mation were encoded in DNA in this fashion, the whole vessel could be copied relatively easily by DNA replication; and likewise that the information in vessels could be readily merged (by physically merging them). DNA-based computing could conceivably provide a technological basis for superhuman intelligence.

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REFERENCES AND NOTES

1. L. M. Adleman, *Science* **266**, 1021 (1994).
2. R. J. Lipton, *ibid.* **268**, 542 (1995).
3. In principle a single molecule would suffice to encode the word. In practice it might be advisable to introduce many copies of the molecule encoding the word.
4. A similar encoding of Boolean vectors was previously used by Lipton (*2*).
5. E. B. Baum, J. Moody, F. Wilczek, *Biological Cybernetics* **59**, 217 (1988).
6. B. Alberts, D. Bray, J. Lewis, M. Raff, K. Roberts, J. D. Watson, *Molecular Biology of the Cell* (Garland, New York, 1994).
7. This splinting technique was used, for example, by Adleman (*1*).
8. A large number of restriction enzymes are known which cleave DNA molecules at particular locations. By subjecting a given DNA molecule to different restriction enzymes, one cleaves it into pieces of different, but well-defined lengths depending on the sequence. The lengths of the segments then provide constraints on the sequence. This is known as "restriction mapping" (*6*, p. 294). In our case, we need merely design sequences that can be readily distinguished one from another by the various lengths they are chopped into by various restriction enzymes. This would not be difficult.
9. J. Sambrook, E. F. Fritsch, T. Maniatis, *Molecular Cloning, A Laboratory Manual* (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, ed. 2, 1989).
10. A reasonable concentration for DNA is 0.06 g/liter of water (*9*). A millimole of molecules each 200 bases long would weigh about 50 g, hence occupy about 1000 liters. It is possible that practical limitations, for example, avoiding excessive annealing times in retrieval, would necessitate assigning a number of identical molecules to code each word.
11. One should, however, wonder whether perhaps huge numbers of bits are stored molecularly in each neuron or synapse, as techniques like those outlined here are available to biology.
12. I thank P. Kaplan and W. D. Smith for helpful comments.

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Neutrophils and Drug Metabolism

In their report (*1*) Xiaoxia Jiang *et al.* studied the role of phagocytes in drug metabolism by measuring the anti-proliferative effect of products from drug-exposed neutrophils. They did not, however, present physicochemical evidence for reactive drug metabolites reportedly generated by these cells and did not provide evidence for an immunostimulatory effect of these products that might lead to drug-induced lupus. We and others demonstrated specific immune reactions to defined metabolites of lupus-inducing drugs. Unlike the parent drugs or unreactive metabolites, the reactive metabolites tested proved immunogenic for T cells and, in a T cell–dependent fashion, activated B cells. Thus, the parent drugs procainamide (PA) (*2*), propylthiouracil (PTU) (*3*) (both of them studied by Jiang *et al.*), and gold(I) thiomalate (*3*) all were shown not to be immunogenic for T cells, and the same results were obtained for the unreactive metabolite *N*-acetyl-PA (*1*). In contrast, the reactive intermediates of these drugs, hydroxylamino-PA (*2*), PTU-sulfonate (*3*), and gold(III) (*4*, *5*) were shown to be immunogenic. Moreover, when the parent drugs PA, PTU, and gold(I) thiomalate were preincubated in vitro with either polymorphonuclear or mononuclear phagocytes, or myeloperoxidase/H_2O_2/Cl^-, the respective immunogenic metabolites, hydroxylamino-PA, PTU-sulfonate, and gold(III) were generated, as detected by chemical analysis (*6*) or specific responses of metabolite-sensitized T cells (*2*, *3*, *5*). Similarly, upon long-term administration to mice of the parent drugs PA (*2*), PTU (*3*), or gold(I) thiomalate (*5*), the respective immunogenic metabolites were demonstrable in phagocytic cells of these animals. In contrast to short-term treatment with the parent drugs, long-term treatment, which allows for more extensive generation of the reactive intermediates, also resulted in sensitization of T cells to the intermediates (*3*–*5*). Both the generation of and the T cell sensitization to these metabolites could be enhanced by stimulating the oxidative burst in phagocytes (*2*, *3*), or, in the case of PA, by using mice that express the slow-acetylator phenotype (*2*). Finally, mice under long-term treatment with gold(I) thiomalate or PTU exhibited immunoglobulin G autoantibodies and signs of vasculitis (*3*).

Thus, the evidence weighs against the hypothesis of papers cited by Jiang *et al.* that reactive drug metabolites may induce lupus because they exert a mitogenic effect on lymphoid cells in vivo. Our findings support the view that the immunostimulation underlying drug-induced autoimmunity involves specific T helper cell responses to hitherto undefined self proteins altered by reactive drug metabolites. We do agree with Jiang *et al.* that generation of the respective metabolites by cells of the immune system itself facilitates the development of adverse immune reactions to drugs.

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REFERENCES

1. X. Jiang, G. Khursigara, R. L. Rubin, *Science* **266**, 810 (1994).
2. M. Kubicka-Muranyi, R. Goebels, C. Goebel, J. Uetrecht, E. Gleichmann, *Toxicol. Appl. Pharmacol.* **122**, 88 (1993); C. Goebel, M. Kubicka-Muranyi, R. Goebels, E. Gleichmann, *Immunobiol.* **189**, 114 (abstr.) (1993).
3. S. v. Schmiedeberg, H.-C. Schuppe, E. Csernok, W. Gross, E. Gleichmann, *Immunobiol.* **191**, 228 (abstr.) (1994); S. v. Schmiedeberg *et al.*, in preparation.
4. D. Schuhmann *et al.*, *J. Immunol.* **145**, 2132 (1990); J. Verwilghen, G. H. Kingsley, L. Gambling, G. S. Panayi, *Arthr. Rheum.* **35**, 1413 (1992).
5. C. Goebel, M. Kubicka-Muranyi, T. Tonn, J. Gonzales, E. Gleichmann, *Arch. Toxicol.*, in press.
6. B. Beverly and D. Couri, *Fed. Proc.* **46**, 854 (1987); J. P. Uetrecht, *Drug Metab. Rev.* **24**, 299 (1992); C. F. Shaw *et al.*, *Metal-Based Drugs* **1**, 351 (1994).

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Response: We presented in our report (*1*) physicochemical evidence showing that all the tested lupus-inducing drugs were transformed by myeloperoxidase [figure 3 in (*1*)]. However, only the cytotoxic metabolite of procainamide, procainamide-hydroxylamine, has so far been identified. It should also be noted that we did reference the Kubicka-Muranyi paper (*2*) on the response of popliteal lymph node cells to procainamide-hydroxylamine. Similar studies on gold salts were not referenced because there have been no reports to our knowledge during the past 25 years of lupus related to gold therapy despite wide use of gold compounds in treatment of rheumatoid arthritis.

Adverse reactions to drugs, some of which are immune mediated, are common, but lupus-like disease related to more than 40 different medications is relatively rare. However, drug-induced lupus is provocative because it strongly resembles systemic lupus erythematosus (SLE), a disease for which there is no known cause. Influenced by the precedent set by penicillin-mediated allergic reactions, most studies have focused on the capacity of drugs or drug metabolites to bind components of the peripheral immune system, such as drug-altered self-proteins, T cells, or their contact sites on antigen pre-

senting cells. Contributions from Gleichmann's laboratory have provided another dimension for this approach by examining lymphoproliferative responses to different xenobiotics in vivo. This work complements our studies because it demonstrated that immune reactivity was not against the administered compound, but a metabolite of higher oxidation state; we showed how such products could be produced within a lymphoid compartment.

In order to account for the autoimmune side effects of drugs, Gleichmann and colleagues adopt a variant of the conventional explanation of drug-altered self-proteins as the initiating event. Other recent proposals include direct activation of lymphocytes through redox cycling or inhibition of DNA methylation reactions. However, the features of drug-induced lupus and the nature of SLE suggest that ultimate understanding might require an explanation for which there is currently no precedent.

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REFERENCES

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2. M. Kubicka-Muranyi, R. Goebels, C. Goebel, J. Uetrecht, E. Gleichmann, *Toxicol. Appl. Pharmacol.* **122**, 88 (1993).

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Thumbs, Tools, and Early Humans

By comparative functional analysis of thumb morphology, the report by Randall L. Susman (*1*) tackles the key question of which extinct hominids used tools. He contrasts living apes and their short, thin, weak thumbs and resulting power grasps with living humans and their long, stout, strong thumbs and refined precision grasps. The latter is said in the report to be correlated with tool behavior of extinct hominids; it is proposed, for example, that *Australopithecus afarensis* with its ape-like thumb was not a toolmaker, but *Paranthropus robustus* with its human-like thumb was.

Even with their inferior thumbs, however, apes engage in dextrous manipulation of objects by precision grasping and make and use a variety of tools (*2*). Most of these tools are made from vegetation and so will not endure in any future archaeological record, but this is beside the point. Some of the tools of wild chimpanzees are of stone and show characteristic wear patterns (*3*). To deny tool behavior to hominids older than 3 million years ago on the basis of their ape-like thumbs is thus unfounded. One could say that a particular kind of hominid technology, flaked stone, has not yet been seen in wild apes, although it has been shown in captive ones (*4*). More fruitful might be detailed studies of living apes and humans in terms of which types of grasps are associated with which types of tool-using and -making, especially in terms of task demands and raw materials.

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REFERENCES

1. R. L. Susman, *Science* 1570, **265** (1994).
2. J. Goodall, *Nature* **201**, 1264 (1964); W. C. McGrew, *Chimpanzee Material Culture* (Cambridge Univ. Press, Cambridge, UK, 1992).
3. C. Boesch and H. Boesch, *Folia Primatol.* **54**, 86 (1990); Y. Sugiyama, in *The Use of Tools by Human and Non-Human Primates*, A. Berthelet and J. Chevaillon, Eds. (Oxford Univ. Press, Oxford, UK, 1993).
4. R. V. A. Wright, *Mankind* **8**, 296 (1972); N. Toth *et al.*, *J. Archaeol. Sci.* **20**, 81 (1993).

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Randall L. Susman (*1*) makes a significant contribution towards our understanding the appearance of toolmaking capabilities in early hominids. He (*1*) proposes a test that "relies on a single thumb element and one that is well represented in the fossil record" to "help resolve the question of which Plio-Pleistocene hominids were responsible for the earliest tool assemblages" (*1*, p. 1572). The inference of behavior from morphology in fossil taxa is warranted if (i) there is some living species that bears the morphological trait, (ii) the trait is used for the same behavior in all living taxa that possess it, (iii) there is a clear functional linkage between the behavior and the trait, and (iv) there is no evidence that the trait arose in the living species before the behavior was adopted (*2*). Given these rules of comparative analysis, we reassess the evidence presented by Susman (*1*) for tool use among fossil hominids with the use of our data on gorilla thumb morphology.

Susman (*1*) describes several thumb muscles present in humans, but absent in apes, which he states are required for using a precision grasp. Noting that large transarticular forces are produced at the human metacarpophalangeal joint by these muscles, Susman (*1*) explains the relatively expanded human metacarpal head as an adaptation to reduce joint stress. He concludes that "humans have broader metacarpal heads than apes" (*1*, p. 1571) and, using a ratio of metacarpal head breadth to metacarpal length, shows that "values for African apes and modern humans do not overlap" (*1*, p. 1571). Susman (*1*) then uses this ratio as a criterion to separate modern toolmakers from non-toolmakers and to infer toolmaking capabilities in fossil hominids.

We tested this hypothesis by measuring pollical metacarpal head breadth and metacarpal length in adult humans, bonobos, and chimpanzees, and expanded the sample to include gorillas (*3*). When these data are plotted along with those of adult humans, following Susman (*1*), metacarpal head breadth of gorillas exceeds that of chimpanzees and overlaps markedly the range of variation shown for humans (Fig. 1A). Applying the ratio used by Susman (*1*), the range of values for mountain gorillas overlaps that of humans more than it does that of chimpanzees (Fig. 1B). The majority of fossil taxa for which tool use is implied by Susman (*1*) fall well within the range of variation observed for gorillas (Fig. 1B) (*4*). Susman also noted "great apes have relatively shorter thumbs than do humans, with metacarpals that are reduced in relative length" (*1*, p. 1571). Plots of thumb metacarpal length against body size (*5*) in adult apes and humans demonstrate that, at comparable body sizes, adult gorillas have first metacarpals that do not differ significantly in length from those of humans (*6*).

The presence of a wide metacarpal head relative to metacarpal length is proposed by Susman (*1*) as a reliable test for human-like precision grasping and tool use in fossil hominids. However, gorillas possess a wide metacarpal head (Fig. 1), but do not use a precision grip and do not manufacture stone tools. Thus, not all living taxa which possess the trait use it for the same behavior, (contrary to ii). Our results (*6*) also demonstrate that the proposed (*1*) functional link between metacarpal length and precision grasping is problematic. The gorilla-human pattern could be interpreted as primitive for African apes and humans, with *Pan* possessing the derived (*6*) morphology as a specialization for arboreal life. Thus (iv) is also violated in light of evidence suggesting the metacarpal proportions of *Homo sapiens* could have evolved before the adoption of tool use.

These conclusions then beg the question of what might be a robust morphological correlate of precision grasping and tool use in fossil hominids. As Napier (*7*) noted, "precision grip . . . is not an essential requisite at this [Oldowan] level of craftsman-