by increasing c-Myc repressive activity. This decreases *CDKN1A* expression and alters the expression of other cell-cycle relevant genes to promote hypoxic cell proliferation (*9*). The role of HIF-2α in DNA replication is unclear.

Consistently, for the inhibition of DNA replication, HIF-1α DNA-binding and transcriptional activities are nonessential; likewise, ARNT has been shown to be dispensable. Hence, HIF-1α possesses an innate, ARNT-independent ability to curtail oxygen consumption, which argues against the notion of a "dead mutant" for a transcriptionally inactive form. Through functional antagonism to c-Myc and suppression of MCM activation, HIF-1α appears to multitask in meeting the demands of survival during hypoxia.

Although functional links between HIF-1α and Cdc6 or c-Myc have been established, details of these interactions are only beginning to be understood. It is unclear how HIF-1α simultaneously increases the abundance of chromatin-bound Cdc6 but prevents Cdc7-mediated phosphorylation of an MCM subunit (MCM2) (*4*). Also unclear is whether the decreased MCM2 phosphorylation is accompanied by an increase in phosphorylation of MCM3 and MCM4 by Chk2, a protein kinase that is activated by hypoxia (*10*), because these modifications block MCM helicase activity under stressed conditions (*11*). Likewise, although phosphorylation serves as a molecular determinant distinguishing between HIF-1α and HIF-2α in c-Myc antagonism (*12*), the signaling pathway controlling the phosphorylation is not known. The same HIF-1α polypeptide fragment engages in both cell cycle and DNA replication control, albeit in disparate ways (*4*, *6*). Assuming that HIF-1α fulfills its function as a transcription factor, could it be that HIF-1α handles its nontranscriptional roles by partitioning in a spatiotemporal order? The answer requires investigation of molecular signaling and biochemistry, and real-time imaging of events in cells. It remains a challenge to validate the nontranscriptional role of HIF-1α in vivo without compromising the transcriptional role. Thus, a loss-of-function approach (the gold standard to validate gene function) will not work unless transcriptional and nontranscriptional roles can be uncoupled functionally. Recognizing the nontranscriptional roles of HIF-1α has advanced the understanding of hypoxic responses in new contexts, including cell proliferation, carbon metabolism, DNA repair, and protein synthesis (*13*, *14*). HIF-1α now appears to be a complex molecule that possesses, for instance, both pro- and antitumor functions. Moreover, HIF-1α and HIF-2α have unique and sometimes opposing biological activities (*15*). Although HIF inhibitors are in clinical trials as cancer therapeutics, precise targeting of these molecules functionally, rather than molecularly, may improve their efficacies.

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ECOLOGY

Not All About Consumption

Resource exploitation can lead to increased ecological impacts even when overall consumption levels stay the same.

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The average barrel of oil on the market today has a larger ecological footprint than did the average barrel in 1950, and the average barrel in 2050 will have a larger ecological footprint than that of today. This tendency is most obvious in the increasing energy inputs required for production (*1*); production of all fossil fuels has an ecological impact, and increases in energy inputs thus translate into increased environmental impact. But exploiting less-accessible resources also requires more inputs, like diluents, water, and land and produces more waste. Furthermore, once resources near population centers are depleted, more geographically remote reserves are accessed, increasing the ecological costs of transport. The implication is simple: Even if consumption is held constant, ecological impact can increase—not only for energy but also for other resources.

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Ricardo offered a similar insight in his law of diminishing returns (*2*), observing that marginal agricultural land requires more inputs and generates less profit, but the perceived implications were entirely economic. Today, environmental awareness is greater, yet the wider implications of Ricardo's Law have gone unnoticed. According to the dominant paradigm in the environmental sciences, ecological impact is a function of consumption, as captured by the IPAT formula (Impact = Population × Affluence × Technology) introduced by Ehrlich and Holdren (*3*–*5*), but it lacks a variable that captures the condition of ecosystems. Humans could continue to extract oil, coal, natural gas, and many minerals for decades, but the escalating ecological implications of doing so demand research and policy attention.

The inverse relationship between resource richness and ecological impact shows in human efforts to meet oil demand. As oil fields decline, more effort must be expended to maintain production (*6*), and due to domestic production declines in consuming nations, exports now constitute 75% of global production (*7*). Newly discovered fields are smaller and geographically dispersed, requiring greater transit distances. They are also deeper, requiring more energy to extract, and entail greater ecological risks, which became clear when BP's 10.7-km-deep Deepwater Horizon well exploded in 2010.

Capturing this relationship empirically can be challenging, particularly at the global scale, but the story becomes vivid once we consider a particular production zone. Alberta has been the seat of Canada's oil production for half a century. Oil production has several ecological impacts, but the most immediate is the consumption of land. If the area of land consumed per barrel of oil produced were constant or improving, the rate of oil production would increase at least as fast as land consumption. This is not the case, however. During an initial period of extraction at a reservoir there may be efficiency gains, but as the reservoir ages the opposite will be true. Alberta's conventional oil production follows this trend: From 1955 to 2006, the area of land required to extract a barrel of oil has increased 12-fold (*8*).

Conventional oil well pads in Alberta consume 3.3 ha on average (*9*), but the ecosystem fragmentation caused by the roads and pipelines required to support the wells results in a much higher total impact (*10*). By law, land cleared for an oil well must be reclaimed after abandonment, but the ecological value of reclaimed sites is not equivalent to their predevelopment condition. Furthermore, reclamation has not kept up. The average number of wells abandoned annually in the past decade was 4111; the number reclaimed averaged 1682 (*11*).

Alberta's declining conventional oil industry has been surpassed by rapidly growing oilsands exploitation, representing a further escalation of impact. A recent study found that emission levels in oil-sands mines are 23 times that of conventional production (*9*). Because less than 20% of the deposit can be accessed from the surface, production will soon be dominated by in situ drilling, substantially increasing cumulative land disruption: Three times as much land is disturbed to produce the natural gas required for oil-sand drilling as is consumed by the wells themselves (*10*).

If the thesis holds that resource quality declines over time as a given reserve is depleted, one would expect the same to hold true for oil sands. But even before evidence of this tendency emerges for the oil-sands reserves themselves, the impact caused by the energy inputs required for oil-sands extraction and processing will escalate. Currently, this energy mostly comes from regional natural gas supplies, which are in steep decline. In the very near future, oil-sands exploitation will require other sources of natural gas, which have a higher ecological impact than do the conventional, regional sources.

Diminishing returns and increasing environmental impacts. The effects of oil production from oil sands in Alberta provide an example of the increasing environmental impacts of energy production.

Declining conventional fossil fuel reserves have motivated much more investment in nonconventional fossil fuel enterprises than in renewable alternatives, representing a global trend toward increased ecological impact per unit of fuel produced. Coal production, which is growing at a faster rate than any other fossil fuel, is increasingly dominated by surface (including mountain-top) mining, which allows more efficient extraction of lower-density deposits but is also more ecologically disruptive than underground mining.

Signs of diminishing returns and increasing environmental impacts are also evident in nonenergy sectors. In China, production efficiency gains in land use for grain production leveled off 30 years ago, but inputs continue to increase, including a 10-fold increase in groundwater extraction to support irrigation since 1961 (*12*) and a nearly 17-fold increase in fertilizer use between 1961 and 2009 (*13*). Global fish catch peaked in the past 10 years at ~90 million tons, yet fishing effort has continued to increase by 1.1% per year (*14*), resulting in more by-catch, damage from fishing equipment, and fuel consumption. Meanwhile, the mean trophic level of fish harvest has declined (*15*).

Even if consumption leveled off, increases in ecological impact could result as global reserves become depleted. The question is not when resources will run out, but how much ecological impact we can tolerate.

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EPIDEMIOLOGY

The SARS Wake-Up Call

Ten years ago, the SARS outbreak spurred efforts by the World Health Organization to improve global responses to health threats and crises.

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In February 2003, a 64-year-old doctor was treating patients with atypical pneumonia in his home town of Guangzhou, in Guangdong Province, China (*1*). He himself had developed a respiratory complaint but felt well enough to travel to Hong Kong and go sightseeing with his brother-in-law. Unknown to him or anyone else, his symptoms were the early stages of "severe acute respiratory syndrome" caused by a previously unknown coronavirus (SARS-CoV) (*2*). The doctor, who had been staying in a hotel during his visit, checked into a Hong Kong hospital, warning staff that he had contracted a virulent disease. He succumbed 10 days later. During his short illness he had infected his brother-in-law (who died shortly after), at least two hospital nurses, and seven hotel guests including three from Canada, Singapore, and Vietnam. One hotel guest admitted to a hospital infected at least 88 health workers and 18 medical students. Another patient discharged from the same hospital started an outbreak affecting more than 200 residents of a housing estate. Infection continued to spread rapidly and widely. Within 5 months, 8096 people had been affected in 30 countries and 774 died, a fatality rate of about 1 in 10. As the emergency unfolded over the following 134 days, it stimulated renewed debate about how countries should work together to combat public health crises that run across national bound-

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