan parasites, based on their unique behavior when faced with the imminent death of their host.

The fact that the lymphocyte population declines with the approach of death in sick human patients is indisputable; although it must be stressed at this point that so far this has only been documented in patients with a chronic illness. A mathematically similar decline in parasite numbers is also seen in overpopulated hosts, where the decline in health status of host is attributable to excessive parasitemia,

The problem lies with the next step in the argument; how do both the lymphocytes and the parasites know about the impending death? It is disappointing that there is no information on this aspect of the biochemistry. as a similar signaling system would make for a more convincing argument to support a congruence straddling what at first glance seem like very different medical fields.

So it became necessary to postulate existence of a new class of signaling proteins, cerebroterminins, and then to try to find evidence to support possibility of their existence. Siamese twins have so far provided the strongest evidence. Hopefully, animal studies like those that showed prion assembly will yield some answers, (Bagriantsev et al, 2004; and Marreiros et al, 2015). (Our review of the literature involving brain dead mothers carrying living fetuses, and conversely a study of the effect of fetal demise on the mother's brain, have not been helpful.) Similarly, our review of Kuru transmission has also not yielded any good clues about short term effects on the brains of tribeswomen handling the fresh, uncooked brain tissue from recently deceased relatives, with their bare and frequently ulcerated, hands. There was also a period of time in 1954, when heart surgery was performed on children by Dr. Lillihei and his team, when their hearts were arrested and their bodies were kept alive by using adults as "living heart-lung machines", a form of cross circulation. Some of the children died, but apparently not while still hooked up to their living heart machines, although his needs further investigation.

In order to complete the comparison with protozoan parasites, it would certainly be fair to ask: how do lymphocytes try to escape their dying host? Two different methods have so far been briefly examined; the Kennedy skin ulcer, and the unanticipated GI bleed seen in terminal patients,.(Hui, 2015), and will be the subject of a future review.

It would thus appear that animal experiments will be required to fully comprehend the signal from brain to parasite, and to compare it with the one from brain to lymphocyte in order to establish their similarities.

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