Psychoimmunology of Nutrition

Bruno Lesourd

Faculté Médecine Clermont-Ferrand, Paris, France

The relationships between behavior and immune responses have been studied for a long time. It is well recognized that persons under psychological stresses, such as depression, marital problems, bereavement or alcoholism, are more susceptible to infections. Nevertheless only a few studies were conducted before the 1970s. Since then, progress in knowledge of the immune system, improvement in questionnaires assessing the characterization and quantification of different moods, and very recently the link between a psychological approach and brain neuron cell functions (neuroimmunology) have pushed to extend research in this new field, called psychoneuroimmunology.

This review will briefly describe the immune system and its roles. Thereafter the most important findings linking psychological stresses and immune responses will be discussed. Recent research at the neuron cell level is reported in order to present the current hypotheses being investigated.

Immune Responses

The immune system is an important body part (3 kg of lymphocytes, 5% of body weight) and is widely spread throughout the body. This large distribution of immune cells enables the development of an immune response at any body site where aggression occurs [1–3]. When activated, the immune system releases numerous mediators (cytokines, immunoglobulins, prostaglandins, etc.) that inform the entire body of the aggression and enabling a large response that mobilizes all the body reserves, including the immune cells and also nutritional body reserves. Such a global response is directly, or indirectly through hormonal response, activated by cytokines inducing inflammatory processes.

Two types of immune responses may reflect immune activation.

The more primitive is called nonspecific immunity. This includes responses from monocytes-macrophages, polymorphonuclear cells and a lymphocyte subset: natural killer (NK) cells. This immune response induces destruction of
contaminating agents, whether intra- or extracellular, through phagocytosis and killing, in a safe manner, mainly by free radical activity within intracellular vacuoles. The specific immune system may help by circulating mediators, such as immunoglobulins or complement factors, for phagocytosis. This immune system is mainly non-antigen-specific and works without any antigen recognition.

Part of this primitive system, namely monocytes-macrophages, also plays an important role in more sophisticated immune responses: (1) through partial intracellular digestion of the aggressive agents enabling the presentation of antigen molecules to lymphocytes, this antigen presentation is able to induce specific antigen responses, and (2) by inducing directly (through proinflammatory cytokines such as IL-1β, IL-6 or TNF) [4] or indirectly (through hormonal responses; fig. 1) a global metabolic response called hypercatabolism that mobilizes nutritional body reserves as well as brain functions to face the aggression. Very little is still known about the importance of brain activation during such responses.

The other immune system is associated with specific antigen recognition at the molecular level. Antigen specificity is related to specific lymphocyte differentiation: on its membrane a lymphocyte bears receptors specific for only one antigen. This system is dual.

(1) B lymphocytes act through secretions of soluble receptors (immunoglobulins) that help to phagocytose the aggressive agents or permit direct killing through the complement cascade. Humoral immunity is mainly active against cells, in particular bacteria.

(2) T lymphocytes, more recent in ontogenesis, act in a more sophisticated way. This immune response is called cell-mediated immunity (CMI). The CD4+ cells recognize the antigen presented by the monocytes-macrophages...
and are then transformed into active cells by the macrophage cytokines. In fact the activity of the CD4+ cells depends on the type of macrophage activation (fig. 2).

The most frequent activation leads to TH1-activated lymphocytes that, in cascade, activate cytotoxic T lymphocytes (CD8+). The cytotoxic T lymphocytes directly kill the infected (or transformed) cells that present an abnormal antigen at the membrane level. This system is the most potent destroying system within the body. It prevents not only proliferation of hidden (intracellular) pathogens but it also enables the elimination of abnormal cells (tumor cells) by inducing apoptosis of these cells.

TH2 lymphocytes are also activated by macrophages but through different mechanisms. They activate B lymphocytes and induce the production of more sophisticated immunoglobulins, such as IgG or IgA.

Activation of cytotoxic T lymphocytes and/or B lymphocytes depends on the cytokines released by TH1 and TH2 lymphocytes. The TH1/TH2 equilibrium is evaluated by quantification of the cytokines released by each lymphocyte type: IL-2, IFNγ or IL-12 for TH1, and IL-4, IL-5 or IL-10 for TH2. This TH1/TH2 equilibrium seems to be of great importance for CMI efficiency (fig. 2). In fact TH1 lymphocytes are predominant in the first part of life during which responses to unknown antigens are driven. TH1 responses decline with age, so that TH2 responses become predominant in old age. TH1 responses decline more rapidly
if antigen boosts are frequent and at a high level (multi-infected patients) during life.

CMI (functions of the T-lymphocyte) is mostly active against intracellular pathogens and transformed cells while humoral immunity mostly acts against extracellular pathogens.

T lymphocytes are rapidly dividing cells. They may induce autoproliferation through IL-2 secretion than binds the IL-2 receptor to the membrane. This rapid proliferation of T lymphocytes is of major importance in the face of aggression. Indeed, there is competition between the replication speed of the aggressive agent and the proliferation of the T lymphocytes. Every disturbance, such as undernutrition, stress, behavioral modification, that slows the proliferation rate, renders the individual more susceptible to infections. This is why lymphocyte proliferation is often used as a pertinent evaluation of the immune system.

**Psychological Stresses and Immune Responses**

In the late 1970s and early 1980s, it was shown in laboratory rodents that different stresses induce decreases in CMI, namely lymphocyte proliferation and/or natural immunity, i.e. NK cell activity. Intense auditory stimulation in mice [5], electric shocks in rats [6] and foot shocks in rats [7] induce similar decreases in CMI. It was shown that these effects might be modulated by opioid peptides [7], drawing evidence from the modulation of immune responses by neuromediators. Nevertheless stress was already known to induce multi-metabolic changes within the body, i.e. changes in nutritional and hormonal status that also affect the immune responses. Such metabolic changes may be more important than behavioral modifications in modulating immune responses. The importance of conducting human studies in which psychological changes may be quantified in more sophisticated ways has arisen.

Glaser et al. [8] conducted several studies in healthy students who clearly showed that psychological stress induced by examination sessions may influence immune responses. In the same students, they showed that the numbers of T lymphocytes (CD3+, CD4+ and CD8+) are decreased during examination periods when compared to immune responses after vacation. In addition lymphocyte proliferations were also lower [8]. Such decreases in CMI have been linked to higher depression, anxiety and hostility scores. Decreased immune responses were observed not only for CMI but also for nonspecific immunity (NK cells) [9] and for humoral immunity [10]. In fact, Epstein-Barr virus antibodies were higher during examination sessions, showing that this immune deficit may lead to reactivation of a permanent virus [9]. The relationship between decreases in IFNγ production and in NK activity points out the importance of a decreased CMI in diminished nonspecific immune responses [9].

Similar findings were observed in medical students feeling loneliness [11], in psychiatric patients feeling alone, in separated/divorced females, in spouses
with poorer marital quality, in males with marital discord, and in caregivers of
dementia patients who are at high risk of depression [12]. The same group
explored similar changes over an entire academic year. They were able to
show that such decreased immune responses during examination periods
were repetitive over the year, and that in between the immune responses
recover [13]. They also showed that cytokine production, i.e. IFN and LIF (leuko-
cyte inhibitory factor) followed the same pattern as lymphocyte proliferation.
In addition, students with lower immune responses during examination peri-
ods had a higher incidence of self-reported symptoms of infectious illness.
This points out the strong relationships between examination-induced psy-
chological stress and immune responses. Decreased immune responses related
to such psychological stress have been linked to hormonal metabolic changes
since urinary cortisol is increased during examination periods [14].

More recently it was shown that psychological stress has clinical conse-
quences by inducing a slowing of wound healing [15], a process dependent on
macrophage functions [16]. They also alter dynamic immune responses: immune
responses to influenza vaccine are lower in stressed elderly [17], a
human group in which immune responses are particularly sensitive to environ-
mental factors [18]. This effect may be more intense in elderly subjects in whom
stress induces longer hormonal responses as shown by longer periods of ele-
vated cortisol levels [19]. It appears that stress-induced elevated serum cortisol
is probably of major importance for the stress-induced decrease in immune
responses. This is probably not related to the nutritional effect of stress since
decreased immune responses in caregivers of dementia patients are related to
a higher increase in salivary cortisol [20], a parameter not dependent on corti-
costeroid-binding protein and therefore on protein nutritional status.

The importance of stress-induced hormonal changes on immune responses
have also been observed in depressive and alcoholic patients, and both diseases
exert cumulative effects on NK cell activity [21].

It is well known that alcoholism is often caused by psychological stress and
is also often associated with undernutrition which is a consequence of such
behavior. Many publications refer to decreased immune responses in relation
to undernutrition [for references see, 22]. It was shown that, in the elderly,
major undernutrition (protein-energy malnutrition) as well as moderate
undernutrition, i.e. micronutrient deficits, are both associated with decreased
immune responses [23]. In addition, refeeding is also associated with
improved immune responses, showing the strong interrelationships between
nutrition and immunity [24].

Mechanisms

Stresses, including psychological stresses (see above), induce chronic
changes in nutritional behavior and hormonal status, i.e. the cortisol level.
The effect of psychological stresses may be related to the chronic effect of a high hormonal level that may induce changes in cell receptor density and/or sensitivity. It was shown that in the elderly, lymphocytes have lower levels of membrane transduction markers, such as CD38+, or of cytotoxic markers (CD56+) on CD8+ cells [25]. This is more pronounced in elderly caregivers who are under chronic stress [25]. Furthermore, lymphocytes from persons under chronic depression (stress) become resistant to the immunosuppressive effect of steroids [26]. This was reported in depressive patients in whom chronically high cortisol levels are noticed [27]. In addition these patients show a failure to suppress endogenous cortisol levels following dexamethasone administration [28], indicating that the chronic stimulation of glucocorticoid receptors induces changes in receptor affinity. Bauer et al. [20] conducted a study in not undernourished caregivers of dementia patients. They expressed greater anxiety and depression (Savage Personality Screening Scale [29]) and greater stress scores (Global Measure of Perceived Stress Scale [30]) than non-caregivers. They also had lower lymphocyte proliferation and lower IL-2 production that was related to higher salivary cortisol levels. In in vitro mononuclear cell cultures, additive suppression of lymphocyte proliferation required higher doses of dexamethasone in caregivers than in non-caregivers, showing the corticoid resistance to glucocorticoid in persons who are under chronic stress. From such findings it appears that chronic stress is related not only to cortisone-induced decreased immune responses but also to some degree of stress resistance that pushes lymphocytes to be less reactive to further glucocorticoid challenge. Therefore, part of the mechanism of stress-induced decreases in immune responses is related to chronic changes in glucocorticoid levels.

Are those changes due to brain activation? Acute gastric injection of alcohol into rats induces decreased immune responses and direct activation of the hypothalamic paraventricular nucleus (PVN): increases in corticotropin-releasing factor mRNA through the activation of early genes such as c-fos (fig. 3) [31, 32]. In contrast, chronic acute injection decreased the response of the hypothalamic-pituitary-adrenal (HPA) axis to further alcohol ingestion but not to stress of another nature, such as immune challenge or electroshocks [33]. This is associated with a lower ACTH response to vasopressin [34] and a lower level of serotonin (a neuromediator) in the PVN [34], indicating a relationship between neuromediator release and HPA axis modulation. A second alcohol challenge, few days after the first, does not lead to activation of early genes but in contrast to lower activation [35]. Such decreased responses may be overpassed by Nω-nitro-L-arginine methyl ester that blocks nitric oxide formation [35] but is not related to higher serotonin secretion in the hypothalamic PVN [36]. This group pointed out the importance of chronic alcohol ingestion-induced nitric oxide production in the PVN [37] and the correlation with HPA axis modulation. Nevertheless, they have been unable to show a correlation with serotonin release, at least in some
stress situations [38]. The link between neurotransmission and HPA axis modulation remains unclear even though the site of such a link is known.

In summary, it was shown that alcohol activates the HPA axis response by inducing the release of corticotropin-releasing factor (and as a result glucocorticoid at the blood level), thus mimicking a stress effect. Even though the mechanism remains unclear, the site at which such an alcohol stress acts, the hypothalamic PVN, may explain many of the behavioral effects of alcohol since the PVN is a central passage for mood adaptation related to stress and the link between HPA axis modulation and the changes in nutritional intakes. Many changes observed in alcoholic patients, such as behavior, decreased food intakes, mood disorders, act in relation to this mechanism.

Chronic insufficient intakes lead to micronutrient deficiency and later to protein-energy malnutrition, both being associated with decreases in immune responses [22–24]. Chronic insufficient intakes are related to behavioral changes [39] such as depression, showing the importance of psychological stress, metabolic changes and immune responses. Numerous articles refer to the importance of neurotransmission changes in eating behavior, showing the major influence of neurotransmission on immune responses [40]. This inter-relationship is more important in aged subjects who are more susceptible to mood changes [40]. Recently, several experiments in rats have investigated these mechanisms, trying to understand which metabolic changes in which brain sites may be associated with changes in immune responses. In healthy albinos rats, it was shown that an increase in age from 3 to 9 months is associated with increased GABAergic hypothalamic activity and no change in immune responses, i.e. lymphocyte proliferation [41], while later on
(9–18 months) GABAergic hypothalamic activity and immune responses both decline while circulatory corticosterone increases [42]. The authors point out the strong link of both changes between the ages of 3 and 18 months [41]. This activity may be altered by changes in protein diet on a long-term (30 days) basis [41, 42]. Short-term (7 days) changes in protein diet have little effect. In contrast long-term (30 days) changes in protein diet induce alterations in immune responses, in circulatory corticosterone and in GABAergic activities. A low protein diet (5% casein) delays the age decline in immune response (lymphocyte proliferation) and in parallel decreases GABAergic activity. In contrast, a high protein diet (40% casein) induces decreases in immune responses and increases GABAergic activities [43], while circulatory corticosterone increases [42]. Those changes in GABAergic activities, mainly related to GABA receptor density [43], are only observed in the hypothalamus and not in the cerebellum or pons medulla showing that hypothalamic activity is of major importance for changes in immunity. This brain area is of major importance, in particular since it is an important site for food intake control. Such findings are even more impressive when one knows that changes in diets induce changes in hypothalamic activation as measured by early gene (Fos) activation. Horn and Friedman [44] investigated brain activation in relation to diet type, i.e. high fat/low carbohydrate (HF/LC) versus low fat/high carbohydrate (LF/HC) diet, in middle-aged Sprague-Dawley rats. Rats fed the LF/HC diet increase food intakes after administration of a fructose analog, 2,5-anhydro-D-mannitol. This treatment induces activation of the PVN of the hypothalamus, and does not have any effect in rats fed the HF/LC diet. In contrast in rats fed the HF/LC diet, the same effect is seen when they are treated with methyl palmorixate, an inhibitor of fatty acid oxidation, but the activation concerns another part of the brain: the solitary tract [44]. Those effects can be blocked by vagotomy, showing the importance of nerve transmission to the brain [45].

**Conclusion**

The importance of hypothalamic functions in food intake and in immune response activities is emphasized by these findings. The activity of the hypothalamus is probably of importance in this regulation, most likely through still unclear modulation of HPA axis responses. The strong simultaneous activities observed in hypothalamic PVN, in HPA axis and in immune responses point to the importance of PVN activation in the regulation of stress responses. The possible neuromediators as well as the receptors involved in this regulation are presently being investigated. This brings new approaches to the understanding of the regulation of psychological stress and its interrelationship with immune responses. In the near future, this approach will probably help to modify metabolic and behavior stress consequences.
References

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Discussion

Dr. Cynober: I really enjoyed your talk. Congratulations because it was probably a really difficult task. From the data you presented I think that the key point, the central element, is certainly cortisol. Are you aware of experiments trying to block the cortisol action, for instance using RU486?

Dr. Lesourd: That was not done. The only thing that has been seen is that there is a blockade when dexamethasone is added after chronic stress, not after a
shock stress. But to block the production of cortisol for a long period, that was not done.

**Dr. Elia:** You focused on cortisol, but of course stress is associated with all kinds of other hormones including catecholamines and so on. Do they play a role?

**Dr. Lesourd:** I don’t know. I mentioned that there are actions on the pituitary hormones secreted during stress, but that was not looked at, and the picture is not clear for catecholamines.

**Dr. Morley:** For the sake of our chairman I do have to point out that ‘psychoimmunology’ was the first used in the late 1950s and early 1960s when people with rheumatoid arthritis were studied. It was shown that with stress the immune function response is altered. After a few experiments the term was changed to psychoneuroimmunology. So that is I suppose the epistemology of this terminology. I have a couple of points about other hormones, both for catecholamines. Actually very interesting work has been done in rats in which the catecholamine response in the spleen was looked at and the alterations during stress were related to immune function changes within the spleen. So there is literature, it is almost all animal literature at that level. The other, relatively well-studied hormone is endorphin which has almost the opposite effects acutely to cortisol. For instance if you do exercise stress the endorphin increases and NK cells increase in proliferation together with the endorphin. If you do long-term morphine addiction studies, you find tolerance and downregulation of the cells. There has been a big argument about whether the changes are all cortisol or tolerance; both of those have to be looked at. But the stress of increased exercise can be blocked with naloxone. So there are a lot of interesting interactions; I think it is very much like feeding. There are so many different things that can cause problems. There are clearly also multiple effects of cytokines on the central nervous system, not only all the effects on feeding but also on memory. Recently it was shown that these effects can be produced both by cytokines directly crossing the blood barrier and also by stimulating the ascending fibers of the autonomic nervous system. It becomes very complex and I think when you have to add nutrition to this, and certainly nutrition alters every one of these factors, it makes it very difficult for any single human being or even all of us together to really understand how these interact. That is why I think you did an incredibly good job of giving us a good concept to pay attention to the role of the psyche along with nutrition and immunology.

**Dr. Lesourd:** I have also looked at the catecholamine publications. It is far more complicated to really understand what is going on and it is impossible to get a really clear picture from that; it is very confusing. This is why I didn’t talk on that.

**Dr. Labadarios:** Have you noticed how President Bush’s hair has gone white over the past 2 months? Regarding the slide that you had on the mechanism where there is actually a blockage in melanocyte-stimulating hormone, do you think psychoimmunonutrition will help President Bush?

**Dr. Morley:** But every United States President goes gray when they are president, there is no question, no matter who they are. But I have also noticed that many South Africans are very gray, so I would guess this is not unique.

**Dr. Labadarios:** If you are referring to our president you are quite right. Actually this is serious, people under stress get gray hair faster for reasons we don’t know, and that is a consistent observation. Now on the more serious side, at least serious until we know better, would you comment on the literature that indicates that stress is a proinflammatory state?

**Dr. Lesourd:** When we are talking about chronic cortisol secretion, for me it is chronic stress. It is chronic deregulation of hormonal production most likely at the level of regulation of the hypothalamus, and the paraventricular nucleus is probably
Dr. Labadarios: A recent article [1] actually associates stress and depression with increased C-reactive protein levels, which really adds to the comment that you are making.

Dr. Thomas: Just to follow up on that. As we look at the causes of anorexia and weight loss, particularly in long-term care chronic settings, they are predominantly associated with depressive reactions such as a chronic stress state, certainly mediated by the catecholamines and serotonin, dopamine, etc., which gives us a real opportunity to improve nutritional status and improve intake by the treatment of the depression.

Dr. Lesourd: I don't have any experience with dopamine. But I do know that when chronically undernourished patients are treated, at the beginning there is always an increase in cortisol and C-reactive protein, a very low level, 20–25 mg/l, but an increase. When the patients are treated and are recovering with the food intake, then it decreases.

Dr. Ockenga: I have a further comment on the link between catecholamines and catabolism as well as psycho-immunology. My former colleagues in Hanover did some elegant studies with students and they showed that increased catecholamines also increase the circulating lymphocytes by decreasing the adherence of molecules [2]. They also did studies on chronic stress and found comparable results [3]. We have just finished some studies in which we found that an increase in sympathetic activity is related to the leptin system, and 2 years ago we published a study in Gastroenterology [4] on the leptin system associated with resting energy expenditure and catabolism. There are probably several links as already mentioned here between sympathetic activity as well as all our regulation systems of food intake and energy homeostasis.

Dr. Lesourd: But you know that leptin could also be activated by the sympathetic system; so it is a link.

Dr. Ockenga: Sure, and at least this has been done in animals. If the sympathetic nervous system in the brain is cut, then the effect of leptin in liver metabolism is regulated, as well as resting energy expenditure and the further release of several hormones.

Dr. Schiffrin: To bring the intestine back into the picture since it is such an important immune organ. Increased bacterial adhesion during stress has been reported. Is stress promoting mast cell degradation? The barrier then becomes leaky? What happens with the stress on the mucosal immune system?

Dr. Lesourd: I have not seen a study that tried to link stress and the function of intestine, even for the immune response.

Dr. Morley: There are a couple of studies, depending on how you want to look at it, on the pure mucosal barrier. Lower down in the gut there are no studies. But looking at the mucosal barrier within the stomach, stress releases and reduces the mucosal barrier and is one of the reasons why it produces stress; the other is alteration in blood flow. Both are most probably more important than increased gastric acid. In addition to that there are fairly good studies looking at the effect of stress on gastrointestinal motility. I think most of them show a decline in gastrointestinal motility. We see both but I think the majority suggested a slowing, but there may be others.

Dr. Lesourd: And a decline in gastric emptying.

Dr. Morley: Yes, certainly a decline in gastric emptying.

Dr. Labadarios: In relation to the last comment: the available motility studies are actually variable and to my understanding that is why we are not trying to classify irritable bowel syndrome into its components of diarrhea or constipation. At the functional
level that is probably the most clearly known association between so-called stress and irritable bowel syndrome.

*Dr. Armstrong:* I congratulate you on the wonderful job you did in trying to put together all the data around the effects of stress. For me the question is whether or not we should be trying to redefine or categorize stress, because what you described is a whole slew of different stresses to the body which are difficult to compare directly from the starvation studies of Soderholm et al. [5] through to food deprivation, through to alcoholism. These all would be expected to produce different sorts of responses in organisms that have adapted over millions of years to life around them. Stress responses presumably have evolved to cope with a number of different external and internal stresses, and to assume that each of them is going to be comparable and is going to work by comparable mechanisms I think does the mechanisms a disservice and makes life very difficult for us to try to differentiate what is going on under different circumstances. The question therefore is, is there a way of separating out different types of stress or categorizing so that we can get a degree of uniformity and dissect the mechanisms, or is that being over optimistic?

*Dr. Lesourd:* What I tried to do is to present stress without any nutritional response because that is really what we would like to know. If there is something that the nutrition response is not involved in, and I know that there are a lot of other stresses where there is a very important change in nutritional behavior, so it is probably different, except for the mechanisms I tried to show you.

*Dr. Lochs:* Just a comment on stress and the gastrointestinal barrier. There are a number of studies showing that different kinds of stress create ulcers, and this also differentiates what kind of stress. Immobilization stress was mainly used in rats. Rats were put in casts so that they couldn’t move their legs which creates an enormous stress and they develop ulcers very quickly. How ulcers develop was also studied: by a reduction in mucosal blood flow. So they have mucosal ischemia and then they get ulcers. To my knowledge, as Dr. Morley said, no studies on the intestine have been done but it is most likely that similar effects happen in the intestine: blood flow is reduced and is one of the major determinants of barrier. You showed very nicely that in young rats a low protein diet causes an increase in cortisol and a decrease in lymphocyte proliferation that could even be dependent on the increase in cortisol, but in older rats this was the opposite, the lymphocytes increased and cortisol. What causes this change? You would expect that if you treat somebody with steroids that the lymphocyte proliferation would decrease? How is that regulated since this regulation is no longer present in older rats?

*Dr. Lesourd:* I have also shown that the lymphocyte at the peripheral level became totally insensitive to dexamethasone, so probably the same occurs at the brain level. This means that cortisol is no longer active and if it does increase it doesn’t do anything.

*Dr. Lochs:* But why isn’t it active? Are there cortisol receptors on the nucleus, or what is it?

*Dr. Lesourd:* There are very few data on that. It has been shown that the reappearance of cortisol receptors is very low and the number of receptors that reappear is far lower than what you have before the stress. So it is probably something that is going on inside the cells that makes the receptors unable to be re-synthesized or it should be modulation of NF-κB or other mediators within the cell but we don’t know which mediators.

*Dr. Morley:* Just to follow up for Dr. Armstrong’s question about defining stress and what kinds of stress. If you take depression as a stress factor in young people, the problem is that about 90% will basically put on weight if they are depressed, and 10% will lose weight. In an older population it will turn out to be that 60% will lose weight.
and 30% won’t. So age interacts with the stress and in addition you also have the genomic effect. Within the immune system there are a number of studies in which the coping indexes have been looked at. The coping index is a psychological term which says how well you handle stress, and it turns out that people who can cope with a similar stress will have much fewer changes in the immune system than people who can’t cope. So we have an enormous challenge if we are trying to look at this because we have got to go from the genome to the brain and the environment all at the same time. Many years ago Pugh, an English man, said that if the human brain was so simple that we could understand it, we would be so simple that we couldn’t. That may be the best way to look at this whole area; it is very difficult to understand.

Dr. Armstrong: A part of the problem then comes down to the definition of depression because depression is not necessarily the stress itself. Presumably some stress or something has lead to depression and whatever it was that lead to the depression may have been different initially and therefore the response may be different. In addition, as you said, there are coping skills, and something with which you can cope is much less likely then to be a stress. So that again is the problem with chronic stress because chronic exposure to something that might cause stress will not cause stress if you learn how to deal with it. So a constant stimulus will produce a changing effect depending on the individual organism’s ability to adapt to that. My question was not really with the expectation that we were going to be able to simplify this, but if we are stacked in a soup of different stresses and different responses, it is going to be very difficult to tease out the particular things we are trying to deal with.

Dr. Morley: Psychologists who work in this area have tried to use defined stresses, such as mental arithmetic and telling the person their answer was wrong even if it was right. They look at the coping skills of the person up front, exercise to define physical stress. I think that is the way to start to tease out an area like this, to use very defined stresses that we can all understand and that are relatively simple. The problem is long-term, it is much harder to manipulate people and stress them for long-term than to define a stressor. We have examples of wars and things like that. In fact during an earthquake at UCLA in Los Angeles, a scientist actually measured the immune system responses to the earthquake and showed major changes that came back over an about 6-month period. So there are in fact ways of looking at those, but it is very difficult and I think we are both saying the same thing, it is an extraordinary complex area. I think that is what you said at the beginning and you did very well.

References