A girl aged 4 years 9 months was referred to the National Research Center for Maternal and Child Health in Astana, Kazakhstan in July 2015 because of seizures, gaze paralysis, hypotonia, intellectual development deterioration and splenomegaly. This patient had been healthy until the age of 2.5 years when she started to exhibit sloppy poor speech, gaze paralysis, ataxia, recurrent falls on her back, and loss of skills.

When she was 4 years old a provisional diagnosis of Lennox-Gastaut syndrome with atonic drop seizures was made. However, the finding of splenomegaly (11.5 x 4.7 cm) in addition to the neurological symptoms modified the initial clinical impression and suggested an underlying enzymatic disease. Niemann-Pick type A/B was ruled out as the acid sphingomyelinase activity was normal (282 pmol/spot x 20 hr; normal range 200–3500). A bone marrow aspiration showed numerous cells with eccentric nuclei, abundant bluish, fibrillary cytoplasm suggestive of Gaucher cells. Beta-glucosidase levels were 119 pmol/spot x 20 hr (normal range 200–2000) and even though molecular genetic testing failed to show characteristic mutations, a diagnosis of Gaucher type 3 disease was made. In February 2016 the patient therefore started treatment with imiglucerase 60 units/kg every 2 weeks and was discharged home.

Six months later a new neurological examination revealed inability to talk or produce any sound, lack of emotions, myoclonic-astatic and propulsive seizures, dystonia, hypotonia, cataplexy, somnolence, upward gaze paralysis and ataxia. Hypersalivation, dysphagia, hyperreflexia, clonus and positive plantar reflex (Babinski sign) were also noted.

A cerebrospinal fluid exam did not show any abnormality while a magnetic resonance imaging scan revealed diffuse brain atrophy, particularly in the frontal lobes [Figure 1]. Electroencephalography showed spike-waves from the left temporal lobe and slow basic activity. The clear failure to respond to the enzyme replacement therapy led us to question the diagnosis of Gaucher disease type 3.

A repeated bone marrow aspiration confirmed the presence of numerous cells with eccentric nuclei and abundant foamy cytoplasm while a new blood enzymatic analysis showed high lyso-sphingomyelin-509 (2.4 ng/ml, normal ≤ 0.9) with normal lyso-sphingomyelin-65. Two heterozygous mutations were found in the NPC1 gene, the first located in intron 9, c.1554-1009G>A and the second in exon 18, c.2728G>A (p.Gly910Ser). Therefore, a diagnosis of Niemann-Pick disease type C (C1) was made and the treatment with imiglucerase was stopped.

Niemann-Pick disease type C is an autosomal recessive condition caused by mutations in the NPC1 (95%) or NPC2 (5%) gene and characterized by abnormalities of the intracellular transport of endocytosed cholesterol, with sequestration of unesterified cholesterol in lysosomes and late endosomes [1]. This rare condition (estimated minimal incidence of 1/120,000 live births) leads to progressive, irreversible, disabling neurological manifestations and premature death [2].

Our patient’s clinical presentation with gaze palsy, seizures, hypotonia, ataxia and splenomegaly was compatible with both Gaucher disease type 3 and Neumann-Pick disease type C. Unfortunately the specific test to diagnose Niemann-Pick disease type C was not included in the initial panel of enzymatic analyses and the diagnosis was initially missed. This case confirms that Niemann-Pick disease type C can be misdiagnosed as Gaucher disease type 3 [3,4]. We suggest that enzymatic analyses for both diseases be conducted when Gaucher’s cells are found in the
bone marrow and beta-glucosidase levels are low [3].

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References

Capsule
Faulty blood cells and heart disease
Recent studies have shown that elderly people's blood cells often harbor mutations in genes encoding certain epigenetic regulators. These mutations can lead to clonal expansion of the mutant blood cells, which increases the risk of blood cancers and cardiovascular disease. Fuster and co-authors generated a mouse model to investigate how one of these genes, Tet2, affects atherosclerosis development. They found that the disease progressed more rapidly in mice transplanted with Tet2-deficient bone marrow cells. This progression was due to increased secretion of interleukin-1β by Tet2-deficient macrophages in a process that depended on the action of inflammasomes.

Nature Med 2017; 23: 327
Eitan Israeli

Capsule
Whole-genome landscape of pancreatic neuroendocrine tumors
The diagnosis of pancreatic neuroendocrine tumors (PanNETs) is increasing owing to more sensitive detection methods, and this increase is creating challenges for clinical management. Scarpa et al. performed whole-genome sequencing of 102 primary PanNETs and defined the genomic events that characterize their pathogenesis. They describe the mutational signatures they harbor, including a deficiency in G:C→T:A base excision repair due to inactivation of MUTYH, which encodes a DNA glycosylase. Clinically sporadic PanNETs contain a larger than expected proportion of germline mutations, including previously unreported mutations in the DNA repair genes MUTYH, CHEK2 and BRCA2. Together with mutations in MEN1 and VHL, these mutations occur in 17% of patients. Somatic mutations, including point mutations and gene fusions, were commonly found in genes involved in four main pathways: chromatin remodeling, DNA damage repair, activation of mTOR signaling (including previously undescribed EWSR1 gene fusions), and telomere maintenance. In addition, our gene expression analyses identified a subgroup of tumors associated with hypoxia and HIF signaling.

Nature 2017; 543: 64
Eitan Israeli

Capsule
Targeting mitochondrial dysfunction can restore antiviral activity of exhausted HBV-specific CD8 T cells in chronic hepatitis B
Hepatitis B virus (HBV)-specific CD8 T cells are functionally exhausted in chronic hepatitis B infection, and this condition can be corrected only partially through the modulation of inhibitory pathways, which suggests that a more complex molecular interplay underlies T cell exhaustion. To gain broader insight into this process and identify additional targets for the restoration of T cell function, Fisicaro and associates compared the transcriptome profiles of HBV-specific CD8 T cells from patients with acute and chronic disease with those of HBV-specific CD8 T cells from patients able to resolve HBV infection spontaneously and influenza (FLU)-specific CD8 T cells from healthy participants. The results indicate that exhausted HBV-specific CD8 T cells are markedly impaired at multiple levels and show substantial downregulation of various cellular processes centered on extensive mitochondrial alterations. A notable improvement of mitochondrial and antiviral CD8 functions was elicited by mitochondrion-targeted antioxidants, which suggests a central role for reactive oxygen species (ROS) in T cell exhaustion. Thus, mitochondria represent promising targets for novel reconstitution therapies to treat chronic hepatitis B infection.

Nature Med 2017; 23: 327
Eitan Israeli
Anti-inflammatory corticosteroids are a first line of defense against many types of asthma, but individuals with severe asthma frequently do not respond to this therapy. Duvall and co-authors reported that this lack of response may be due in part to defects in natural killer (NK) cells, which are important mediators of inflammation resolution. NK cells from patients with severe asthma had impaired killing abilities, and corticosteroids inhibited the function of these cells further. The pro-resolving mediator LXA\(_4\) preserved NK cell effector mechanisms. Thus, corticosteroids may be counterproductive for severe asthma, and specifically activating NK cells may provide an alternate therapeutic target.

_Philip Duvall, MA, PhD, FMedSci, FMedP, James P. McAlinden, MA, PhD, and Chin-Yee O. Hui, MA_ 

### Malaria parasites increase attractiveness of humans to mosquitoes

People infected by malaria become more attractive to the mosquito vectors of the disease, which facilitates the spread of malaria. Emami and colleagues found that red blood cells of the host respond to a parasite-derived isoprenoid called HMBPP by increasing the production of carbon dioxide and several monoterpenes and aldehydes. Mosquitoes fed HMBPP-spiked blood displayed malaria parasite-specific changes in gene transcription, which reinforced attractiveness for the mosquito. HMBPP also stimulates mosquito feeding and malaria parasite reproduction. Thus, the parasite manipulates its mammalian host to make it more attractive to the insect vectors and exploits the same molecule to amplify transmission.

_Eitan Israeli_ 

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### Natural killer (NK) cells in severe asthma: failed resolution

Anti-inflammatory corticosteroids are a first line of defense against many types of asthma, but individuals with severe asthma frequently do not respond to this therapy. Duvall and co-authors reported that this lack of response may be due in part to defects in natural killer (NK) cells, which are important mediators of inflammation resolution. NK cells from patients with severe asthma had impaired killing abilities, and corticosteroids inhibited the function of these cells further. The pro-resolving mediator LXA\(_4\) preserved NK cell effector mechanisms. Thus, corticosteroids may be counterproductive for severe asthma, and specifically activating NK cells may provide an alternate therapeutic target.

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### A needle-free drug delivery device that works orally

No one likes to be on the receiving end of a needle, which can make routine childhood vaccinations especially problematic. Aran et al. developed a needle-free drug delivery device that works orally. The MucoJet™ device uses a simple chemical reaction to deliver a jet of vaccine, in this case ovalbumin, which penetrates the buccal mucosa when placed against the inside of a rabbit's cheek. The rabbits showed evidence of antibodies against ovalbumin in cheek tissue and ear vein blood samples 6 weeks after vaccination.

_Eitan Israeli_ 

_Philip Aran, PhD, and Christopher Annis, PhD_ 

### A traditional blood typing assay

Blood type matching is important for pregnancy, blood transfusion, and bone marrow transplantation. Zhang and colleagues developed a blood typing assay based on color changes assisted by a common pH indicator dye. Red blood cells (RBCs) and plasma were separated from small blood samples by using antibodies immobilized on paper test strips. The assays allowed forward grouping (detecting anti-A and/or anti-B antigens on RBCs) and reverse grouping (monitoring agglutination between RBCs and anti-A and/or anti-B antibodies in plasma) within 2 minutes. The test could also perform Rh and rare blood typing. This economical and robust assay will be useful in time- and resource-limited environments.

_Eitan Israeli_ 

_Philip Zhang, MD, PhD, and Philip Zhang, MD, PhD_ 

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_“The force which makes for war does not derive its strength from the interested motives of evil men; it derives its strength from the disinterested motives of good men”_  

Sir Ralph Norman Angel (1872-1967), English lecturer, journalist, author, and Member of Parliament for the Labour Party. He was knighted in 1931 and awarded the Nobel Peace Prize in 1933