

The Small and the Special

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How Stress gets 'under the Skin'

Ever wondered why people look older if they have undergone long periods of stress? The fact that stress affects health adversely has long been known. The exact mechanisms are still under study. In this simple and spectacular study designed to investigate the underlying cellular mechanisms of stress, Epel et al investigated 58 healthy pre-menopausal women, 39 of which were mothers of a chronically ill child (care-giving group) and 19 were mothers of a healthy child (control group).¹ The participants were administered a 10 point questionnaire to assess level of perceived stress over the past month. In addition, blood samples were obtained and lymphocytes analyzed for mean telomere length, telomerase activity and F2-isoprostane levels (a measure of oxidative stress).

These three parameters were found to be similar between the groups. However, within the care-giving group, number of years-of-care-giving were significantly associated with mother's shorter telomere length, lower telomerase activity and higher oxidative stress at the cellular level- all of which have been proven previously to be indices of cell senescence and longevity. Interestingly, telomere length was related to perceived stress in both groups. The groups were similar in age, tobacco use, and vitamin use, but the high stress group had significantly higher BMI. Independent for age and BMI, the care-giving group had significantly shorter telomeres (3,110 bp telomeres in the care-giving group, compared to 3,660 bp telomeres in the control group). Translating telomere shortening to years of aging (based on previous studies which have estimated rate of telomere shortening with age), the authors calculated that the 550 bp shortening in the high stress group was equivalent to aging by 9-17 years, as compared to the control group.

The mean telomerase activity after adjustment for age and BMI, was 48% lower in the high stress group as compared to the control group. This is an intriguing demonstration of the relation between stress and aging and opens several avenues for further research.

1. Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, Cawthon RM. Accelerated telomere shortening in response to life stress. *Proc Natl Acad Sci* 2004;101:17312-5.

Miracle Babies

The previous decade has witnessed several advances in perinatal and neonatal care, such that there is now hope of survival for infants born at 22-25 weeks of age. However, these infants do suffer neurologically and developmentally throughout life. In the largest prospective study of preterm infants (born at 22-25 weeks) so far, Marlow et al followed preterm infants from birth to six years of age.¹ At six years of age, these children were assessed using standardized cognitive and neurologic measures and were compared to classmates born full term. Among the four domains, neuromotor, cognition, hearing and vision, cognitive impairment was the most common disability, present among 21% of the children born pre-term. This value rose to 41% when compared to their classmates. Twenty two percent of the children born pre-term had severe disability, 24% had moderate disability and 34% had mild disability.

The rates of survival with no disability at six years of age were: none among infants less than 22 weeks of gestation, 1% at 23 weeks, 3% at 24 weeks, and 8% at 25 weeks.

This study is critical for several reasons.² It is the largest and most up-to-date study of children born pre-term; it indicates limitations in current practice of saving such children and also in supporting their neurologic and cognitive development; it sheds light on guidelines to resuscitate infants born younger than 23 weeks of gestation; and it calls for comprehensive educational support for such children.

1. Marlow N, Wolke D, Bracewell MA, Samara M; EPICure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. *N Engl J Med* 2005;352:9-19.

2. Vohr BR, Allen M.N Extreme prematurity--the continuing dilemma. *Engl J Med* 2005;352:71-2.

My name is Serine

A case report from the Netherlands illustrates yet again a principle of medical management: '...that prenatal pharmaceutical and biochemical intervention of an affected fetus can prevent a severe and potentially lethal disease.'

Koning and colleagues diagnosed a fetus affected by 3-PGDH deficiency (an L-serine biosynthesis disorder) by DNA mutation analysis.¹ Ultrasound assessment

revealed a reduction in fetal head circumference from the 75th percentile at 20 weeks gestation to the 29th percentile at 26 weeks. At this point, L-serine was given to the mother (three doses of 5g of L-serine (190mg/Kg)) in an attempt to reverse the deceleration in brain growth.

At 31 weeks the fetal head circumference had enlarged to the 76th percentile, after which its growth slowed down again.

A baby girl was born after an uncomplicated pregnancy and delivery, with height and weight in the 40th percentile and head circumference in the 30th percentile. The child is presently four years old with normal growth, neurologic status and psychomotor development. She is receiving L-serine treatment at 500mg/kg per day.

1. de Koning TJ, Klomp LW, van Oppen AC, Beemer FA, Dorland L, van den Berg I, Berger R. Prenatal and early postnatal treatment in 3-phosphoglycerate-dehydrogenase deficiency. *Lancet* 2004;364:2221-2.

Members of the Group A Streptococci family - Please stand up!

Group A Streptococci (GAS) are the most common cause of bacterial pharyngitis among children and adults; they are the leading cause of acquired heart disease among children around the world, and they are increasingly responsible for deaths attributable to bacterial sepsis among children and adults. A four-year longitudinal study of school-aged children was conducted in Pittsburgh, Pennsylvania, to describe the clinical characteristics and epidemiological features of GAS infections.¹ This large prospective study is unique in several ways: GAS isolates were differentiated on the basis of emm types (designation of emm type is based on sequencing the 5'end of the emm gene) as opposed to serotyping; data were collected in a systematic longitudinal fashion which overcomes the problems of sporadic data obtained in clinical situations; all children in this cohort were accurately classified into four categories (single episodes, recurrent episodes, carriers, and no infections). The authors found that single episodes were most common (20% of children on average per year), while recurrent episodes were infrequent (8% of children on average per year). Among single episodes, 21% were atypical in presentation, 23% were completely asymptomatic and the remaining were typical cases. Approximately one half of the recurrent episodes were caused by a GAS isolate of the same emm type as the first infections, regardless of the time between episodes and previous antibiotic treatment. This suggests that infection with a specific emm type does not guarantee immunity against that specific type, or that early treatment may abort the development of type-specific immunity. A striking 40% of the children remained uninfected each school year, despite the fact that

their classmates had infections or were GAS carriers. More than one half of those who were uninfected in 1 year remained free of infection in a subsequent year. 31% of children (on average per year) were found to be carriers of GAS. The study revealed that carriage is both common and persistent. The duration of carriage of a single emm type persisted between 3 and 123 weeks. Children who cleared the carrier state demonstrated that they were likely to become carriers again, most probably of a new emm type. This has implications in clinical management: children who are carriers of a GAS may be at risk for acute rheumatic fever when they acquire new emm types. The authors advise that children who present with typical symptoms (sore throat and absence of cough and nasal congestion) and are found to have a GAS-positive throat culture should be treated, even if the child is known to be a carrier. The American Academy of Pediatrics and the Infectious Disease Society of America recommend that a rapid streptococcal test or throat culture for detection of GAS be performed only in children who present with typical symptoms.

1. Martin JM, Green M, Barbadora KA, Wald ER. Group A streptococci among school-aged children: clinical characteristics and the carrier state. *Pediatrics*.2004;114:1212-9.

Leave me alone - I'm tired!

Constantly tired and no probable cause- what could the matter be? Previously, higher rates of psychological disturbance have been shown to be associated with Chronic Fatigue Syndrome or Myalgic Encephalomyelitis (CFS/ME). Suggested risk factors are atopy, higher levels of physical exercise, parental illness, childhood or adolescent psychological distress. A recent study examined data from the 1970 British birth cohort.¹ Over 16,000 babies born during 5-11 April 1970 were followed up at 5, 10, 16 and 29-30 years of age. Data for children under 16 was collected from parents and teachers. At 29-30 years, participants self-reported CFS/ME and filled out a questionnaire which assessed predictors of CFS/ME. The lifetime prevalence of CFS/ME in this cohort was 0.8%.¹ None of the predictors assessed (including maternal or child psychological stress, academic ability, parental illness, atopy, birth order, birth weight or obesity) were associated with the risk of lifetime self-reported and physician diagnosed CFS/ME. Sedentary lifestyle was the only factor identified as a possible risk. Still tired? Try Exercise!

1. Viner R, Hotopf M. Childhood predictors of self reported chronic fatigue syndrome/myalgic encephalomyelitis in adults: national birth cohort study. *BMJ* 2004;329:941.

Dead beat?

Domestic violence (DV) has long been proven to have a strongly negative impact on children, affecting their physical, mental, emotional and cognitive well-being. The American Academy of Pediatrics recommends routine screening of female caretakers of paediatric patients, but this practice is not completely implemented and few studies have evaluated the problem from this angle. Holtrop and colleagues used the Partner Violence Screen (PVS) tool in an urban, resident-run paediatric clinic to assess if this increases the detection of DV and to test the mechanics of implementing the PVS in busy training clinics.¹ The results of this study were appalling. During the year that the PVS screen was used, the prevalence of DV was 3.7%, with a positive predictive value of 91.5%. During the previous year (when the PVS screen had not been implemented), DV was reported to have a prevalence of 0.2% ($P < 0.0001$). Thus PVS appears to be an essential screening tool but its mechanics of implementation in each clinic still need to be worked out. It would probably require more resources from social workers and family practitioners.

1. Holtrop TG, Fischer H, Gray SM, Barry K, Bryant T, Du W. Screening for domestic violence in a general pediatric clinic: be prepared! *Pediatrics* 2004 Nov;114:1253-7.

Two Tests for TB

TB in pediatric patients presents non-specifically and is difficult to diagnose in children who are less than 3 years of age, under weight and HIV infected. The TB Skin Test (TST) has poor sensitivity and does not reliably exclude TB in this population, resulting in over diagnosis

in an area where resources are strained. Liebschuetz and colleagues studied the usefulness of a rapid T-cell based blood test for detecting *Mycobacterium tuberculosis* (Mtb) infection in South Africa.¹ This is an enzyme-linked immunospot assay (ELISPOT), which detects T cells specific for antigens in Mtb but absent in BCG and most environmental mycobacteria. The results are therefore not confounded by previous BCG vaccination, and the test is more specific than TST. The specificity of ELISPOT has been proven to be high in previous studies. This study found that the sensitivity of ELISPOT was 83%, compared to 63% of TST ($P < 0.001$), and was not greatly affected by age, malnutrition and HIV infection (as is the case with TST). In children with both test results available, sensitivity of both tests combined was 91%. Thus using the tests together could provide clinically useful and increase diagnostic sensitivity in children with moderate to low index of suspicion for active TB. If both tests are negative, the child would be unlikely to have TB. However, if a child had a high pre-test probability of TB, both negative results would be unlikely to alter management, since the combined sensitivity of the tests is not 100%. Double positives and an asymptomatic patient can indicate Mtb infection and not active disease. The study concludes that ELISPOT together with TST could help clinicians exclude TB in 1/3 of children with suspected TB. The authors advise that the tests should be interpreted in light of the overall clinical picture.

1. Liebschuetz S, Bamber S, Ewer K, Deeks J, Pathan AA, Lalvani A. Diagnosis of tuberculosis in South African children with a T-cell-based assay: a prospective cohort study. *Lancet* 2004;364:2196-203.