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Some Dimensions of Remembering: Steps Toward a Neuropsychological Model of Memory

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INTRODUCTION

Interest in the relation of macromolecules to behavior centers on the memory process. It is memory that allows an organism to act on the basis of occurrences removed in time—past and future. It is memory also that allows an organism to act appropriately to present circumstances, for without memory these constitute nothing more than William James' "buzzing, blooming confusion." The guiding assumption is that this "memory" is effected by macromolecular change in protoplasm, especially in brain tissue. A good part of the search has been for *the* memory macromolecule; the contents of this volume attest to the success attained by this approach.

Yet, psychology and neurology and even molecular biology stand to lose much if this continues to be the main approach to the problem. Memory is not of-a-piece; it is multi-dimensional. Psychologists have long been aware of the differences between recognition and recall, between long- and short-term memory span, and like dichotomies. And neurologists have been concerned not only with memory storage but also with the mechanism of retrieval. As a rule, macromolecular processes have been dismissed by these disciplines as important only at the most

reductive level—i.e., usually macromolecules have been relegated to the task of long-term storage—period. This makes sense only if the sole dimension of memory recognized is that of duration.

There are, however, complexities in the process of remembering which are not easily resolved by this time-honored—I am tempted to say hoary—approach. Perhaps the most obvious regards one already mentioned: appropriate reactions to present circumstances. For example, recognition involves not only a memory mechanism of such short duration that it is practically instantaneous (how many faces can one recognize in a second?) but also a memory store which is practically unlimited in duration ("you look just the same as when I last saw you—no, it couldn't be twenty years, could it?").

A fresh look at memory seems in order. In the following account I have drawn freely from both old and new knowledge in experimental psychology, neurology, computer and information sciences, as well as from classical molecular biology, for suggestions about the dimensions of remembering and a model of memory. Much of what I have to say is speculative, but the speculation rests solidly on data ordinarily ignored in discussions of memory. The hope is that in this context memory molecules will become properly plural and some of the old pros and cons will give way to new questions for experimentalists.

Experiencing experience

Look at a friend, then look at his neighbor, and immediately you experience the difference. In the auditory mode, such transient, rapidly-paced recognition—of phrases in music, of phonemic combinations of speech, and so forth—are commonplace. Ordinary views of the memory mechanism have considerable difficulty handling the immediacy, precision and apparent multidimensionality of the evanescent experience. Here a unique process must be in operation. What could it look like; how might it work?

Habit and habituation

Let me begin by detailing a paradox concerning habit and habituation. If we are repeatedly in the same situation, in an invariant environment, two things happen. One is that if we have consistently to perform a similar task in that environment, the task becomes fairly automatic, i.e., we become more efficient. We say the organism (in this case, our-

self) has learned to perform the task; he has formed *habits* regarding it. But at the same time the subject *habituates*, by which we mean that he no longer produces an orienting reaction; he no longer notices the events constant to this particular task in this environment. His verbal reports of introspection, his failure to move his head and eyes in the direction of the stimulus—electrophysiological measures such as galvanic skin response, plethysmography and EEG—all attest to the disappearance of orienting with repetition of unvarying input in an unvarying situation. Habituation, however, is *not* an indication of some loss of sensitivity on the part of the nervous system. Sokolov (1960), for example, has demonstrated that if he decreases the intensity of a tone which has been repeatedly given to a subject, orienting or alerting will recur. Further, if he again habituates the subject and then shortens the duration of the tone, orienting again will take place, but this time to the unexpected *silence*. These things led Sokolov to propose that a neural model of the environment is produced in the nervous system. This model would then constitute an expectancy, a type of memory mechanism against which inputs are constantly matched. The nervous system is thus continually tuned *by* inputs to process further inputs.

It is hardly necessary to state that the habitual performance of the organism is also due to neural activity. The point to be kept in mind is this: in the case of expectancy there is a diminution of neural activity with repetition, while in the case of performance, enhancement seems to occur. So the question is: What is the difference between these two kinds of neural activity that appear at first sight to be inversely related to each other? Neurophysiology provides us with some sound clues.

Graded potential changes at synapto-dendritic locations in nerve tissue, on the one hand, and nerve impulses on the other, are available as two kinds of processes which could function reciprocally. The channeling of nerve impulses obviously is related to performance. Graded neural events are therefore left as candidates to account for the orienting reaction of the organism and its habituation.

Further, a synapse does not work by itself. Nerve impulses arrive at many synapto-dendritic junctions simultaneously. In essence, such arrivals occur in patterns which generate stationary wave fronts. These, once established, can interact and produce patterns similar to moiré (Oster and Nishijima, 1963) or interference effects. These effects act as immediate analogue cross-correlation devices to produce new figures from which departure patterns of nerve impulses can be initiated. The orienting reaction could well be a function of such interference effects.

Subjectively, the orienting reaction is correlated with awareness, habituation with unawareness. What evidence do we have to suggest that the graded electrical activities of the central nervous system are involved in awareness? Kamiya (in preparation) at the University of California Medical School in San Francisco has shown, using instrumental-conditioning techniques, that people can be aware of whether their brains are producing alpha rhythms or not. Evidence for the occurrence of an "expectancy wave" concommitant with the occurrence of imperative stimuli will be described below (p. 179). Specifically, but briefly, the hypothesis reads that we are indeed able subjectively to tell one brain pattern of graded potential changes from another. My suggestion is, therefore, an old-fashioned one: that we experience some of the events going on in the brain, but not others. More experiments of the kind Kamiya has performed are urgently needed—the point is an important one. If accepted, it carries with it a corollary, *viz.* that nerve impulse patterns *per se* must be unavailable to awareness.

The neural hologram

But in order for recognition to be effected some more permanent alteration of substrate must act to influence the configuration of arrival patterns. If one looks at EEG records coming off an EEG machine for a number of hours during the day, and then goes home to try to sleep, what happens? The day's records go by in review; but note—they go by *in reverse!* This is known at the "waterfall effect."

Obviously, some neural change has taken place to allow the record to be re-viewed but also obvious is the fact that the re-viewing takes place from a different vantage point than did the original viewing. The record must therefore have "stereo"-like properties that allow it to be examined now from this, now from that, standpoint. This re-viewing from various vantages must not lose its identity relative to the entire record: a familiar face gains, rather than loses, its familiarity and recognizable identity by being viewed from different angles.

Recently important new advances have been made in the study of interference effects. Moiré patterns, as mentioned above, have been explored and unexpected varieties of figures can be produced by the interaction of relatively simple grids. But even more startling in their similarity to perceptual processes are the results of a new photographic process which produces images by way of a record called a hologram (Leith and Upatnieks, 1965). The hologram does not visually resemble the

original object—rather, it is a record of the wave patterns emitted or reflected from an object. As these authors say (p. 25), "Such a record can be thought of as 'freezing' of the wave pattern; the pattern remains frozen until such time as one chooses to reactivate the process, whereupon the waves are 'read out' of the recording medium." The process of producing an image from a hologram is called wave-front reconstruction photography.

Holograms are produced by virtue of interference effects. A photographic recording of these effects will yield a grating-like, grid-like structure

> that can be regarded as a two-dimensional analogue of the sinusoidal wave produced by an electric oscillator. The important point of this analogy is that just as an electric wave can be modulated to serve as a carrier of information, . . . , so can the interferometrically produced wave pattern be modulated to serve as a carrier of information about the light waves that produced it (*ibid.*, p. 27).

There are many startling attributes of holograms. Among these the following are of greatest interest to us in our search for the mechanism by which experience can be experienced.

First, the image which is seen by looking through the hologram is complete, three dimensional.

> As the observer changes his viewing position the perspective of the picture changes, just as if the observer were viewing the original scene. Parallax effects are evident between near and far objects in the scene: if an object in the foreground lies in front of something else, the observer can move his head and look around the obstructing object, thereby seeing the previously hidden object . . . In short, the reconstruction has all the visual properties of the original scene and we know of no visual test one can make to distinguish the two (*ibid.*, p. 30).

Second, holograms have the property that

> several images can be superimposed on a single plate on successive exposures, and each image can be recovered without being affected by other images. This is done by using a different spatial-frequency carrier for each picture . . . The grating carriers can be of different frequencies . . . and there is still another degree of freedom, that of angle (*ibid.*, p. 31).

Finally, "each part of the hologram, no matter how small, can reproduce the entire image; thus the hologram can be broken into small fragments each of which can be used to construct a complete image. As the pieces become smaller, resolution is lost (*ibid.*, p. 31)." However,

as successively larger parts of the hologram are used for reconstruction the depth of field of the image decreases, i.e. focus becomes narrowed, so that an optimum size for a particular use can be ascertained. These curious properties derive from the fact that "each point on the hologram receives light from all parts of the subject and therefore contains, in an encoded form, the entire image (*ibid.*)."

The properties of the hologram are just those demanded by us to account for ordinary perception. I have already made the suggestion that arrival patterns in the brain constitute wave fronts which by virtue of interference effects can serve as instantaneous analogue cross correlators to produce a variety of moiré-type figures. Now, by means of some recording process analogous to that by which holograms are produced, a storage mechanism derived from such arrival patterns and interference effects can be envisioned. This is possible, since reconstructions of images from holograms have many of the attributes of perceptions.

I present these analogies advisedly. Only through them can we at this stage of knowledge of brain mechanisms begin to arrive at the "possible." Too long has neurophysiology been restricted to the nerve impulse and its transmissibility at the synapse as the one legitimate function worthy of extensive study. Connectivity and nerve impulse propagation are crucially important in themselves and, as will be seen below, important to the memory problem also. But connectivity and nerve impulse conduction are not enough to handle the richess of behavior and of psychological experience. Nor are they enough to provide a complete understanding of the brain. So, with the reader's indulgence, I will attempt to take the step from the photographic to the neural hologram, before considering more traditional memory mechanisms.

A possible mechanism by which neural holograms are produced suggests itself: Could the conformation of proteins and even longer-range anisotropic orderings of protein structure be altered in one direction during exposure and then later reversed such that, as it were, "the tape plays backward"? And would this "drift" in protein memory produce a reverse drift in the synaptically-produced patterns?

L. L. Whyte (1954) has proposed a mechanism which might operate in just this fashion:

> A polarization pulse passing through a region of cortical cytoplasm in a given direction may produce a cumulative residual effect by introducing an element of long-range anisotropic

ordering into previously disordered protein chains or fibrils, or by increasing an existing element of such order, of such a kind that the region thereafter responds more easily to a repetition of the same stimulus.

Similar but less definite suggestions have already been made by Whyte (1949, 1953) and Halstead (1951). Monne has stated that 'memory must be associated with some permanent structural changes of the cytoplasm (cytoplasmic fibrils) of the neurones.' But he considers mainly chemical changes (i.e. the synthesis of new specific proteins) as the basis of memory, whereas the present suggestion relies on the establishment of components of directional ordering in the already-existing fibrillar texture of the neuroplasm.

The rhythmically pulsating cytoplasm may possess a self-moulding property, so that as it pulsates along a particular axis it tends to order its own structure, to work in parts into position in relation to the axes of polarization and propagation, with the result that the system repeats the pulsation more easily, with less energy consumption.

This cumulative medium- and long-range ordering of some of the protein chains throughout a particular volume of cortical cytoplasm is a kind of growth process of a pattern determined not by heredity but by activity, and involving the development not of a differentiated tissue but of an element of ordering in the molecular arrangement of an extended mass of cytoplasm. Here we are concerned with the *differentiation of particular vector directions*, possibly parallel to the cortical surface, in particular cortical layers. The templates of memory are not single localized molecular structures, but extended components of long-range order set at various angles to one another. [However,] the ordering will correspond only to the *statistically dominant pattern of activity*, or simplest overall pattern common to the successive activity patterns. Moreover this tendency to select the dominant pattern will be reinforced by the fact that the simplest overall patterns will be the most stable, since their parts will mutually support one another. The random protein structures may thus act as a structural sieve taking a stable

> impress at first only of the simplest, most unified, and statistically dominant component in all the patterns of activity of a given general form.
>
> In general [, then,] the development of the modification proceeds from a grossly simplified to a less simplified and more accurate record. This process of the development of a hierarchically organized modification corresponds to Coghill's 'progressive individuation' of behavior patterns during ontogeny, and may hold the clue to the self-coordinating capacity of cortical processes.
>
> This hypothesis, whether valid or not, may provide fresh orientation and assist the design of new experiments. For it implies that in certain regions and layers still to be identified, the functional element in relation to memory processes is not a cell assembly, a neural circuit or net, a synaptic pattern, or any other arrangement of cell surfaces, but an effectively continuous three-dimensional mass of cortical cytoplasm whose *cyto*-organization is irrelevant to its function.

How then can we approach the problem of changes in protein conformation as a basis for memory? Sensitizations akin to the development of immunities have been proposed. And some initial experimental efforts have been directed toward this view (Mihailović and Janković, 1961). Another lead comes from some incidental observations made during the course of experiments carried out for initially different purposes. In my laboratory we have had occasion to cause epileptic seizures in monkeys by implanting aluminum hydroxide cream in their cortex (Pribram, 1951; Kraft et al., 1960; Stamm and Knight, 1963; Stamm and Pribram, 1960, 1961; Stamm, Pribram, and Obrist, 1958; Stamm and Warren, 1961). Such implantations cause havoc in the learning process. Yet, even a major convulsive episode will leave the immediate performance of a learned task unimpaired in these animals. Only 24 to 48 hours *after* such seizures does performance deteriorate—and this in the absence of further seizures. Further, the deterioration is temporary, lasting only about 48 hours. In short: some process takes this many hours to build up sufficiently to challenge the otherwise dominant neural pattern established by learning. And the challenge is temporary; apparently total recrudescence of the learned pattern is re-established shortly. Organic chemists must have available many macromolecules with similar peculiar

characteristics. Are protein conformations subject to such temporary deformations and is the time course of such alterations consonant with that observed in these experiments?

Arranging memories

As I have already indicated, there are many memory processes in which permanent and impermanent features mingle in a variety of ways: memorization of telephone numbers in a strange city, the use of experience in a related-but-novel situation, the schedules which guide us through our daily tasks and pleasures, the recrudescence of extinguished performances when the conditions of extinction are lifted—these are some memory processes in which more or less temporary rearrangements are produced by more permanently stored mechanisms.

Memory and circuitry

Does the suggestion of a protein conformation mechanism for memory storage dispose, then, of the "neural" or "synaptic growth," or "strengthening" hypothesis? Not necessarily. As I pointed out on another occasion (Pribram, 1963), the electroconvulsive shock experiments have provided evidence that consolidation of the memory trace is at least a two-fold process. Immediately after an experience—or five seconds after, or even up to an hour after—all traces of the experience can be wiped out. This suggests, as already noted, that the protein conformation change mechanism is disruptible during this period. After this, more permanent changes gradually take place. But concommitant with the protein conformation change, alterations in the design of the neural circuitry must also take place. Otherwise, retrieval through the generation of appropriate arrival patterns becomes impossible.

Thus, another aspect of brain function needs to be called into account: *viz.*, some change in neural connectivity that accompanies the protein changes. A problem arises here mainly because the brain's nerve cells do not divide. However, they can grow new branches. This has been dramatically demonstrated (Rose, Malis, and Baker, 1961) in a study of the effects on brain of high-energy radiations produced by a cyclotron. Remarkably minute, sharply-demarcated laminar destructions (often limited to a single cell layer, and this not necessarily the most superficial one) were produced in rabbit cerebral cortex when high-energy beams were stopped short by the soft tissue. The course of destruc-

tion and restitution was then studied histologically. Intact nerve cells were seen to send branches into the injured area; these branches became progressively more organized until, from all that could be observed through a microscope or measured electrically, the tissue had been repaired.

The organization of the branches of nerve cells could well be guided by the glia that pervasively surround these branches. Such directive influences are known to be essential, for example, in the regeneration of peripheral nerves. Schwann's cells, close relatives of glia, form a column into which the budding fibers must grow if they are not to get tangled in a matted mess of their own making.

The operative assumption is that glial cell division is somehow spurred by those same activities recounted above as important to memory storage. Data to support this assumption are presented below (p. 185). The resulting patterns of the glial bed would form the matrix into which nerve cell fiber growth occurs. Thus guided, fiber growth is directed by its own excitation—with the whole mechanism based, however, on the long-lasting intervention of glia. This "arranging" mechanism would account for the later "interfering" effects obtained in the consolidation experiments and in the spontaneous "restitution" as well: the growing nerve cell fiber is ameboid and can temporarily retract its tip which is made up of a helical winding of small globular protein molecules. After the convulsive "insult" is over, first tentative, then more vigorous probings are found to be resumed in some "random-walk" fashion by the nerve fiber tip (as has been suggested regarding normal growth by von Foerster, 1948). The glial substrate, assumed undamaged in this experiment, will perform its guiding function to effect the apparent restitution. Support for the glially guided "growth" hypothesis comes from the work of Krech, Rosenzweig, and Bennett (1960). These investigators found that the cerebral cortex of rats actually becomes thicker as a function of experience—thickening of visual cortex with visual experience and of somatic cortex with somatic experience were demonstrated. The increased cortical volume was not due to an increase in the number of neurons—rather, glia and fibers were responsible for the change.

The glially guided neural growth hypothesis, in addition to accounting for the late-interference effect data, has another attractive feature. The electrochemical memory storage process *per se* has no built-in mechanism which satisfactorily explains retrieval. A neural network structured through growth glially guided by experience, could on the

other hand, serve retrieval much as do the "feelers" on the magnetic memory core of a computer. The patterns of electrical signals that activate particular network configurations would then correspond to the lists or programs fed to a computer, as well as to the schemata proposed by Bartlett (1961) to account for the results of his studies on memory in man.

Dismembering and remembering

According to the view developed thus far, inputs are both isomorphically recorded as protein-conformation changes and coded into programs through neural growth. These programs, when properly activated, reconstruct the appropriate protein conformation, i.e., the "memories." Three observations in addition to the facts of recognition given earlier support the isomorphic recording of input items. One is the occurrence of eidetic imagery; another is the phenomenon of hypnotic regression (Gebhard, 1961); and a final one is the evocation of "memories" by electrical brain stimulation. There are limitations to all of these. The evidence for verisimilitude in hypnotic regression has been questioned. Evocation of "memories" by electrical brain stimulation occurs only in epileptic (i.e. scarred) cortex and is subject to influences of environmental set (Mahl et al., 1962). The occurrence of eidetic imagery in the adult is extremely rare and—curiously, considering the interest such a phenomenon must arouse in psychologists—studies on eidetics are practically nonexistent. The evidence is thus overwhelmingly in favor of the suggestion that, in addition to some memory storage record, memory processing depends heavily on programs. Bartlett (1961) amply documented the view that schemata are stored in the head.

In many ways this clarifies the memory problem considerably. If storage were only isomorphic to experience, one should be able to locate and find direct correspondences between all of the stored items and the world "out there." In a schematic or programmed memory no such isomorphic relation would have to obtain. The difference is essentially that between, say, a dictionary and a typewriter, between a trigonometry table in a handbook of physics and chemistry and a calculating machine. For example: if I take a simple adding machine and add to it the capability to multiply, I am putting a new memory mechanism into it. If I look into the machine I will find a change and that change may be the addition of a set of registers. Yet I will never find any specific "product" by opening the machine. "Products" are obtained when the machine is

presented with inputs which "signal" that a product is required, inputs anismorphic to the "products" themselves. This seems self-evident enough; but the self-evident is often forgotten in our more erudite arguments about memory.

Much confusion would be resolved if we adhered to the notion—deceptively simple, yet immensely significant—that "remembering" is the opposite of "dismembering." Even our language reflects that remembering is a putting together, a reconstruction. Once accepted, the conclusion this leads to is remarkable; namely: *it means that a good deal of what we call the memory storage problem is a hoax.* Most "memory" is stored in our libraries and in our jobs and homes as inputs to our brain machines. The human organism is thus signalled to remember what he is programmed to remember. The very word "remember," as I have suggested, reflects this process of reconstruction from parts as by a machine. A word of caution is appropriate at this point, however: in no sense do I want to imply that man is "nothing but a machine." Man does more than "just remember." Nor do I want to suggest that all remembering is passively induced by an appropriate environment. Man as often as not goes to the library in search of the appropriate signals; he plans and controls, as often as not, the significant, i.e. signifying, aspects of his home and job. The point is that, in these respects as well as in the assembly of appropriate routines and programs, remembering is an *active* not a passive process.

The numbers game

Once we dispose of the hoax that isomorphic coding and recording of all inputs is the sole necessity for a "proper" memory mechanism, we can also get rid of the "numbers game" that is constantly being played when memory is discussed. Bits of information are thus seen as irrelevancies—every book an author writes can be "stored" in his typewriter which possesses fewer than 50 symbols on its registers. Now, you can raise the objection that the brain must be more complicated than a typewriter—and I agree; but the number of states that it can register involves an experimental rather than this type of logical or psychological debate. An alphabet of only 26 letters does an heroic job.

I have repeated these things, which by now are almost truisms, because I find that in our discussions and our literature we *do not* hold these facts in mind. Over and over, the argument revolves only around storage of particulars. There need *not* be 10^{10} units for storage; there

need *not* be an RNA change specific to a Y maze but not to a T maze. The rules of the numbers game hold only if one selects to play it. Only if the model one holds is one based *exclusively* on item storage—the storage of inputs in some isomorphic manner—is this kind of argument valid. And the evidence is overwhelming that there is more to memory than bit-by-bit storage.

Hierarchy

Implicit in this then, is the idea that our memory machinery is capable of hierarchical organization—that all small units and probably some larger combinations of the memory machinery are permanent and undamageable, but that at least some of the larger units can be flexibly combined through programming operations initiated either by the input or by even larger permanent units. Also implicit is the suggestion that a particular memory unit or state can serve in a variety of combinations and thus participate in the production of a variety of re-membrances.

"Hierarchy" here implies several things: first, on any occasion I know all-of-a-piece whether I have anything at all relevant in memory to express; second, the mechanics of expression demand that I produce only one memory at a time. This limitation on output is the "keystone in the construction of the individual" as Sherrington (1947) so beautifully stated it. Thus, serial ordering accomplished by an hierarchy of processes prior to output is yet another dimension essential to remembering (see e.g. Hart, 1965).

The temporal code

This flexible rearrangement of hierarchically organized memories demands that some important attribute of neuronal function is sufficiently flexible to be temporarily but effectively alterable. This attribute might well be the temporal code with which the nerve discharges, or to which it is sensitive (see e.g., Hydén, 1961; Landauer, 1964).

Direct experimental evidence for any such flexibility in the temporal code with which neurons fire has hitherto been sparse. Almost the sole evidence that the brain is at all capable of altering its rhythms as a function of experience comes from the pioneering studies of John and Killam (1959). These investigators flashed light to their subject at certain frequencies (e.g., 30/sec.) and recorded from various locations in the brain.

In brief, their experiments demonstrate that, at the beginning of

training the electrical activity of a wide variety of brain structures appears synchronous with a repetitive stimulus. After learning has occurred and performance is at criterion, the electrical activity synchronous with the stimulus can be recorded only from the appropriate projection system. In the earlier phases of learning, the electrical activity of many of the core areas of the brain stem and forebrain show such synchrony: the reticular formation, hippocampus, amygdala, are only a few of the structures involved. The synchronous rhythms drop out progressively and the dropping out is correlated with progressively better performance on the part of the animal.

An additional observation which may point the way toward which future efforts for evidence of temporal coding may be directed comes from my laboratory (Spinelli and Pribram, unpublished data). Small wire electrodes were implanted in the lateral geniculate body and in the striate cortex of monkeys. Those in the geniculate were so placed that electrical stimulation would encompass a large portion of the entire nucleus, and continuous stimulation with 5-volt biphasic pulses, occurring at approximately 8/sec. was applied. Bipolar recordings were made from the cortical electrode placements. Most of these reflected more or less accurately the rhythm of stimulation imposed on the geniculate station of the visual system. From some of the cortical placements, however, arrhythmic recordings were consistently obtained. These sounded like a complex tap dance when transduced by a loudspeaker. The brain cortex apparently has a remarkable power to alter a rhythm imposed at an adjacent station.

The temporal hold

This observation leads us immediately to the question: How, then, are rearrangements among temporal codes accomplished? As yet no biological mechanism has been proposed to effect flexibility; nor will I attempt to propose one in detail here. But the imposition of local D.C. potentials on brain tissue is effective not only in altering the firing pattern of nerve cells but also in maintaining, i.e., temporarily storing this change (Chow, 1964; Chow and Dewson, 1964; Dewson, Chow, and Engel, 1964).

Further, lesions of the limbic forebrain and of the anterior frontal isocortex impair just the type of task which demands the flexible rearrangement of memory processes. I have elsewhere (Pribram et al., 1964) suggested that this deficit is due to a failure in the regulation of the

"temporal hold" imposed by an input on a particular matrix of registers. This "temporal hold" is assumed to be accomplished through an operation similar to that which gives rise to a temporary dominant focus in the experiments of Ukhtomski (1962), Rusinov (1956), and Morrell (1961). Without regulation by such a hold mechanism, the organism fluctuates inordinately among possible temporal codes and thus produces only a jumble of arrival patterns. In such circumstances even temporary combinations, i.e., moiré effects necessary to the registration of interference patterns as holograms cannot be achieved. Support for some sort of temporal hold process emanating from the frontolimbic portions of the brain comes from electrical recordings made in man:

> When conditional and imperative stimuli are presented in this way a remarkable change appears in the frontal brain response; a negative potential appears immediately after the conditional response and endures until the imperative response, when it declines rapidly to zero or becomes positive. This has been described as the "Contingent-Negative Variation" or Expectancy Wave (Walter, et al., 1964). In conditions such as those described, the E-wave is the most constant and stable of all electrocerebral phenomena in normal adults. It does not depend on the character of the intrinsic normal rhythms and is as large and extensive with the eyes open as shut. In children, however, and in mentally disturbed patients, the E-wave is often elusive and variable; above all, it is extremely sensitive to social influences.
>
> As already mentioned the E-wave arises always and only during sensory-motor association, but both the sensation and the motion may be of quite a subtle nature. In the simplest case the presentation of a conditional stimulus in any modality, followed by an imperative stimulus in another modality, evokes an E-wave following the primary conditional responses and lasting until the moment when the imperative response would have occurred.
>
> The striking feature of the E-wave is that it appears, as it were, to submerge the imperative response, and terminates very abruptly at the instant when the latter would have subsided. The typical sawtooth waveform of this phenomenon is remarkably like that of the time-base of an oscilloscope, rising

> steadily toward a maximum value over a time determined by the established stimulus interval, and dropping suddenly to zero. The duration of the E-wave as studied systematically so far is several seconds, but in some subjects the potential difference seems to be sustained much longer during "extinction" trials when there is no imperative stimulus to act as a "fly-back" trigger. Sometimes there is even a suggestion of a staircase or "Treppen" effect when conditional stimuli are presented at intervals of a few seconds without reinforcement to subjects with a very slow rate of extinction. Since the E-wave presumably represents depolarization of the apical dendritic plexus, the possibility of "recruitment" in such a mechanism would be interesting to study in more detail. The subjects who have shown signs of this effect are highly suggestible and easily hypnotized (Black and Walter, 1963); the capacity to maintain a high and even cumulative level of expectancy may be typical of this disposition, and may depend on some idiosyncrasy of the electrochemical relations in the superficial cortical levels. (Walter, 1964, pp. 310-313.)

And so we are back to the protein conformation model discussed in the first section.

RNA and reinforcement

RNA and behavior

Despite the difficulty in ridding ourselves of conceptual shackles, progress *is* being made by leaps and bounds. Hydén's work has been often criticized by both psychologists and biochemists; yet the picture he began to draw for us is nevertheless taking form. The RNA changes he reports may indeed be occurring—but not necessarily as evidence of item storage on evanescent messenger molecules, but as evidence of derepression of genomes. Bonner's theory (this volume) and Hydén's (1961) evidence are in accord.

But greater difficulties are posed by such phenomena as cannibalism and the injection of "knowledgeable" RNA. Here is a focus of discrepancy —here is the point where experiment must take the offensive and attack. The evidence must be firmed-up; new directions must be taken to de-

cipher the relationship. But again the problem comes into better focus if RNA is not considered *the* memory molecule. Rather, the question might be put: Just what *is* the relation between RNA and derepression? An increase in RNA can signal to the experimenter merely that derepression has occurred. Could it also be that RNA in some way can *initiate*, i.e., *induce*, derepression? There is good evidence from embryology that this may actually be so. The process of induction in the embryo has many similarities to the process of reinforcement which establishes the memory trace in the adult.

Inductors in review

In essence, induction is a "chemical conversation"—as Bonner has called it—between the intrinsic determining mechanisms of the morphogenetic field (or its already-independent differentiated parts) and the extrinsic organizing properties which guide its flowering. An early experiment, the classic example, is that of the determination of the lens by the eye vesicle. Contact between this vesicle with the overlying epidermis stimulates the latter to form a lens in the region of contact. If the eye vesicle is removed the epidermis fails to differentiate a lens. This experiment raised a whole set of problems which generated a direction of research in experimental embryology bearing a striking resemblance to current explorations in experimental psychology and ethology (see e.g., Hamburger and Levi-Montalcini, 1950).

The first and logical assumption was that the inductor acted merely as a trigger; that, in the classical example, the head skin is already "predisposed" to form a lens and that it requires only a signal to start. Two lines of evidence disproved this concept of induction. First, the optic vesicle was shown by transplantation to induce a lens in skin other than head skin—for example, flank skin. Second, the area of head skin which normally forms a lens was shown by other transplantation experiments to be *polypotential* and therefore definitely not "predetermined" for lens formation *only*. If the region of the head epidermis which normally forms the lens is combined with an ear induction, for example, it will respond with ear formation; if combined with a nose inductor, it will form a nose.

These facts do not deny, however, that the reacting system, must be "ready" or "competent," i.e., in the proper state of responsiveness, to allow induction to become effective—e.g., tissue which is already launched, as it were, toward a different destination, will fail entirely to respond.

Another point is that inductors are not species-specific. An inductor can be effective on tissues which belong to a different species, genus, or even order. The suggestion is, therefore, that inductors are made up of chemicals common to many organisms (more of this in a moment). These chemicals apparently determine the overall character of the induced structure while the hereditary equipment of the cells of this structure determines its detailed form. For example, when the flank skin of a frog embryo was induced to form head structures by salamander tissue into which it was transplanted, the embryo had a salamander head with the horny jaws and other features of the frog.

A long series of chemical experiments has currently culminated in the view that the ribonucleic acids (RNA's) are most likely and perhaps uniquely responsible for the inductive effect (see Niu, 1959), though ribonucleoproteins and steroids have not been entirely ruled out. For the most part RNAase destroys the inductive effect, although the problem remains that RNAase has other effects on the induced tissue which may disrupt its differentiation. More direct evidence, however, comes from demonstrations of the inductive effect of RNA extracted from different organs. Not only has this been accomplished, but RNA isolated from different sources was shown to be capable of inducing the recipient tissue to differentiate into different specific structures. These experiments suggest that there are *many* species of RNA in an organism and that each has a specific function.

With the use of C^{14}-labeled RNA, another problem has been tackled. Evidence has been established to show that it is possible for RNA molecules actually to move from the microsomes of the inductor tissue into the cells of the tissue induced, most likely by a process of pinocytosis.

To sum up: embryogenesis is dependent not only on the inherited and inherent properties of the genetic constitution of the organism; rather, these properties are also evoked and organized by the inductive capacity of the milieu in which the cells grow. The inductive capacity is itself specific, but in a somewhat different sense than is the genetic potential. The *genetic capability* is individual-, species- (and genus- and order-) specific. Hereditary factors proscribe commonalities with the past and future while assuring variation within any single generation. *Inductors*, on the other hand, are non-specific with respect to individuals, species, and so forth. They are relatively simple chemicals—RNA's—common to all living organisms. Inductors thus provide the existential commonality which allows the possibility of modification of whole generations according to the exigencies of the time.

Induction and reinforcement

The superficial descriptive similarity between induction as studied in embryological tissue and reinforcement as studied in conditioning situations is easily drawn: (a) Inductors evoke and organize the genetic potential of the organism. Reinforcers evoke and organize the behavioral capacities of organisms. (b) Inductors are relatively specific as to the character they evoke but are generally non-specific relative to individuals and tissues. Reinforcers are relatively specific in the behaviors they condition but are generally non-specific relative to individuals and tasks. (c) Inductors determine the broad outlines of the induced character; details are specified by the action of the substrate. Reinforcers determine the solution of the problem set; details of the behavioral repertoire used to achieve the solution are idiosyncratic to the organism. (d) Inductors do not just trigger development; they are more than just evanescent stimuli. Reinforcers do not just trigger behavior; they are a special class of stimuli. (e) Inductors must be in contact with their substrate in order to be effective. Contiguity is a demonstrated requirement for reinforcement to take place. (f) Mere contact, though necessary, is insufficient to produce an inductive effect; the induced tissue must be ready, must be competent to react. Mere contiguity, though necessary, is insufficient to produce reinforcement; shaping, deprivation, readiness, context, expectation, attention, hypothesis—these are only some of the terms used to describe the factors which comprise the competence of the organism without which reinforcement cannot become effective. (g) Induction usually proceeds by a two-way interaction—or as stated earlier by way of a chemical conversation. Reinforcement is most effective in the operant situation where the consequences of the organism's own actions are utilized as the guides to its subsequent behavior.

But when this much has been said, the question still remains as to whether these descriptive similarities point to homologous mechanisms. My hypothesis states that they do. What evidence is there in support? What neural processes become operative during conditioning?

A good deal of experimentation and speculation has been aimed at this problem. Much of it, unfortunately, has been concerned not with reinforcement but with inhibition. And, similarly, the emphasis in experimental embryology has been segregation. However, it has been well established (Hartline, Wagner, and Ratliff, 1956) both for the retina and for the cerebral cortex, that an externally-derived excitation at any locus

will produce inhibition in the surrounding tissue—i.e., the frequency of spontaneously-occurring electrical discharges of the inhibited cells will diminish. This "surround" or "lateral" inhibition will tend to isolate the focus of excitation and enhance the contrast between stimulated and non-stimulated regions. Such isolation is necessary for differentiation to be accomplished neurally and behaviorally as well as embryologically.

The neural processes evoked during extrinsic reinforcement are as yet untapped. Instead, direct electrical intervention in the nervous system has been shown capable of guiding and modulating behavior. Electrical stimulation with alternating or pulsed currents, or polarization with direct currents, speeds or slows learning according to the parameters of stimulation used. Especially effective guides to behavior are brain excitations which the organism itself can produce. Such self-stimulations are, if anything, more potent than extrinsic reinforcers.

But such experiments tell us only that certain neural processes set up by direct manipulation are behaviorally more or less equivalent to those set up when reinforcement is manipulated extrinsically. Somewhat closer to demonstrating the mechanism with which we are concerned are experiments in which a temporary dominant focus is produced in the brain. The classical example is the chemical stimulation of the exposed motor cortex of a dog that has been conditioned to lift his left forepaw. When the chemical (strychnine) is placed on the cortical area that controls the right hind limb, the dog will lift the right hind limb instead of the left forepaw when given the usual signal. Once the chemical is removed the dog reverts to its former behavior unless the stimulation has been often repeated. It is plausible to conclude that field-like configurations of such temporary dominant foci as these are produced during conditioning and then function to organize subsequent neural, and therefore behavioral, activity. But this, although relevant, is another story and has already been alluded to (p. 172).

A more chronic and therefore more easily studied change in neural discharge can be obtained by making epileptogenic lesions in cortex with implantations of aluminum hydroxide cream or by locally freezing the cortical tissue. Morrell (1960) put such epileptogenic foci to ingenious use. He based his experiments on earlier reports that an irritative lesion made in one cerebral hemisphere produces, after some months, a "mirror focus" of altered electrical activity in the contralateral cortex by way of the interhemispheric connections through the corpus callosum. This "mirror focus" has, of course, not been directly damaged chemically, yet it possesses all of the epileptogenic properties of the

initial irritative lesion. Morrell ascertained that the RNA in this mirror focus was considerably altered when compared to that found in normal brain tissue.

In my own laboratories, as already mentioned (Henry and Pribram, 1954; Kraft et al., 1960; Pribram, 1951; Stamm, Pribram, and Obrist, 1958; Stamm and Pribram, 1960, 1961; Stamm and Warren, 1961) different areas of the brain cortex of monkeys were treated with aluminum hydroxide cream to produce local irritations, as manifested by altered electrical activity (abnormally slow waves and spike discharges). While such irritative lesions do not interfere with monkeys' capacity to remember the solution to problems repeatedly solved prior to the irritation, they do slow the original learning of these problems some fivefold. Moreover, problem-solving in general is not affected; rather, the defect is specific for solutions to those tasks which also cannot be remembered when that particular part of the brain has been removed. These results can be interpreted to suggest that such irritative lesions delay the consolidation process—i.e., the process through which memory traces are fixed in the brain. A test of this interpretation could come from a comparison of learning by irritative-lesioned monkeys under spaced and massed trial conditions. Tentatively though, for our present purposes, the conclusions indicated can be accepted: that irritation with aluminum hydroxide cream interferes with memory induction and consolidation—i.e., with reinforcement.

CONCLUSION

I have outlined here some of my thoughts stimulated by the topic Macromolecules and Behavior. These thoughts have centered on the process we call remembering but the interwoven complexities of the psychological mechanism have taken me into a discussion of awareness; of temporal coding in the nervous system; of the "holding" functions I attribute to the frontal and limbic forebrain; of a molecular mechanism of reinforcement. I have not given all of the evidence available in support of the proposals made, nor have I given evidence to jeopardize the views presented. I have chosen this course deliberately—for, aside from pressing the fruitful course of laboratory exploration now in progress, I feel a great need to re-view, restructure, my image of the problem. For I fear that the present views of the memory problem will soon—or perhaps already have begun to—lead prematurely to a dead-end and thereby

permit the experimental challenge to wither away unanswered. Already I am tired of hearing that RNA *really* doesn't have anything to do with learning—i.e., not *real* learning—because it has not been shown to store the "associations" necessary to learning. And how many times have we heard the memory problem reduced to information storage? I can image as many bits of succulent and poignant detail about a loved one as you will give me time and an interested ear. And in my imagination I can do this while processing the routine of my daily affairs, with hardly a perceptible effect on my behavior. Just where *are* the questions about "short-term," "intermediate" and "long-term" memory processes leading? Are there more types than these (e.g., very, very short), or are we dealing with a continuum? So goes the argument which unfortunately misses the point that memory has structure; that in order to process nonsense syllables, man must know language; that to "forget" the irrelevant, the relevant must be properly available.

This need to restructure my thinking has thus produced this paper. In it *novelties* are emphasized at the expense of tried truths: the neural hologram, rearrangements among neural configurations, a biochemical-RNA-mechanism of reinforcement by induction. Here are some new possibilities which may finally enable us to realize that memory mechanisms are no more monolithic in their structure than are macromolecules.

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REFERENCES

Bartlett, F. C. (1961). Remembering: A Study in Experimental and Social Psychology. Cambridge: The University Press.

Chow, K. L. (1964). Neuropsychologia, 2: 175.

———, and J. H. Dewson III (1964). Neuropsychologia, 2: 153.

Dewson, J. H., III, K. L. Chow, and J. Engel, Jr. (1964). Neuropsychologia, 2: 167.

Foerster, Heinz von (1948). Das Gedächtnis. Vienna: Franz Deuticke.

Gebhard, J. W. (1961). Amer. J. Clin. Hypn., 3: 139.

Hamburger, V., and R. Levi-Montalcini (1950). In: Weiss, P., ed., Genetic Neurology: Problems of the Development, Growth, and Regeneration of

the Nervous System and of its Functions. Chicago: University of Chicago Press.
Hart, J. T. Recall, Recognition, and the Memory-Monitoring Process. Ph.D. Dissertation, Stanford University, July, 1965.
Hartline, H. K., H. G. Wagner, and F. Ratliff (1956). J. Gen. Physiol., 39: 651.
Henry, C. E., and K. H. Pribram (1954). Electroenceph. Clin. Neurophysiol., 6: 693.
Hydén, H. (1961). Biochemical aspects of brain activity. In: Farber, S. M., and R. H. L. Wilson, eds., Man and Civilization: Control of the Mind. New York: McGraw-Hill.
John, E. R., and K. F. Killam (1959). J. Pharmacol. Exp. Ther., 125: 252.
Kraft, M. S., W. D. Obrist, and K. H. Pribram (1960). J. Comp. Physiol. Psychol., 53: 17.
Krech, D., M. Rosenzweig, and E. L. Bennett (1960). J. Comp. Physiol. Psychol., 53: 509.
Landauer, T. (1964). Psychol. Rev., 71: 167.
Leith, E. N., and J. Upatnieks (1965). Sci. Amer., 212: 24.
Mahl, G., A. Rothenberg, J. Delgado, and H. Hamlin (1962). Psychological responses in the human to intracerebral electrical stimulation. Presented at Annual Meeting of the American Psychosomatic Society, 1962.
Mihailović, L. J., and D. B. Janković (1961). Nature, 192: 665.
Morrell, F. (1960). Epilepsia, 1: 538.
———. (1961). Lasting changes in synaptic organization produced by continuous neuronal bombardments. In: Delafresnaye, J. F., A. Fessard, and J. Konorski, eds., Symposium on Brain Mechanisms and Learning. Oxford: Blackwell.
Niu, M. C. (1959). Current evidence concerning chemical inducers. In: Evolution of Nervous Control from Primitive Organisms to Man. Washington: Amer. Assoc. Adv. Sci., Publ. no. 52.
Oster, G., and Y. Nishijima (1963). Sci. Amer., 208: 54.
Pribram, K. H. (1951). Surg. Forum, 36: 315.
———. (1963). In: Glaser, G. H., ed., EEG and Behavior. New York: Basic Books.
———, A. Ahumada, J. Hartog, and L. Roos (1964). In: Warren, J. M., and K. Akert, eds., The Frontal Granular Cortex and Behavior. New York: McGraw-Hill.
Rose, J. E., L. I. Malis, and C. P. Baker (1961). In: Rosenblith, W. A., ed., Sensory Communication. New York: Wiley.
Rusinov, U. S. (1956). 20th Internat. Physiol. Cong. (Brussels), 785. (Abstr.)
Sherrington, C. (1947). The Integrative Action of the Nervous System. New Haven: Yale University Press.
Sokolov, E. N. (1960). In: Brazier, M. A. B., ed., The Central Nervous System and Behavior. New York: Josiah Macy, Jr. Foundation.
Stamm, J. S. (1964). J. Neurophysiol., 24: 414.
———, and M. Knight (1963). J. Comp. Physiol. Psychol., 56: 254.
———, and K. H. Pribram (1960). J. Neurophysiol., 23: 552.
———, and K. H. Pribram (1961). J. Comp. Physiol. Psychol., 54: 614.
———, K. H. Pribram, and W. Obrist (1958). The Effect of Cortical Implants of Aluminum Hydroxide on Remembering and on Learning. Presented at Annual Meeting of the American EEG Society, June 13, 1958.
———, and A. Warren (1961). Epilepsia, 2: 229.
Ukhtomski, A. A. (1927). Psychol. Abstr., 2388.
Walter, W. Grey (1964). Arch. Psychiat. Nervenkr., 206: 309.
Whyte, L. L. (1954). Brain, 77: 158.

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