and individually matched by year of birth and date of insurance (*5*).

The permanent files of personnel and medical records of World War II army veterans include the immunization register, with signed and dated statements for all vaccinations; for yellow fever vaccination the date is always recorded and the vaccine lot number is given for 65 percent of the vaccinations (*6*). Since army personnel were neither all nor randomly immunized (*7*), information for both cases and controls was also abstracted on a number of other variables that might conceivably influence the risk of subsequent cancer, namely, state of birth, urban-rural classification of residence at induction, prior education, civilian occupation, date of entering service, arm or service to which assigned, blood type, cholera or typhus immunizations, overseas theater of service, religion, and rank at separation.

Cases and controls were first compared according to history of vaccination and the type of cancer classified (see Table 1). There is no suggestion of association between yellow fever vaccination and cancer as classified there. This is true not only for the material as a whole, but also when comparisons were controlled on year of birth and other variables mentioned above. The main comparisons were also done in the matched-pair fashion (*8*), with similarly negative results. We divided the material by date of entry into service not only because the vaccination rate changed abruptly and markedly over the period from 1942 to 1944, but also because the vaccine used until April or May 1942 led to a large epidemic of serum hepatitis (*9*), attributed to the use of human serum in the preparation of the vaccine. Vaccine used after 1 June 1942 was prepared without serum. In Table 2 the observations on lymphoma are divided by the date of entering service so as to reflect the change in vaccine. No significant differences were observed within each time interval. Because of the epidemic, all cancer cases and controls were further compared on the basis of the incidence of hepatitis during service—no significant difference was found. Within the cancer series, prior hepatitis was not selectively associated with liver neoplasia.

Table 2 also shows the results by date of death, the deaths from 1950 to 1954 representing an interval of 5 to 13 years after immunization, the deaths from 1959 to 1963, an interval of 14 to 22 years after. Finally, comparisons such as those in Table 1 were repeated for each major group of sites (buccal cavity and pharynx, gastrointestinal, respiratory, and so forth) without finding any evidence that yellow fever vaccination had influenced the risk of subsequent cancer.

A relation between yellow fever vaccination and cancer mortality would have been missed if the latent period were shorter or longer than the interval covered in this study, that is, less than 5 years or more than 22. The sample consisted of healthy young adult males; other persons, such as nonwhites, women, or children, who might be more susceptible to a specific agent, were not included in the study. The study was, however, fairly powerful in the statistical sense, varying, of course, with the frequency of the specific form of cancer examined. For example, the upper limit of a 95-percent confidence interval on the relative risk of lymphoma (relative to that among the unvaccinated) is 1.63; for leukemia it is 1.74; and for all other forms of cancer, 1.24.

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10. This investigation is part of a program of studies of the Follow-up Agency, Division of Medical Sciences, National Academy of Sciences–National Research Council, carried out in cooperation with the Veterans Administration, Department of Defense, and National Institutes of Health, and was supported by contract No. PH43-64-44, T.O. 23 and 54, with the National Cancer Institute.

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Perceiving Real-World Scenes

Abstract. *When a briefly presented real-world scene was jumbled, the accuracy of identifying a single, cued object was less than that when the scene was coherent. Jumbling remained an effective variable even when the subject knew where to look and what to look for. Thus an object's meaningful context may affect the course of perceptual recognition and not just peripheral scanning or memory.*

In experiments on perceptual recognition, a subject typically sees either a single item surrounded by homogeneous space or an array of unrelated ("random") items. In the real world, such meager perceptual experiences are rare. Outside the laboratory, objects are almost always perceived in some setting or context.

Given conventional stimulus displays, it is not surprising that the results of much perceptual research can generally be reconciled with a class of models that hold that the various items of the display are treated as separate entities; that is, they are initially processed independently in a very short-term sensory store (lasting just fractions of a second), and then transferred serially to a longer-term storage system [see (*1*)]. It is in this longer-term storage system that meaningfulness and long-term

memory are seen as having their effects.

In contrast to laboratory modeling is the following thought. If we glance at the world, even at a scene rich with detail that we have never experienced before, our subjective impression is of clear and almost instantaneous perception and comprehension of what we are looking at. That is, one feels that the various parts of a scene are simultaneously identified and related. One possible source of this discrepancy between the laboratory and the real world is the presence, in the real world, of a meaningful context. Creatures and things in the real world rarely appear, as they typically do in the laboratory, surrounded only by homogeneous space or unrelated entities. Instead, things occur in some predictable relation to other things, that is, in some setting.

The results I report show that meaningful context does affect perceptual recognition (*2*). A secondary purpose of this study was to advance a methodology whereby real-world scenes could be used as stimuli in experiments on perceptual recognition, so that context effects could be studied more systematically (*3*).

Subjects briefly viewed pictures of many varied scenes: for example, streets, kitchens, desk tops, and so forth. Their task was to identify which object occupied a given cued position in the scene. The technique was derived from Averbach and Coriell (*4*). By requiring a report of only part of a complex display, memory and response factors were greatly reduced. The major experimental variable was whether the scene was coherent or whether it was jumbled —cut into sixths and rearranged (but never rotated) so as to destroy the natural spatial relations of the components. This jumbling was assumed to be a manipulation of the meaningfulness of the object's setting independent of the complexity of the scene.

The scenes were 35-mm black-and-white positive slides. For each scene, two versions—one coherent and one jumbled—were made by photographing a print, 20 by 25 cm, which had been cut into six sections (generally with one horizontal and two vertical cuts) so that at least four well-defined objects were left intact (Fig. 1). The coherent slide was taken after the sectioning, so that the section lines appeared in both versions (*5*). When sections were arranged for the jumbled version, one was left in its original position. This section always contained at least one well-defined object. The position of the section remaining constant was balanced across the different scenes; for example, for one-sixth of the scenes, the top left section was identical in both jumbled and coherent versions.

Subjects viewed slides in a three-channel tachistoscope (*6*). Slides were shown for 300, 500, or 700 msec, and they subtended visual angles of 5° horizontally and 3.5° vertically. An arrow was presented for 300 msec, immediately after the scene in half the trials and immediately before the scene in the other half. The arrow pointed to an area associated with an object. The subject's task was to indicate, by point-

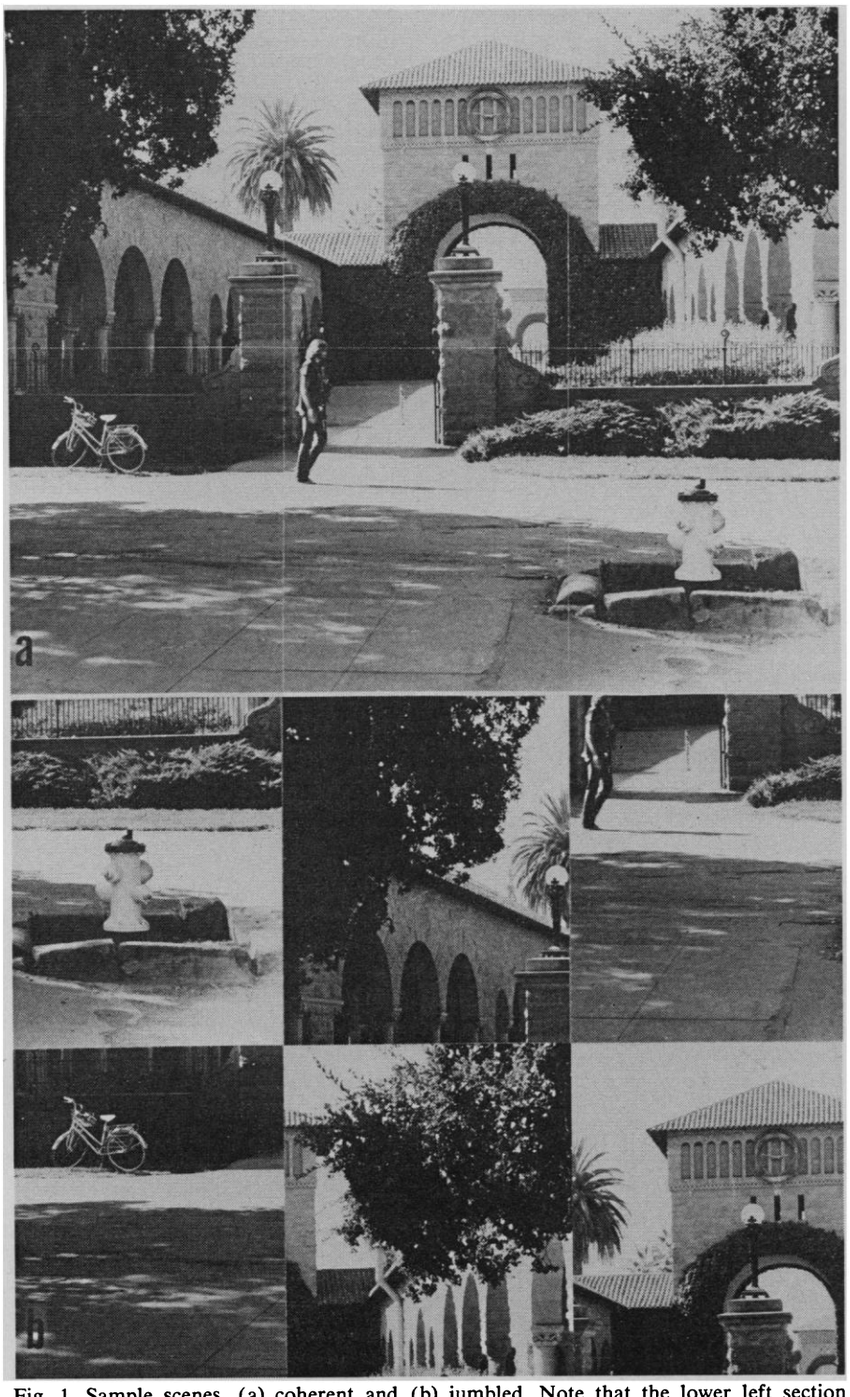

Fig. 1. Sample scenes, (a) coherent and (b) jumbled. Note that the lower left section is the same in both versions. The bicycle would have been the cued object.

ing to one of four object pictures, which object had been cued. These object pictures were cut from the original print used in making the scene and were mounted on index cards displayed in a photo album. The cued object was the same in both coherent and jumbled versions of each scene and always came from the section of the scene that remained in its original position.

In addition to the jumbling and cue-order variables, the order in which the subject viewed the scene and the response alternatives was also varied. In the alternatives-before condition, the subject was allowed to peruse the four object pictures before the scene was shown. In the alternatives-after condition, the subject viewed the response alternatives only after he viewed the scene. Thus, in the latter condition a few seconds elapsed between presentation of the scene and presentation of the response alternatives.

Each of 24 subjects viewed four blocks of 32 slides each. Within each block, the slides were equally divided between jumbled and coherent scenes. The four possible combinations of alternative-order and cue-order variables were used, one combination in each block. The first eight slides in each block were considered practice trials and were not included in the data analysis. In the remaining 24 slides, the cued object occurred in each of the six sections an equal number of times (four). All variables were balanced across slides. Each subject viewed only the jumbled or coherent version of a given scene but never both.

Results are shown in Fig. 2. The effects of jumbling [$F(1,22) = 5.17$, $P < .05$], cue order [$F(1,22) = 27.98$, $P < .001$], and alternative order [$F(1,22) = 9.01$, $P < .01$], were all significant (*7*). The effect of jumbling tended to be reduced in the cue-before and the alternative-before conditions, although none of the interactions among jumbling, cue order, and alternative order approached significance. However, the variability of these data was not low enough to warrant acceptance of the null hypothesis. The same must be said for varying presentation times of scenes; the effects were neither consistent nor significant.

The experiment was designed to minimize peripheral-scanning effects (since the cued object was in the same position in both scene versions, and since brief durations and relatively small

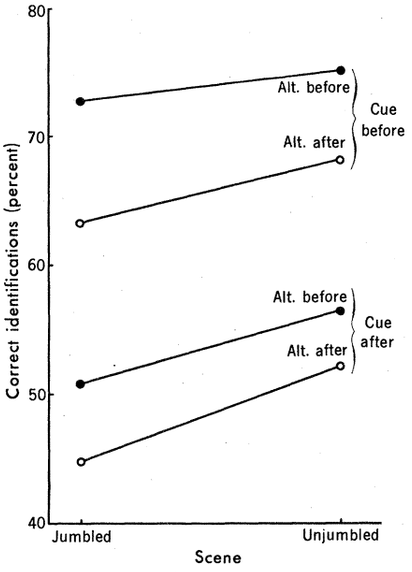

Fig. 2. Correct identifications (mean percentage) as a function of scene version and order of presenting the cue and response alternatives (alt.).

visual angles were used) and to minimize memory and response effects (by requiring the subject to simply point to one of a small set of well-defined and nameable objects). That jumbling remained an effective variable even when the subject knew where to look (when the cue preceded the scene) and what to look for (when the response alternatives preceded the scene) further limits the roles played by peripheral scanning and memory factors, respectively, in accounting for the jumbling effect. It is most likely that jumbling affected an early, but not peripheral, stage involved in the perceptual recognition of the cued object.

A number of theoretical issues present themselves when one attempts to account for the context effect, that is, the advantage of coherent over jumbled scenes. One issue concerns identification of the functional units involved in the perception of scenes. Is the functional unit an individual object, or does an observer have access to more global units or schema? A second issue is the determination of the locus, in the sequence of processing, where context has its effect. Is it in the initial manner in which objects are physically processed—in the initial segmentation, testing, and weighing of features? Or does the context influence a stage subsequent to that involved in the physical processing, so that physically ambiguous stimuli are interpreted to be consistent with other aspects of the scene already identified?

This experiment was not analytic for these issues, but Sternberg's additive factors method (*8*), coupled with reaction time measurements in the present task situation, might bring these issues under experimental scrutiny (*9*). For example, if jumbling is affecting a cognitive inferential stage, then an interaction would be expected between the magnitude of the effect of jumbling on reaction times and the magnitude of the effect of the probability of the cued object's being in the scene (*10*). (For example, this probability could be varied by cueing a bowl or a baseball glove on a formally set dining room table.) In a similar manner, interactions between jumbling and (i) the size and contrast of the cued object or (ii) the presence or absence of background and contiguous areas would be expected if jumbling were affecting physical-feature testing or object segmentation, respectively.

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2. In several studies with rigorous controls for guessing and memory effects, it was shown that an individual letter within a word is more perceptible than that same letter in a string of random-appearing letters, or even than the letter by itself [D. Aderman and E. E. Smith, *Cogn. Psychol.* **2**, 117 (1971); G. M. Reicher, *J. Exper. Psychol.* **81**, 274 (1969); D. D. Wheeler, *Cogn. Psychol.* **1**, 59 (1970)]. A possible implication of these results, as well as the results I report, is that the functional perceptual unit can be something larger than the individual items (letters or objects).
3. Research with real-world scenes as stimuli has generally been limited to studies of eye movements or memory. The thrust of this report is the effect of an object's setting on its perceptibility in a single glance.
4. E. Averbach and A. S. Coriell, *Bell Syst. Tech. J.* **40**, 309 (1961).
5. The end product of four photographic cycles was less-than-optimum clarity. Undoubtedly, performance would have been better if original positive slides had been used and the scenes had been larger.
6. Model GB Auto-Tach, Scientific Prototype Corp.
7. It could be argued that the effect of jumbling is due to the presence of a greater number of object segments, which created visual noise in the jumbled pictures. Since the fragments did not overlap the cued object, it is not clear how this factor could be operative. My observation is that literally adding external noise by scattering segments of other pictures over a photograph—compared to jumbling the photograph—does little to degrade the intelligibility of the scene. That jumbling is primarily affecting the relation of objects is, perhaps, evidenced by the minimum of 10 to 15 seconds of effort needed to determine how the sections of a scene were to be reassembled to the original. A more rigorous test of the noise interpretation would involve stimulus scenes that were made by either cropping out background objects that extended

across the section lines or else by drawing scenes in which none of the objects would extend across the section lines.

8. S. Sternberg, *Acta Psychol.* **30**, 276 (1969).

9. Reaction times could be measured by providing the subject with a target object before the scene was presented. When the scene and cue are presented, the subject would respond, "Yes," as quickly as possible if the cued object was the target, and, "No," otherwise.
10. The logic of the additive factors method (AFM) holds that if two factors, for instance jumbling and probability, are affecting the duration of separate and independent information-processing stages, then their combined effects on reaction time (RT) should be additive. That is, if jumbling adds 50 msec to the average RT and probability adds 25 msec, then the RT for a low-probability target in a jumbled scene should be, on the average, 75 msec longer than that for a high-probability target in a coherent scene. The AFM may also be applicable to error probabilities, but, in that case, if factors are influencing different information-processing stages, the logarithms of the errors should add.

11. I thank E. W. Stacey, A. L. Glass and S. L. Cook for invaluable assistance and E. E. Smith and G. R. Lockhead for careful readings of the manuscript. Supported by NIMH special fellowship MH 50632-01 and grant 050-7201-A from the Research Foundation of the State University of New York.

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Increased Tolerance of Leukemic Mice to Arabinosyl Cytosine with Schedule Adjusted to Circadian System

Abstract. *Mice (BDF_1) inoculated with L1210 leukemia survive for a statistically significantly longer span when four courses of arabinosyl cytosine are administered at 4-day intervals—not in courses consisting of eight equal doses at 3-hour intervals, but in sinusoidally increasing and decreasing 24-hour courses, the largest amount being given at previously mapped circadian and circannual times of peak host resistance to the drug. This finding relates to the many therapeutic situations involving rhythmic, and thus predictable, cycles in the host's tolerance of undesired effects from the agent used.*

The mortality of BDF_1 mice receiving arabinosyl cytosine (ara-C) at the same "time of day" for five consecutive days was previously shown to depend on the circadian system phase of the animals at the time the drug was administered (*1*). In mice kept on a regimen of 12 hours light and 12 hours dark ($LD_{12:12}$), with light from 06^{00} to 18^{00} and dark from 18^{00} to 06^{00}, a circadian cycle of susceptibility and resistance to ara-C was found; a superimposed, possibly circannual, variation was found for the circadian acrophase, that is, for the time of highest values—determined as the lag (from local 00^{00}, phase reference) of the crest time of a cosine function fitted to approximate the rhythm. During January and February 1971, the susceptibility acrophase occurred in mice treated during the first half of the dark span (at 18^{00} and at 23^{00}), the lowest mortality rate being found in animals treated during the light span (at 08^{30} and at 13^{00}) of the $LD_{12:12}$ synchronizer cycle (*1*).

The capacity of ara-C, 5-fluorouracil, or actinomycin D to inhibit mitotic activity in the cornea of rats in single doses that are compatible with survival of the animals depends, to a statistically significant degree, on the time of treatment (*2*). This finding was subsequently extended to include doses of dexamethasone (*3*). Isoproterenol altered the circadian rhythm of mitoses in mouse cornea; it was suggested that the response to this drug also is time-dependent (*4*). The scope of circadian rhythms in susceptibility to physical, chemical, and bacterial agents in experimental animals and in man (*5, 6*) was thus extended to include certain drugs used in the clinical chemotherapy of malignancies.

Earlier experiments (*1*) measured the effects and the toxicity of ara-C after administration as single injections or after a short course of treatment during only one circadian system phase. We therefore studied the rhythm in susceptibility to ara-C for the longer course schedules that are currently regarded as optimal for the treatment of experimental leukemia (*7*).

Without using any reported chronobiologic consideration, precaution, or method, such as an explicit control of the lighting regimen in the animal room (*6*), Skipper *et al.* (*7*) inoculated L 1210 mouse leukemia cells in BDF_1 mice, and then eradicated consistently 10^5 leukemia cells (and in some cases 10^6 cells) without animal deaths caused by drug toxicity; this important result was accomplished by giving four treatments of 120 mg of ara-C per kilogram of body weight in eight equal doses spaced at 3-hour intervals over a 24-hour span. Courses of 240 mg of ara-C per kilogram, given by the same schedule, were toxic, reportedly killing all animals, and were not used for treating leukemia from inocula containing more than 10^6 L 1210 cells.

By applying chronobiologic methods and concepts, we attempted to improve the tolerance of BDF_1 mice to the reportedly toxic four-daily courses of ara-C of 240 mg/kg. We adjusted the administration schedule to the circadian susceptibility rhythm previously mapped on similar animals under standardized conditions (*6*); we compared this sinusoidal treatment (*5*) with a reference treatment (R) used earlier by others (*7*) (Table 1).

Male BDF_1 mice, 4 to 6 weeks of age, were singly housed in sound-deadened rooms on a lighting regimen of $LD_{12:12}$ with light from 06^{00} to 18^{00}. The temperature in the rooms was $24° \pm 1°C$; Purina Laboratory Chow and tap water were freely available to the animals. The mice were kept on this regimen for 7 days, and were then given, by intraperitoneal injection, L 1210 leukemia cells obtained from ascitic fluid of DBA_2 mice carrying the leukemia. In our first two experiments we injected 10^6 cells suspended in Eagles minimal essential medium. Skipper *et al.* (*7*) had been able to achieve a 40 to 60 percent "cure rate" of this inoculum with ara-C (four courses of 120 mg/kg per day) on the schedule outlined as reference treatment below (R). In our third experiment, we injected 10^7 leukemic cells. With this increase of inoculum, no "cures" of the leukemia had previously been achieved (*7*).

In the studies reported here, the first course of chemotherapy with ara-C was begun approximately 44 to 48 hours after inoculation of the malignant cells. Each animal received eight intraperitoneal injections of ara-C in saline at 3-hour intervals over a 24-hour span, the total dose being consistently 240 mg/kg in 24 hours (Table 1). The duration of each series of injections was less than 90 minutes for the entire group, with the direct involvement of each individual animal limited to less than 3 minutes. A total of four courses of eight injections each was given with a 3-day interval free of therapy between the treatments.

One group of mice in each experiment received eight equal doses of ara-C every 3 hours for 24 hours, every fourth day. This schedule had been suggested (*7*) as the optimal daily dose regimen in the treatment of L 1210 leukemia by ara-C. This treatment is referred to as the reference treatment (R). It