900.000 Belges évitent le médecin pour raisons financières

- La presse de ce jeudi matin révélait le médiocre classement de la Belgique dans l'enquête Qualicopc. Cette enquête internationale et financée par Commission européenne a pour objet la recherche sur la qualité et le coût des soins de santé.

- Selon les résultats divulgués par la presse, un peu plus **de 8 % des Belges** éprouvent des difficultés financières pour se rendre chez le médecin. 900.000 Belges éviteraient ou reporteraient une visite médicale pourtant nécessaire.

- Le pourcentage augmente lorsque les personnes uniquement interrogées ont des faibles revenus. **Plus de 20% d'entre elles reconnaissent avoir reporté au cours de l'année une visite médicale pour des motifs financiers.**

- La Belgique se place dans l'enquête Qualicopc à la 20e place, sur un classement de 31 pays. En comparaison**, 1 % seulement des Autrichiens renoncent à leur visite** médicale pour des raisons d'argent. A contrario, la Chypre voit ce chiffre, concernant ses ressortissant, grimper à 27,8%.

- - See more at: http://www.actualitesdroitbelge.be/droit-des-affaires/actualites/900000-belges-evitent-le-medecin-pour-raisons-financieres/presentation-des-faits#sthash.bTcemJJt.dpuf

Pénurie de médecins urgentistes en Belgique

- D'après les dernières estimations, il manquerait environ **1.200 médecins urgentistes** en Belgique.
- Le manque de spécialistes a pour conséquence l'absence de médecin urgentiste dans les services d'urgence. Diverses communes flamandes se sont d'ailleurs déjà retrouvées dans ce cas lors de services de nuit aux urgences.

- Cette pénurie présente aussi des répercusions sur le service mobile d'urgence et de réanimation (SMUR). Si un médecin urgentiste tombe malade, il n'a souvent pas de remplacement. Le SMUR ne peut alors se déplacer. Le patient doit alors attendre qu'un médecin se déplace depuis son domicile.

- S'il faut en principe deux médecins urgentistes pour assurer le SMUR, ce n'est souvent pas le cas. « C'est pourquoi dans ce cas, la législation prévoit que si un médecin urgentiste est effectivement présent, un autre doit rester de garde et pouvoir se rendre à l'hôpital dans les quinze minutes, quand le SMUR doit intervenir. » explique Jan Stroobants, président de l'association des médecins urgentistes, à Belga.

- Le médecin spécialiste en médecine d'urgence est généralement d'abord spécialiste dans un autre domaine (chirurgie, **médecin internet, (sic)** anesthésiologie,...) et « a suivi une formation complémentaire de compétence particulière en soins d'urgence. » Le médecin urgentiste peut aussi avoir suivi, depuis la rentrée scolaire 2005-2006, une formation orientée vers la médecine d'urgence. Celle-ci consiste en une spécialisation en médecine aigüe suivi en un cycle de trois ans, suivie par une deuxième période de trois ans pour être spécialiste en médecin d'urgence. Les médecins généralistes qui possèdent le brevêt (sic) de médecine aiguë peuvent également exercer la spécialisation

- - See more at: http://www.actualitesdroitbelge.be/presse/penurie-de-medecins-urgentistes-en-belgique#sthash.FPJmSlva.dpuf

Quelque 500 médicaments en pénurie en Belgique

- **Près de 500 médicaments sont actuellement difficilement accessibles voire indisponibles en Belgique. Cela peut être la conséquence d'un problème technique dans la production ou en raison de quotas dépassés, écrit Le Soir mercredi.**
- Un grossiste estime à 340 le nombre de médicaments contingentés, c'est-à-dire qui doivent être acquis directement auprès du producteur car le quota alloué à la Belgique a été dépassé. Ces quotas ont été instaurés par les firmes pharmaceutiques afin d'éviter que certains médicaments soient importés de pays où ils sont vendus moins cher.

  Environ 180 autres médicaments sont eux actuellement indisponibles en raison de problèmes techniques de production. Cela porte au total à un peu plus de 500 produits pharmaceutiques le nombre de médicaments en pénurie en Belgique, soit quasi 5% du total des spécialités en circulation. Le problème est d'autant plus criant que ces médicaments sont le plus souvent utilisés pour soigner des maladies chroniques et que, dans la plupart des cas, il n'existe pas de générique disponible pour remédier à la pénurie.

Les chauves-souris et d'autres prédateurs se servent des sons pour détecter leurs proies. Mais celles-ci ont développé des stratégies de camouflage acoustique.

Une course aux armements acoustiques

William Conner

Avez-vous déjà vu un hibou fondre sur un campagnol qui se déplace sous une couche de feuilles sèches ? Dans l'affirmative, vous avez pu constater l'efficacité de sa stratégie de détection, fondée sur une écoute passive, c'est-à-dire sur la détection des sons émis par ses proies. D'autres animaux – la plupart des chauves-souris et certains odontocètes (des cétacés à dents, tels les dauphins) – ont une stratégie active : ils émettent des sons et captent les échos, une technique qualifiée d'écholocalisation ou de sonar biologique. Les échos leur permettent de s'orienter dans leur environnement et de détecter les proies. En quelque sorte, ils voient grâce au son.

L'écholocalisation s'est développée il y a plus de 65 millions d'années chez les chauves-souris, et plus récemment chez les odontocètes. Le sonar biologique est une merveille technique, qui inspire les ingénieurs. Ces derniers ont développé des systèmes équivalents, les radars et les sonars, installés dans des stations au sol ou dans des véhicules aériens et sous-marins. Ces systèmes partagent de nombreuses caractéristiques avec l'écholocalisation animale dans la façon de produire, d'émettre, de recevoir et de traiter les signaux. Et le plus étonnant est peut-être que, chez les animaux comme chez les hommes, des contre-mesures sont apparues, telles des méthodes de furtivité et de brouillage du signal.

Un radar (*RAdio Detection And Ranging*, en français détection et télémétrie radio) émet des ondes radio, dont les échos après réflexion sur les objets sont détectés par une antenne. Si l'objet se déplace, les signaux réfléchis ont une fréquence différente, ce qui permet de déduire la vitesse de la cible. On utilise les ondes radio parce qu'elles parcourent de grandes distances dans l'air, même en présence de brouillard et de précipitations. Les ondes sonores se propagent mieux sous l'eau, ce qui a conduit au développement du sonar (*SOund Navigation And Ranging*, en français navigation et télémétrie par le son) pour la détection dans ce milieu. Le signal est différent, mais le principe est le même.

De nombreux scientifiques ont contribué au développement du radar, tels l'inventeur américano-serbe Nikola Tesla, et Guglielmo Marconi, l'ingénieur italo-britannique qui fut le premier à transmettre un signal radio d'un côté de l'Atlantique à l'autre. La mise au point de systèmes fonctionnels s'est accélérée à l'approche de la Seconde Guerre mondiale. Le premier d'entre eux, nommé *Chain Home*, comprenait une série de stations radar réparties sur les côtes sud et est de l'Angleterre. Il visait à détecter les bombardiers allemands qui se massaient dans l'espace aérien français, afin de permettre aux avions de combat anglais de se positionner à haute altitude pour les repousser.

Le développement du sonar précède d'une trentaine d'années celui du radar. Il s'intègre également dans une course aux armements, puisque l'objectif était de repérer les sous-marins de la Première Guerre mondiale. Les premiers dispositifs, installés sur des navires allemands, étaient fondés

LOGIQUE & CALCUL

Indécidables utiles et inutiles

Les affirmations sur la complexité sont souvent indécidables. D'où l'idée d'en utiliser comme axiomes pour limiter la désagréable incomplétude de toute théorie mathématique, découverte par Kurt Gödel il y a 80 ans.

Jean-Paul DELAHAYE

Ce qui est simple peut se dire en peu de mots et donc ce qui est complexe en demande beaucoup. Le hasard ne pouvant pas se résumer, il est incompressible et fournit les objets les plus complexes. Ces idées élémentaires servent de fondement à la « théorie algorithmique de l'information » ou théorie de la « complexité de Kolmogorov ». Créée il y a 50 ans par le mathématicien russe Andreï Kolmogorov et quelques autres théoriciens, son importance se confirme d'année en année : on l'utilise en physique pour définir l'entropie, en biologie pour concevoir des algorithmes de comparaison de séquences, en psychologie pour mesurer la capacité des humains à reconnaître et simuler le hasard, etc.

En logique mathématique et en philosophie des sciences, les multiples facettes de cette théorie définissent ce qu'est une suite infinie aléatoire ou une théorie complexe *(voir la rubrique du numéro de mai 2013 : « Qu'est-ce qu'un objet complexe ? »)*. Nous verrons ici que des axiomes portant sur le hasard et la complexité enrichissent une théorie mathématique et augmentent son pouvoir de démonstration. Cinq mathématiciens d'origines variées, Laurent Bienvenu et Antoine Taveneaux, de l'Université Paris 7, Andreï Romashchenko et Alexander Shen, aujourd'hui à l'Université de Montpellier, et Stijn Vermeeren, de l'Université de Leeds en Grande-Bretagne, ont dans un article récent fait avancer notre compréhension du hasard et du rôle logique de la complexité.

1. La complexité ne peut être calculée

La complexité de Kolmogorov d'une suite finie s de 0 et de 1 est la taille du plus court programme écrit dans un langage assez puissant qui produit s. On la note $K(s)$. Une suite d'un million de 0 a une faible complexité de Kolmogorov, car il existe des programmes courts qui l'engendrent (par exemple : « Pour i de 1 à 1 000 000, print '0' »). C'est vrai aussi de la suite composée d'un million de chiffres de π ou de e, car, grâce aux nombreuses séries qui donnent π ou e, on sait écrire des programmes courts qui calculent un million de chiffres de π ou de e. Il existe un programme de moins de 200 caractères (J. Gibbons, *Amer. Math. Monthly*, vol. 113, pp. 318-328, 2006) qui réussit l'exploit de calculer indéfiniment des chiffres de π. Bien sûr, il les calcule de plus en plus lentement, mais il ne s'arrête que lorsque toute la mémoire de la machine a été utilisée. Il ne s'arrêterait pas si l'on ajoutait progressivement de la mémoire à la machine.

Il est assez facile de montrer qu'il existe des suites s de complexité $K(s)$ aussi grande qu'on le souhaite ; mais Gregory Chaitin a établi que si l'on se donne une théorie formalisée T, elle ne peut démontrer qu'un nombre fini de théorèmes de la forme « $K(s) = n$ » ou « $K(s) > n$ ». Cela signifie que, sauf pour un nombre fini de suites s, la théorie T ignore tout de la complexité de s : la complexité est, sauf rares exceptions, indécidable. La situation est presque paradoxale : une théorie T (par exemple l'arithmétique de Peano, formalisation la plus naturelle des modes de raisonnements en arithmétique) prouve qu'il existe des suites de grande complexité, mais n'en connaît aucune. Cette forme particulière de l'incomplétude est remarquable, car contrairement aux formules dont Kurt Gödel a démontré l'indécidabilité, les formules concernant la complexité de Kolmogorov sont immédiatement compréhensibles.


Andreï Kolmogorov


Gregory Chaitin


Giuseppe Peano


Kurt Gödel

Under these circumstances, and however anomalous it may seem, the idea of bringing death with dignity to the ICU is highly germane. I believe that not only should the barriers between family and patient in the unit be minimized (and indeed many ICUs have now implemented such policies), but the process of decision making should also more fully reflect the principles of palliative care. Such an ICU culture would not only promote aggressive treatment but also help patients and their families make wise decisions about managing the end of life. This approach, as Cook and Rocker observe, may seem paradoxical, but it is nevertheless altogether essential.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Center for the Study of Society and Medicine, Columbia University College of Physicians and Surgeons, New York.

1. Rothman SM. Living in the shadow of death: tuberculosis and the social experience of illness in American history. New York: Basic Books, 1994.
2. Faust DG. This republic of suffering: death and the American Civil War. New York: Vintage Books, 2009.
3. National Center for Health Statistics. Health, United States, 2010: with special feature on death and dying. Washington, DC: Government Printing Office (http://www.cdc.gov/nchs/data/hus/hus10.pdf).
4. Teno JM, Gozalo PL, Bynum JPW, et al. Change in end-of-life care for Medicare beneficiaries: site of death, place of care, and health care transitions in 2000, 2005, and 2009. JAMA 2013;309:470-7.

DOI: 10.1056/NEJMp1404427

Drug Safety in the Digital Age

Thomas J. Hwang, A.B., Florence T. Bourgeois, M.D., M.P.H., and John D. Seeger, Pharm.D., Dr.P.H.

The Internet is increasingly redefining the ways in which people interact with information related to their health. The Pew Internet Project estimates that more than half of all Americans sought health information online in 2013, mostly through search engines such as Google and websites such as Wikipedia and WebMD.

In this digital age, engaging with new media offers an unparalleled opportunity for medical and public health professionals to find information they need and to interactively reach out to patients and their support networks. One domain where these capabilities may have far-reaching effects that are currently undefined is drug safety. As the volume of health-related information on the Internet has grown, important questions have emerged. How are messages from regulators — for example, warnings against using a drug in a specific patient population — diffused digitally? And are the messages still accurate when they reach the general population?

To explore these questions, we selected new drug-safety communications related to prescription medicines that were issued by the U.S. Food and Drug Administration (FDA) over a 2-year period between January 1, 2011, and December 31, 2012 (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Despite debates over its credibility, Wikipedia is reportedly the most frequently consulted online health care resource globally[1]: Wikipedia pages typically appear among the top few Google search results and are among the references most likely to be checked by Internet users.[2] We therefore evaluated Google searches and Wikipedia page views for each drug in our sample. We also examined the content of Wikipedia pages, looking specifically for references to safety warnings. To control for secular trends, we examined results from a 120-day window around the date of the announcement (from 60 days before the announcement to 60 days after it) and constructed a baseline period for comparison that ran from 60 days to 10 days before the period of interest began.[3]

We identified safety warnings for 22 prescription drugs that are indicated for a range of clinical conditions, including primary hypertension, chronic myelogenous leukemia, and hepatitis C. Collectively, these drugs triggered 13 million searches on Google and 5 million Wikipedia page views annually during the study period. FDA safety warnings were associated with an 82% increase, on average, in Google searches for the drugs during the week after the announcement and a 175% increase in views of Wikipedia pages for the drugs on the day of the announcement, as compared with baseline trends (see line graph and Fig. S1 in the Supplementary Appendix).

Did users find accurate information on the drugs' safety? We found that 41% of Wikipedia pages pertaining to the drugs with new safety warnings were updated within 2 weeks after the warning was issued with information provided in the FDA an-

ware-laden e-mail, the hospital took the precautionary step of temporarily shutting down its entire e-mail system. The shutdown gave IT staff time to quarantine malicious e-mail and to notify staff of the absolute importance of not clicking links or opening attachments without being certain that they were safe. And although having no e-mail was a minor inconvenience for most employees (and a nice respite for some), many internal processes actually depend on e-mail for normal operations, so workarounds had to be developed.

As health care organizations push forward to further enable electronic health records (EHRs), many of which are hosted remotely, the potential effect of losing Internet connectivity is large, and the analysis required to understand that effect is complex. As an organization that achieved the highest stage (Level 7) on the Health Information Management Systems Society's Analytics Electronic Medical Record Adoption Model several years ago[1] — which indicates the degree to which we have automated our inpatient care processes — our hospital has invested substantial time and resources in putting these kinds of contingency plans and security technologies in place. For organizations just beginning their EHR journey, this advance planning and attention to information security and business continuity cannot be stressed enough, especially in this new world where a cyberattack on a hospital is possible.

Health care organizations can no longer assume that they are immune from organized attacks like the one described above. As in any other industry, in addition to safeguarding against the compromise of sensitive data, health care entities must now protect themselves against direct attacks meant to disrupt operations. In clinical settings, such attacks can clearly have adverse effects on patient care. Health care organizations should strongly consider investing the time and resources in IT security systems and operational best practices to ensure that they are prepared to endure and defend against these new threats, if and when they occur.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Information Services Department, Boston Children's Hospital; and the Department of Pediatrics, Harvard Medical School — both in Boston.

1. Electronic Medical Record Adoption Model (EMRAM): Stage 7 case studies, Children's Hospital Boston. Chicago: HIMSS Analytics (http://www.himssanalytics.org/emram/stage7caseStudies.aspx?hospID=3).

DOI: 10.1056/NEJMp1407326

Cybersecurity in Health Care

Eric D. Perakslis, Ph.D.

Most of us are aware of cyberthreats — if not because of personal experience, then thanks to a barrage of news stories. We've read that many of our banks, credit-card companies, and favorite retailers have been hacked and that tens of millions of consumers had their personal financial information stolen during the 2013 holiday season. In addition, last year brought stories of successful cyberintrusion at the Food and Drug Administration (FDA) and of the theft of the designs of major U.S. military weapons systems by foreign governments. Health care data and infrastructure are at least as vulnerable as most financial and military data. And beyond the pecuniary, regulatory, and reputational risks associated with data and identity theft lie even graver threats to health care infrastructure and patient safety.

In a recent study, a whopping 94% of health care institutions reported having been victims of cyberattacks.[1] To date, cybercrime against health care has manifested as four specific threats: data loss, monetary theft, attacks on medical devices, and attacks on infrastructure. Some cybercriminals are motivated by financial gain, whereas others seek to obtain intellectual property or consumer information, to damage an institution's reputation, or to make a political statement through "hacktivism." The privacy and security rules put in place by the Health Insurance Portability and Accountability Act (HIPAA) have raised awareness of the importance of protecting personal health information and have provided a regulatory framework to encourage compliance — but compliance does not necessarily translate into security. The fact is that most current HIPAA protection strategies rely on standard technological methods of isolating critical data, but this recent study indicates that many attackers are bypassing these types of protections and do not require stealth techniques to

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Ebola — A Growing Threat?

Heinz Feldmann, M.D.

The recent emergence of *Zaire ebolavirus* in West Africa[1] has come as a surprise in a region more commonly known for its endemic Lassa fever, another viral hemorrhagic fever caused by an Old World arenavirus. Yet the region has seen previous ebolavirus activity (see map). In the mid-1990s, scientists discovered *Côte d'Ivoire ebolavirus* (now known as *Taï Forest ebolavirus*) as a cause of a single reported nonfatal case in a researcher who performed a necropsy on an infected chimpanzee. The episode initiated a major research investigation in and around the Taï Forest region — an effort that failed to identify the reservoir of this new Ebola species. Since that incident, West African countries have not reported any evidence of the presence of ebolavirus.

Ebolaviruses belong to the family Filoviridae, a taxonomic group of enveloped, nonsegmented, negative-strand RNA viruses that includes the genera marburgvirus and cuevavirus, with a single species each, and ebolavirus, with five distinct species (see figure). All known African ebolaviruses can infect humans and cause similar symptoms, but they vary in terms of disease progression and virulence, with case fatality rates ranging from less than 40% for *Bundibugyo ebolavirus* to approximately 50% for *Sudan ebolavirus* to 70 to 90% for *Zaire ebolavirus*.[2] The virulence of *Taï Forest ebolavirus* is difficult to assess because there has been only a single recorded case, and the only identified Asian species, *Reston ebolavirus*, seems to cause asymptomatic infection in humans.

Humans infected with ebolaviruses commonly present initially with nonspecific symptoms such as fever, vomiting, and severe diarrhea, with visible hemorrhage occurring in less than half the cases,[2] as in the current outbreak.[1] Owing to poor infrastructure, biosafety concerns associated with processes of patient care and autopsy, and the essential focus on disease containment during outbreaks, there has been little empirical study to elucidate the pathogenesis or pathology of human ebolavirus infection. The closest surrogate disease models are cynomolgus and rhesus macaques, which show clinical signs of viral hemorrhagic fever when infected with most ebolaviruses. *Zaire ebolavirus* is uniformly lethal in these macaques, and experts have assumed that its

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Chikungunya at the Door — Déjà Vu All Over Again?

David M. Morens, M.D., and Anthony S. Fauci, M.D.

In 2008, we noted that the global reemergence of dengue fever threatened U.S. residents.[1] An outbreak of locally acquired dengue subsequently occurred in Florida, and the risk of U.S. dengue outbreaks will probably continue indefinitely.

We now face a new threat posed by the unrelated chikungunya virus, which causes a disease clinically similar to dengue in a similar epidemiologic pattern, which is transmitted by the same mosquito vectors, and for which we also lack vaccines and specific treatments.

In December 2013, an outbreak of chikungunya fever appeared in the French sector of Saint-Martin/Sint Maarten and spread epidemically throughout the French West Indies to other Caribbean islands and contiguous Central and South American countries. By July 11, 2014, the Pan American Health Organization had reported more than 355,000 suspected and confirmed cases of chikungunya fever from more than 20 countries or jurisdictions in the Americas, with continuing local transmission and epidemic spread.

In 2014 in the continental United States, 232 imported cases of chikungunya fever had been reported as of July 15, according to the National Center for Emerging and Zoonotic Infectious Diseases at the Centers for Disease Control and Prevention (CDC); many of these cases occurred in the 14 or more states that harbor the classic mosquito vector, *Aedes aegypti*, that is capable of supporting local chikungunya transmission. Moreover, an even more tenacious vector mosquito, *Ae. albopictus*, has established itself in at least 32 states over the past three decades.

Chikungunya is an arbovirus (arthropod-borne virus) first described during a 1952 outbreak in southern Tanganyika (now Tanzania). It is an RNA virus within the alphavirus genus of the Togaviridae family. The name "chikungunya" derives from a word in the Kimakonde language meaning "to become contorted" or "to walk bent over," an apt description of the appearance of some infected people with arthralgias.

Typically, chikungunya disease manifests as acute onset of fever and prostration, muscle and joint pains, lymphopenia (as in many arboviral diseases), and frequently a nonspecific maculopapular

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Elizabeth G. Phimister, Ph.D., *Editor*

Diagnostic Clinical Genome and Exome Sequencing

Leslie G. Biesecker, M.D., and Robert C. Green, M.D., M.P.H.

From the National Human Genome Research Institute, National Institutes of Health, Bethesda, MD (L.G.B.); and the Division of Genetics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, and Partners HealthCare Personalized Medicine — all in Boston (R.C.G.). Address reprint requests to Dr. Biesecker at 49 Convent Dr., Rm. 4A56, Bethesda, MD 20892-4472, or at lesb@mail.nih.gov.

N Engl J Med 2014;370:2418-25.
DOI: 10.1056/NEJMra1312543

SEQUENCING OF THE GENOME OR EXOME FOR CLINICAL APPLICATIONS, hereafter referred to as clinical genome and exome sequencing (CGES), has now entered medical practice.[1] Several thousand CGES tests have already been ordered for patients, with the goal of establishing diagnoses for rare, clinically unrecognizable, or puzzling disorders that are suspected to be genetic in origin. We anticipate increases in the use of CGES, the key attribute of which — its breadth — distinguishes it from other forms of laboratory testing. The interrogation of variation in about 20,000 genes simultaneously can be a powerful and effective diagnostic method.[2]

CGES has been hailed as an important tool in the implementation of predictive and individualized medicine, and there is intense research interest in the clinical benefits and risks of sequencing for screening healthy persons[3]; however, current practice recommendations[4] do not support the use of sequencing for this purpose, and for that reason we do not further address it here. We have also limited this overview of CGES to the analysis of germline sequence variants for diagnostic purposes and do not discuss the use of CGES to uncover somatic variants in cancer in order to individualize cancer therapy.

An interactive graphic giving an overview of the steps in CGES is available at NEJM.org

Clinicians should understand the diagnostic indications for CGES so that they can effectively deploy it in their practices. Because the success rate of CGES for the identification of a causative variant is approximately 25%,[5] it is important to understand the basis of this testing and how to select the patients most likely to benefit from it. Here, we summarize the technologies underlying CGES and offer our insights into how clinicians should order such testing, interpret the results, and communicate the results to their patients (an interactive graphic giving an overview of the process is available with the full text of this article at NEJM.org).

TECHNICAL OVERVIEW AND LIMITATIONS OF CGES

Detailed technical descriptions of sequencing can be found elsewhere,[6-9] and we provide a graphical summary of one method of CGES in Figures 1 and 2. Regardless of the specific technology that is used, the process begins with the extraction of DNA from white cells, after which the DNA is broken into short fragments, the sequences of which are determined with the use of one of various sequencing technologies. The sequencing instrument generates millions of short sequence reads, which are strings of data representing the order of the DNA nucleotides, or bases, in each fragment. These sequence reads are then aligned to specific positions in the human genome reference sequence (see Glossary) with the use of computers.[10] Similarities and differences between the patient's sequence and the reference sequence are tabulated, and a computerized determination of the specific genotype (A, C, G, or T) at each position in the exome or genome is performed, resulting in an output file along

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Edward W. Campion, M.D., *Editor*

Cancer of Unknown Primary Site

Gauri R. Varadhachary, M.D., and Martin N. Raber, M.D.

CANCER OF UNKNOWN PRIMARY SITE IS A HETEROGENEOUS GROUP OF cancers for which the anatomical site of origin remains occult after detailed investigations.[1,2] The emergence of sophisticated imaging, immunohistochemical testing, and molecular-profiling tools has influenced our approach to unknown primary cancer, although it has also increased the ambiguity of designations for this disorder. In the era of tailored therapeutic strategies, this situation presents both an opportunity and a challenge.

The past four decades have seen a shift in our understanding of unknown primary cancer (Fig. 1). First, improved imaging techniques increased our confidence in the classification of some cancers as having an occult primary origin. Later, subsets of unknown primary cancers with an apparently favorable prognosis were identified, primarily on the basis of histopathological findings, the pattern of spread, and serum markers.[2] Subsequently, with the advent of new immunohistochemical markers and advances in diagnostic pathological tests, tissue-of-origin profiles were described that assigned additional putative primary sites to unknown primary cancer on the basis of immunohistochemical patterns.[3-6] Current research involves the application of proteomic and genomic tools to unknown primary cancer.

Cancer of unknown primary site was once viewed almost as a separate type of cancer, with the assumption that, regardless of the site of origin, the tumors in unknown primary cancers shared biologic properties, perhaps including rapid progression and dissemination, which contributed to their presentation. This view drove the conduct of phase 2 empirical trials over the past three decades, with the goal of developing standard chemotherapy regimens that would be effective in all patients with unknown primary cancer. The underlying assumption was that variations in presentation would not have a substantial effect on therapeutic approaches or survival.

Our view of unknown primary cancer has evolved as our understanding of cancer biology in general has matured to become much more personalized. Many people now believe that tumors in unknown primary cancer may retain the signature of the putative primary origin and that extending the management of known cancers to subtypes of unknown primary cancer can contribute to advancements in therapies for this disease. Cancer of unknown primary site could even be seen as the epitome of personalized medicine, with individualized treatment driven by the mutational status of each patient.

The biologic events that allow the primary site to remain obscure after the development of metastases have not yet been defined. Studies that have shown chromosomal abnormalities, microvessel density, aneuploidy, and overexpression of several genes suggest that these abnormalities are not unique to unknown primary cancer.[7-11] With the use of the Sequenom MassARRAY platform, a study involving consecutive patients with unknown primary cancer showed a low rate of mutations (in 18% of patients).[12] No new, low-frequency mutations were found with the use of a panel of mutations involving the phosphatidylinositol 3-kinase

From the Department of Gastrointestinal Medical Oncology, University of Texas M.D. Anderson Cancer Center, Houston. Address reprint requests to Dr. Varadhachary at the Department of Gastrointestinal Medical Oncology, Unit 426, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030-4009, or at gvaradha@mdanderson.org.

N Engl J Med 2014;371:757-65.
DOI: 10.1056/NEJMra1303917

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Barrett's Esophagus

Stuart J. Spechler, M.D., and Rhonda F. Souza, M.D.

From the Esophageal Diseases Center, Department of Medicine, Veterans Affairs (VA) North Texas Health Care System, and the University of Texas Southwestern Medical Center, Dallas. Address reprint requests to Dr. Spechler at the Division of Gastroenterology and Hepatology (111B1), Dallas VA Medical Center, 4500 S. Lancaster Rd., Dallas, TX 75216.

N Engl J Med 2014;371:836-45.
DOI: 10.1056/NEJMra1314704

IT HAS BEEN ESTIMATED THAT 5.6% OF ADULTS IN THE UNITED STATES HAVE Barrett's esophagus,[1] the condition in which a metaplastic columnar mucosa that confers a predisposition to cancer replaces an esophageal squamous mucosa damaged by gastroesophageal reflux disease (GERD).[2] GERD and Barrett's esophagus are major risk factors for esophageal adenocarcinoma, a deadly tumor whose frequency in the United States has increased by a factor of more than 7 during the past four decades.[3,4] The metaplastic columnar mucosa of Barrett's esophagus causes no symptoms, and the condition has clinical importance only because it confers a predisposition to cancer.

PATHOGENESIS

Metaplasia, the process wherein one adult cell type replaces another, is a consequence of chronic tissue injury.[5] In patients with chronic esophageal injury from GERD, Barrett's metaplasia develops when mucus-secreting columnar cells replace reflux-damaged esophageal squamous cells. The cells that give rise to this metaplasia are not known. It has been proposed that GERD might induce alterations in the expression of key developmental transcription factors, causing mature esophageal squamous cells to change into columnar cells (transdifferentiation) or causing immature esophageal progenitor cells to undergo columnar rather than squamous differentiation (transcommitment).[5,6] In a rat model of reflux esophagitis, metaplasia develops from bone marrow stem cells that enter the blood and settle in the reflux-damaged esophagus.[7] Studies in mouse models have suggested that metaplasia might result from upward migration of stem cells from the proximal stomach (the gastric cardia)[8] or from proximal expansion of embryonic-type cells at the gastroesophageal junction.[9] It is not clear which of these processes contribute to the pathogenesis of Barrett's esophagus in humans.

DIAGNOSIS

The diagnosis of Barrett's esophagus requires findings on endoscopy that columnar mucosa extends above the gastroesophageal junction, lining the distal esophagus, plus esophageal-biopsy results that confirm the presence of columnar metaplasia.[2] Endoscopically, the gastroesophageal junction is identified as the most proximal extent of gastric folds, and the columnar mucosa is salmon-colored and coarse, in contrast to the pale, glossy esophageal squamous mucosa (Fig. 1). The extent of esophageal columnar metaplasia determines whether long-segment or short-segment Barrett's esophagus (≥3 cm or <3 cm of columnar metaplasia, respectively) is diagnosed.[10] However, authorities disagree on the histologic type of columnar mucosa that establishes a diagnosis of Barrett's esophagus.

U.S. gastroenterology societies require esophageal biopsies showing intestinal metaplasia with goblet cells (also called specialized intestinal metaplasia or specialized columnar epithelium) for a definitive diagnosis of Barrett's esophagus

SOIGNER LES SOIGNANTS… SI POSSIBLE AVANT QU'ILS NE DEVIENNENT MALADES… ET LES SOIGNÉS ENCORE DAVANTAGE !

Ce texte ne peut pas être modifié par quelqu'un d'autre que YC, mais les commentaires sont autorisés bienvenus !!!!!

Blog : http://souffrancesoignants.blogspot.be/

Le Médecin malgré lui. Molière

ACTE II SCÈNE IV

LUCINDE, VALÈRE, GÉRONTE, LUCAS, SGANARELLE, JACQUELINE.

SGANARELLE.— Est-ce là, la malade?

GÉRONTE.— Oui, je n'ai qu'elle de fille: et j'aurais tous les regrets du monde, si elle venait à mourir.

SGANARELLE.— Qu'elle s'en garde bien, il ne faut pas qu'elle meure, sans l'ordonnance du médecin.

Les Morticoles. L.A. Daudet

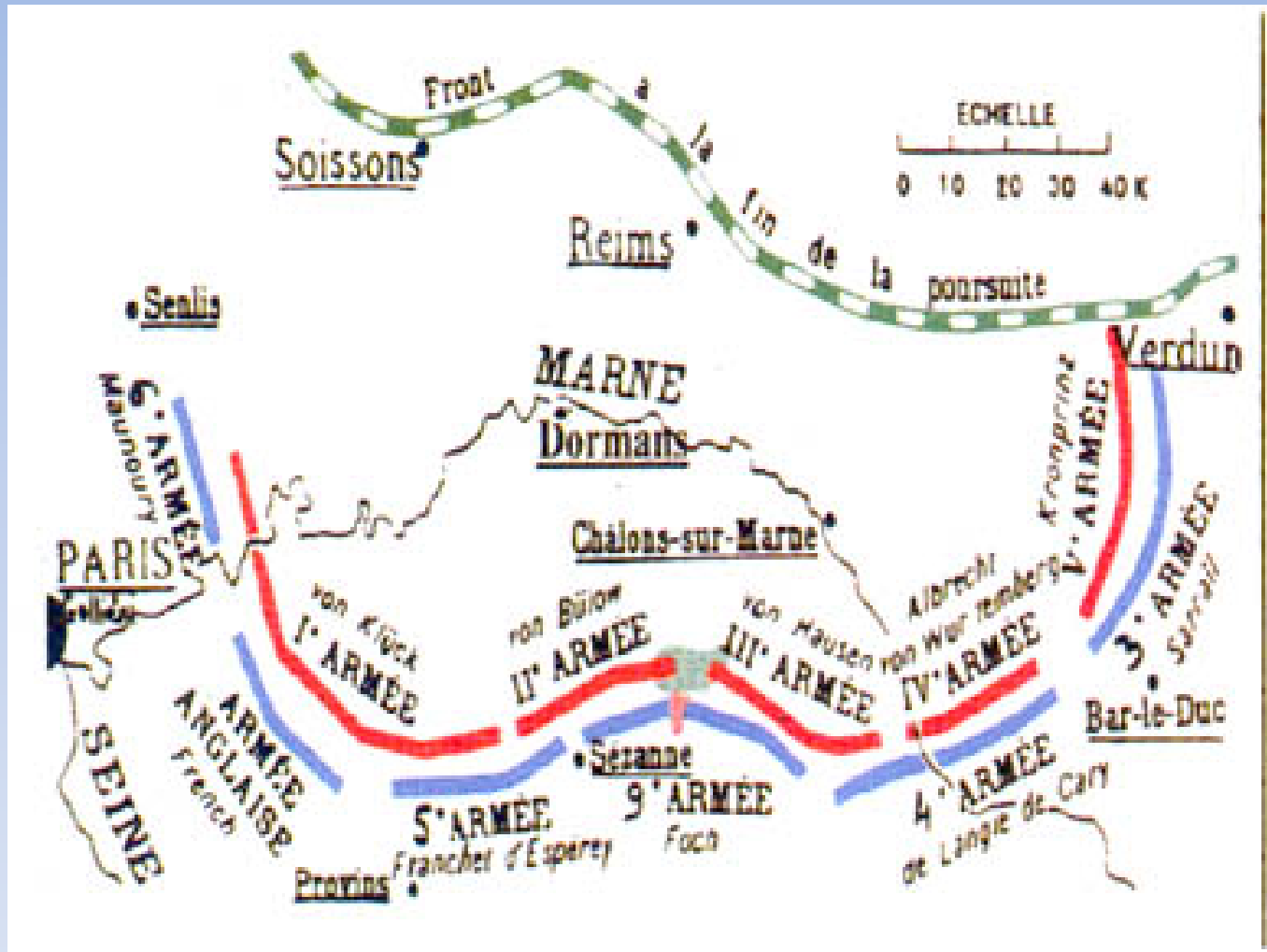
« Notre capitaine était soumis au même atroce régime, car les Morticoles sont passionnés pour une égalité apparente » p13 Ed. 1894 Bibliothèque Charpentier

Utopie noire. Les Morticoles sont des médecins, maîtres de leur domaine où ils imposent la Lex Medica.

http://gallica.bnf.fr/ark:/12148/bpt6k64582q/f8.image

Citation de Oscar Wilde ; Œuvre : Véra ou les Nihilistes - 1880

« Il n'y a pas de limite à la tyrannie d'un homme, mais il y aura une limite à la souffrance de tout peuple.



13 sept.

←

Positions avant et après la Bataille de la Marne

←

5 sept.