TRANSCRIPTION FROM SHORTHAND NOTEBOOKS OF DR. LEO SZILARD'S PAPER -

"ON MEMORY AND RECALL"

PUBLISHED IN THE PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES

JUNE 1964

(Transcribed posthumously - October, 1964)

Note for information: Dr. Szilard refers to his plans for writing the second part of this paper on Pages: 66, 103, 115, 124, 125 and 128.

Reference is made to Dr. Bronowski's solution of the mathematical problem on Pages: 83, 84, 85 and 86.

INSERT: I propose to describe here a hypothetical molecular process which represents both a mathematical model and a physical model which is biologically plausible. I am about to present this model here because I surmise that it represents an efficient system for recording and recalling an experience. It remains to be seen how much and whether it is more efficient than other models which have been concocted. If my surmise is correct then if worse came to worst the final verdict would be si non avero..... which is more than can be said about some of the other models that have been concocted.

The chances are that we do not know enough about biological processes that may take place in the living cell to hazard a guess regarding the nature of the relevant molecular processes that take place in the Central Nervous System. Nevertheless, one may ask whether it is possible to think of a hypothetical molecular process which is biologically plausible on which an efficient system of recording and recalling an experience could be based in neural networks which are adapted for the purpose.

I propose to describe here a hypothetical molecular process on which a system of recording an experience could be based. The particular model given below is not meant to represent a unique solution to the problem of memory. As far as the details are concerned there a number of guesses involved and we cannot expect correctly to guess the details. Yet, if we were lucky, we might have correctly guessed the general nature of the molecular processes..... yet it is conceivable that we might have correctly guessed the general nature of the molecular processes which take place in the Central Nervous System when an experience is recorded and when it is recalled. Failing this, the final verdict might well be si non averro..... provided that it is possible to base highly efficient system for recording and recalling an experience on the mathematical model which corresponds to the hypothetical molecular processes here postulated - which is more than can be said for certain mathematical models that have been concocted. A mathematical model of this sort may be regarded as efficient if the number of neurons in which a memory is recorded would tie down is comparatively small and if the neural networks which would be adequate for the recall of an experience in the right circumstances would involve a comparatively small number of neurons. It remains to be seen just how efficient the mathematical model here presented will turn out to be.

MEMORANDUM ON DISCRIMINATION IN CLASSICAL CONDITIONING

We shall consider several hundreds of memory cells. Each of them has an input coming from neuron Ai and each of them has an input from neuron B and, further, all of them have an input from a neuron of Class C. We shall consider several hundred memory cells and assume that each one of them sends inhibitory.....
Further, each of them has a transprinting input coming from neuron Ai and a transprinting input from one neuron of type B. Further, all of them have a non-transprinting input from a neuron of type C. For any of these plastic neurons to be transprinted it is necessary that they receive an input from the neuron of class C. Concerning a neuron of Class C, we postulate the following: This neuron will fire if either neuron B or one of the plastic neurons which has been transprinted with B fires, but the C neuron will not fire if both neuron B and the plastic neuron which has been transprinted with B, fires. One might say that a neuron C responds to the pleasure which the excitation of neuron B represents or to the anticipation of the pleasure which the firing of one of the B transprinted plastic neurons represents but that if a B transprinted plastic neuron fires..... but if the anticipated pleasure is followed by the pleasure that is nothing to get excited about from the point of view of a neuron of Class C. The plastic neurons we considered can either be transprinted simultaneously by Ai and B or they can be transprinted by Ai alone. We shall in the example considered below number them in the order in which they get transprinted, using odd numbers for those neurons which will be transprinted by both Ai and B and even numbers for those which are transprinted only by B. Let us start out with the statement that none of the plastic neurons in a group considered has been transprinted and let us now establish conditioning by exciting the neuron Ai and B simultaneously. On the assumption made, above all plastic neurons will receive volleys from Ai, B and C and at some point one of them will begin to fire.

Quotes: March 24, 1964

"We may not yet have modelled the mechanisms that the brain employs but we have modelled possible mechanism"

"There are exhibitory and inhibitory impulses reaching a neuron"

I now propose to discuss how the neurons presented above may be applied to the classical conditioned reflexes - the discrimination which an animal can learn in such a reflex and the extinction of the conditioned reflex. In the classical Pavlovian experiments dogs were employed. If food was squirted into the mouth of the dog, the dog responded with salivation (the congenital response) If the dog received a light signal shortly before having food squirted into its mouth and if this was repeated a number of times, after a while the dog responds with salivation to the light signal even if no food is squirted into his mouth. If the dog learns through such an experiment to respond to a light signal coming from a certain part of the visual space, say the upper right quadrant and if the light is red and if the dog so conditioned is then presented with the light signal which comes from the upper right hand quadrant but is not red, for the first time the dog will again respond with salivation, Similarly, if after the conditioned response the dog is presented for the first time with a signal which does not come from the upper right hand quadrant but is red, the dog will be expected to respond with salivation. However, if the dog is repeatedly exposed to the light signal and the conditioned response is each time reinforced by squirting food into the dog's mouth following the presentation of the light signal, whereas if the dog is presented with the wrong signal, the conditioned reflex is not reinforced, then after a number of exposures the dog will cease to respond with salivation to the wrong signal, whereas it will respond with salivation to the right signal., i.e. the dog has learned to discriminate.

According to our notions, the ability of the dog to discriminate is closely related to the phenomenon of the extinguishing of the conditioned response. If the dog is conditioned to respond to a given signal and subsequently, the same signal is given without reinforcement, after a certain number of exposures the dog will cease to respond with salivation to the right signal. In our theory a rather simple neural network to be described below can model the above features of the conditioned response.

If we make certain assumptions concerning the natural coding of the visual system . . . . If we make a rather plausible assumption about the congenital coding pattern of the congenitally-determined neurons involved in responding to the perception of light signals at a certain level of organization of the brain.....

MEMO ON CONDITIONED RESPONSES - March 25

I now propose to discuss how the classical conditioned response and the discrimination which an animal can learn to exhibit in such a response may be interepreted on the basis of the notions presented above. If food is squirted into the mouth of a dog, the dog responds with salivation - the congenital response. If, after the repetition of the classical Pavlovian experiments, a dog is given a particularly well-defined kind of light signal and if this is then followed, after a short period of time, with the squirting of food into its mouth, then after being exposed a number of times to the experience, the dog will respond with salivation to the light signal even if no food is squirted into its mouth. (The conditioned response).

Let us now consider a dog that has been thus conditioned. If the dog has been thus conditioned to respond to a light signal coming from a certain part of the visual space, say the upper right hand quadrant, and having a certain colour, say red, and if a dog which has been thus conditioned is then for the first time presented with the wrong light signal, either/a signal which comes from the upper right hand quadrant of the visual space but is not red, or a signal which is red but does not come from the upper right hand quadrant of the visual space, the dog will again respond with salivation. However, if such a dog is repeatedly exposed to both the wrong signal and the right signal, and if the wrong signal is not reinforced by squirting food into its mouth, and the right signal is reinforced in such a manner, then after a number of such exposures the dog learns to discriminate between the right signal and the wrong signal and responds with salivation only to the right signal,given a sufficiently long series of exposures, the dog can exhibit a much higher discrimination than is indicated in the above quoted example. According to our notions, the ability of the dog to learn to discriminate in a conditioned reflex is closely related to the phenomenon of the extinction of the conditioned response and as we shall see below, discrimination consists in a partial extinction. (If a dog is

conditioned to respond to a given signal and subsequently the same signal is given without reinforcement then after a certain number of exposures the dog will cease to respond with salivation to the signal) This is a phenomenon of the extinction of the conditioned reflex. As we shall see below, the ability of the dog to learn to discriminate in a conditioned response is closely related to this phenomenon of extinction and according to our notions, discrimination must be interepreted as partial extinction). Before attempting to interpret the ability of the dog to learn to discriminate to a conditioned response, we shall have to say something about the system of coding that we assume is employed by nature in the sensory systems in general and the sensory system which responds to light in particular and describe what we shall call here the orderly overlap of the congenital coding.

Before attempting to interepret the ability of the dog to learn to discriminate in a conditioned response we must say something about "orderly overlap of the congenital code" which, according to our notions, characterizes the congenitally-determined neurons of the neural systems which respond to sensory stimulation at a certain level of the brain. I propose roughly to illustrate at this point what I mean when I speak of the orderly overlap of the congenital code of these neurons. Let us consider a particular congenitally-determined neuron of Class A, for example, one which will respond to a change of light intensity by sending volleys into its axon provided that the change in illumination is localized in the upper right hand quadrant of the visual space and provided that the colour of the light employed is red. We have postulated above that the chemical specificity of such a neuron is determined by a set of n neuro-specific proteins according to the notions here adopted. This particular neuron will share a sub-set of these proteins, with all other neurons which respond to a change in illumination localized in the upper right hand quadrant of the visual field, and it will share another subset of these proteins with all other neurons which respond to a change of illumination in the red region of the spectrum. This is meant to be a particular example of our notion that as a general rule, two congenitally-determined neurons, which respond to visual stimuli, share a subset of the neuro-specific proteins (i.e. there is a small or large overlap between the set of neuro-specific proteins which are elevated provided that they both respond to visual stimuli having something in common with each other that is verbalized in a comparatively

simple term within the common usage of the language. We assume the same principle to hold also for a third class of congenitally-determined neurons which respond to a class of sensory stimuli.

We assume that the amount of overlap between any two such neurons is a measure of the resemblance of the visual signals to which these two neurons preferentially respond.

The same principle is presumed to hold also within any class of congenitally-determined neurons which respond to a given class of sensory stimuli, such as stimuli of either light or sound or the sense of touch, etc.

According to the notions here adopted, the essential feature of a conditioned response, such as a Pavlovian conditioned response, is that if the conditioned response has been established and maintained then when the dog is exposed to the right light signal there is an expectation of the squirting of the food into the mouth, i.e. there is an expectation of a sensory input F. This expectation is embodied by the firing of at least one memory neuron E which has been transprinted during the establishment of the conditioned response and is characterized by the set L and the set F, to which we shall attribute the key role in the establishment of the conditoned response to a neuron, which we shall designate as a neuron of Class C which receives fibres both from an F neuron and a large number of neurons E. We shall assume this neuron C is characterized by the same set of neuro-specific proteins which characterizes F and that it will respond to signals only from those E neurons which have been transprinted and have acquired the character of f. In the brain of mammals there are neurons which respond to auditory stimuli and which receive fibres from both ears..... In the brain of mammals there is a particular class of neurons which respond to stimuli and which receive fibres from both ears and the neurons of this class fire only if they receive signals from both ears. The neurons of this particular class do not fire, however, if they receive a signal from both ears but they do fire if they receive a signal from one of the two ears only.

We postulate that the neurons of Class C are similar and that a neuron of Class C fires if it receives a signal from the neuron F and that such a neuron will fire if it receives a signal either from neuron F or from one of the neurons E but it does not fire if it receives a signal from neuron F as well as one from more of the neurons E.

We shall now describe what happens according to the notions here adopted, when a dog is for the first time exposed to a particular light signal followed by the squirting of food into its mouth. Let us assume that the light signal consists of a flash of light appearing in the upper right quadrant of the visual field of the dog and having the colour of red and that the neuron Li, represented in Figure - preferentially responds to this kind of light signal by sending volleys of nerve impulses along its axon. Any neuron designated by F will fire volleys along its axon when food is squirted into the dog's mouth. We shall assume that when neuron F fires any neuron designated by C which we assume plays a key role in conditioning and about which we shall have to say more below, also fires. This neuron C is characterized by the same set f which characterizes the neuron F.

We shall now assume that conditioning takes place because when the memory neuron E receives nerve impulses simultaneoulsy from the neuron C and from neurons Li and F, the relevant membranes become permeable and neuron E takes on the character of the neurons F and Li, so that it will be henceforth characterized by the sets li and f. This neuron thereafter will cease to be plastic as indicated by the non-dotted circle drawn inside the dotted circle. If, subsequently, the dog is exposed to the light signal which excites the neuron Li then the neuron E will fire and nerve impulses from neuron E will reach both the neuron C and the neuron I. Neuron I is a congenitally-determined neuron which is inhibitory rather than exhibitory and which sends inhibitory fibres to all neurons of Class E.

We postulate that the amount of overlap between any two such neurons is a measure of the resemblance of the two visual signals to which these two neurons preferentially respond. The same principle is presumed to hold within the classes of congenitally-determined neurons which respond to a one-dimensional or a two-dimensional class of sensory stimuli, such as an auditory stimulous, or a visual stimulus or a tactile stimulus .

INSERT

The neuro-specificity of the neuron Li is characterized by the set of neuro-specific proteins li and the chemical specificity of the neuron F is characterized by the set of neuro-specific proteins f. The neuron C, represented in the figure, is also characterized by the set of neuro-specific proteins f and when the neuron F is fired exhibitory impulses are transmitted to the neuron C. This neuron C is also characterized by the same set of neuro-specific proteins f as the neuron F. When the dog is first exposed to the light

signal and food is squirted into its mouth then the neuron F fires volleys because then the neuron C also will fire volleys. As will be discussed later, the neuron C plays a key role in the conditioning process.

MEMO ON CONDITIONED RESPONSES

According to our notions, the establishment of such a conditioned response is based on the transprinting of the memory neuron of class E, characterized by a set of neuro-specific proteins e which is transprinted in certain circumstances described below when it receives simultaneously nerve impulses.

If, in a classical Pavlovian type experiment, a dog is given a light signal, for instance a flash of red light coming from the upper right hand quadrant of his visual space, and if this signal is then followed, after a short period of time, with the squirting of food into the dog's mouth, then after having been exposed a number of times to such an experience, the dog responds with salivation to the light signal alone even if no food is squirted into its mouth. This is a condition ed response.

If, subsequently, the dog is exposed to the light signal but no food is squirted into its mouth, neuron Li will be excited but not neuron F. The excitation of the neuron Li will be transmitted to the neuron E which has been transprinted and neuron E will fire volleys to its axon.

Because the transprinted neuron E is characterized by a subset e the transprinted neuron E will excite the neuron F* and the neuron F* will begin to fire volleys into its axon.

Insert: After transprinting the memory neuron E represented in the Figure A, this neuron ceases to be plastic which we have indicated by representing this neuron in Figure B with another circle drawn inside of the dotted circle.

We shall first of all describe what happens according to the notions here adopted, when a dog which is yet unconditioned is exposed to a very specific light signal followed by the squirting of food into its mouth. Let us assume that the light consists of a flash of red light appearing in the upper right quadrant of the visual field and that the neuron Li,represented in the figure, preferentially responds to this kind of

light signal by sending volleys of nerve impulses along its axon. Another neuron, represented in the figure and designated F, fires volleys along its axon when food is squirted into the dog's mouth.

The neuro-specificity of the neuron Lk is characterized by the set of neuro-specific proteins lk and the chemical specificity of the neuron F is characterized by the set of neuro-specific proteins f. Another neuron, F*, also represented in the figure, is characterized by the same set of neuro-specific proteins f which characterizes the neuron F / and, according to our notions, assists in the transprinting of a plastic neuron E by the neurons Li and F under the influences which occur when this plastic neuron receives nerve impulses simultaneously from the transprinting neurons Lk, F and from the non-transprinting neuron F*. Figure A depicts the plastic neuron E before transprinting when it was characterized by a set of proteins e and after transprinting when it is charcterized by the set of proteins e, lk and f.

After transprinting, the memory neuron E, represented in the figure, ceases to be plastic which we have indicated by drawing a circle inside the circle of the dotted line. If, subsequently, either neuron Li or neuron F, or both neuron Li and neuron F, are excited and fire volleys, the excitation will be transmitted to neuron E also and unless neuron E is inhibited by volleys reaching it through a uninhibitory fibre, it will fire volleys into its axon. Because the transprinted neuron E is characterized by a subset f, the transprinted neuron E can, in principle, excite the neuron F*. This does not necessarily mean, however, the neuron F will fire volleys, rather we assume that the neuron F* to which we are attributing the key role in conditioning, behaves in the same peculiar fashion as do certain neurons which respond to an auditory stimulus and which receive a fibre from each of the two ears and which fire only if an auditory stimulus reaches them through one of these two fibres but does not fire if a stimulus reaches it simultaneously through both fibres. We assume that the neuron F* fires when it is reached by a stimulus from the neuron F or from a neuron of Class E but does not fire if it receives simultaneously stimulus from both.

According to the notions here adopted, the essential feature of a conditioned response is that if it is established, then when the dog is exposed to the correct light signal, there is an expectation of a sensory input into neuron F. This expectation is represented by the firing of a neuron F*. We shall attribute here to the neuron F* a key role which accounts for a number of different aspects of the conditioning response which we shall discuss below

In the brain of mammals there is a peculiar class of neurons which respond to auditory stimuli and which receive auditory signals from both ears. The peculiarity of these neurons is that they do not fire if they receive the signal from both ears while they do fire if they receive the signal from one of the two ears only. We postulate that the neuron F* is peculiar in a similar sense, i.e. We postulate that it fires only if it receives an input either from the neuron F or one of the neurons E which have been transprinted and are characterized by the subset f.

March 25, 1964

According to the notions here adopted an ..... aspect of a conditioned response is characterized by the fact that when the dog is exposed to the correct light signal there is an expectation that a sensory input into the neuron F will follow. In our model this expectation is repeated by the state of excitation in the neural network F*.

According to our notions, the neural network F* plays the key role in the establishment of the conditioned response and it accounts for a number of aspects of the conditioned response which we shall discuss below.

We assume that a network of F* resembles, regarding one relevant aspect of its behaviour, the neural networks composed of large cells which are located in the superior olive and which receives signals from both ears. These networks receive signals from both ears. It is their peculiarity, however, that they are excited by signals from either ear alone whereas contemporaneous signals from both ears cancel each other, leaving the networks unaffected. By these cell networks we detect the directionality of a sound and hear a signal in one ear despite a large common background noise in both. We assume that the network of neurons F* has a similar peculiar behaviour and that it sends out a volley of nerve impulses only if it receives signals either from the neuron F or one of the neurons E while signals simultaneously arriving form the neuron F and one

or several of the neurons E, would cancel out.

It should be noted on this occasion that a neuron E can transmit a signal to the neural network F* only if it has been previously transprinted by the neuron F.

ON THE MOLECULAR BASIS OF LONG TERM MEMORY - APRIL 1 VERSION

Introduction

The subject matter of this paper is a molecular process on which the capability of the Central Nervous System to record and to recall an experience could conceivably be based. The chances are that we do not know enough about the biological processes that may take place in the living cell to be able to guess what the relevant molecular processes may be but even if we should fail to present a model for the mechanism that the brain employs in recording and recalling ane experience we might still succeed in describing a mechanism which is biologically plausible and which could serve as a basis for a highly efficient system for recording and recalling an experience. Such a system may be regarded as efficient if the number of neurons which a unit of recorded memory would tie down is compratively small and if the neural networks which would be adequate for the recall of an experience in the right circumstances would involve a comparatively small number of neurons only.

According to the notions here adopted, the unit of recorded memory which may be recorded within a neuron is not a bit but something considerably more complex than a bit. There is a class of dreams first described by Freud and discussed by him in great detail which is centered on what he calls "ein traumgedanke". In a dream of this type the same traumgedanke appears in a number of different representations and if, within one night several dreams of this type follow each other the same traumgedanke is repeated in all of them.

According to the notions here adopted, a traumgedanke is a special case of what Wertheimer and Koehler have called "gestalt" which can be recorded in a single neuron. It is conceivable that a Freudian dream is generated because one single neuron gets excited during the night and because it remains excited at least until the individual wakes up, becomes conscious and the dream enters consciousness. If an individual were able to retain information of the complexity of a traumgedanke given to him every few seconds, twenty-four hours a day for one hundred years then the memory stored by such an individual would irreversably tie down just about 10^9 neurons of his brain. This would be still 10 times less than the total number of neurons in the brain of man which is usually quoted to be 10^{10}. The model here adopted could not account for a great

amount of storage per neuron than a gestalt of the maximum complexity of ein traumgedanke. This limitation does not seem to get us into trouble however.

March 30, 1964

Fig. 2 shows schematically four differently shaped neuro-specific proteins contained in the bouton embedded in the membrane covering the bouton. Each of these is dimerized with a molecule of its own kind contained in the neuron. In addition, the figure shows three different neuro-specific proteins contained in the neuron for which there is no counterpart in the bouton. This is just a rough illustration "pour fixer les idees". For the sake of simplicity of discussion, we shall assume here that every neuro-specific protein embedded in the membrane covering the bouton inactivates cholinesterase at the same rate, i.e. the number of cholinesterase molecules destroyed is proportionate to the cholinesterase concentration in the bouton and the number of dimers at the interface of the neuron and the bouton. Further, for the sake of simplicity, we shall here assume that each neuro-specific protein which belongs to the set that characterized the bouton and that each neuro-specific protein which characterized the neuron is represented by the same number of molecules at the bouton neuron interface. With these simplified assumptions one might then say that the rate at which cholinesterase is inactivated in the bouton is proportionate to its concentration and is for any given concentration proportionate to the overlap number of the sets of neuro-specific proteins characterizing the bouton and the neuron depicted in Fig. 2 respectively. The overlap x is defined as a number of neuro-specific proteins which these two sets have in common.

If the neuron is one which is congenitally-determined and if the bouton also comes from a congenitally-determined neuron, then the overlap x is a number between zero and n. The same holds true if the neuron is congenitally-determined but the bouton belongs to the memory neuron or vice versa. However, if the neuron is a memory neuron the endbulb of a branch fibre of an axon rides across this gap on a chemical carrier. Each nerve impulse triggers a release of a certain amount of transmitter substance which diffuses through the liquid of the synaptic gap into a dendrite or directly into the cell body of the neuron.

We assume the neurons to be of two kinds. There are neurons whose endbulbs release

at the synapse a transmitter substance which raises the level of excitation of the neuron that lies across the synapse and these we shall call exhibitory neurons. We know that in a certain class of neurons the transmitter substance which raises the level of excitation of a neuron across the synapse is acetylcholine which is produced and that its rate of production is determined by the frequency of the nerve impulses into an endbulb by an excitatory neuron. The rate of production of acetylcholine increasing with the frequency of the nerve impulses. We know that in the case of an excitatory neuron which is cholinergic the rate of acetylcholine in the endbulbs belonging to the neuron increases with increasing frequency of the nerve impulses which the neuron sends along its axon. We also know that there is present in the endbulb and in the dendrite across the synapse an enzyme cholinesterase which destroys acetylcholine at the rate which is proportional to the concentration of this enzyme and the concentration of acetylcholine.

We shall use the more general term of excite instead of the more special term of acetylcholine and we shall designate the enzyme "excitinase" rather than cholinesterase. This seems to be preferable at the moment particularly because we do not know the chemical nature of any of the transmitter substances which are secreted by the endbulbs of neurons that are inhibitory rather than excitatory and which presumably secrete an antagonist of the excitine. We shall call the transmitter substance secreted by the endbulbs of inhibitory neurons "antogonine" and assume that its rate of production increases with increasing frequency of the nerve impulses that an inhibitory neuron sends along its axon. Concerning the rate of destruction of antogonine, we shall assume this is proportional to its concentration and the concentration of an enzyme which we shall designate as "antagonese".

The dendrite tree of any one neuron may have several hundreds of filamentous branches and the axon of any one neuron may end in a very large number of branch fibres each ending in an endbulb. The rate of excitation which controls the rate of firing of a neuron which receives an input through its dendrites from a large number of excitatory and inhibitory neurons depends on the concentration of excitine and inhibitine and these concentrations, in their turn, depend on the rate at which these two substances are produced and the rate at which they are destroyed. We may assume that the destruction of

of the transmitter substances is reasonably fast so that if the rate of production changes from one value to another, the new stationery value is approached half way within about 5 or 10 milliseconds. Thus, one may say in these circumstances what a neuron does is draw some sort of a balance between excitatory and inhibitory impulses which reach it simultaneously where simultaneity is defined by the period of time of 5 or 10 milliseconds, i.e. simultaneously or very precisely within a unit of time which amounts to about 5 or 10 milliseconds. We might, for instance, imagine that the firing frequency might be given by:

(FORMULA)

According to this formula, the neuron would not fire if it did not receive impulses from any excitatory neurons and it will fire only at a low rate if the preponderance of the impulses it receives comes from inhibitory neurons.

Our next postulate relates to a network of neurons, rather than to a single neuron and it relates to neural networks which have the following kind of characteristics: Each neuron has one axon and may send volleys of nerve impulses along this axon with the frequency nu which increases with the level of excitation of the neuron. The axon of each such neuron branches into a similar or larger number of fibres and each of these fibres ends in an andbulb (bouton). Each endbulb belonging to one neuron is in physical contact with a dendrite of some other neuron (or directly with the cell body of another neuron) and the location of such an area of physical contact is referred to as a "synapse".

There is always a gap of about one millionth of an inch between the cell membrane covering the endbulb and the cell membrane covering the dendrite (or the cell body itself) and we assume that the nerve impulses which feed into the endbulb of a branch fibre of the axon rides across this gap on a chemical carrier - a transmitter substance. Each nerve impulse reaching the endbulb may be assumed to trigger the release of a certain amount of this transmitter substance which diffuses across the synaptic gap into the dendrite of the other neuron (or directly into the cell body of this neuron).

We assume neurons to be of two kinds:

(a) excitatory neurons whose endbulbs release at the synapse a transmitter substance into the dendrite which raises the level of excitation of the neuron to which the dendrite belongs, and

(b) inhibitory neurons

In a certain class of neurons -- the cholinergic neurons -- the transmitter substance is acetylcholine. The rate of production of acetylcholine in the enbulbs of such neurons increases with increasing frequency of the nerve impulses that the neuron sends along its axon. Acetylcholine is destroyed at the synapse by the enzyme cholinesterase and it is destroyed at the rate which may be assume to be proportionate both to the concentration of this enzyme and the concentration of acetylcholine itself.

For the sake of greater generality, rather than to speak of acetylcholine and cholinesterase, we shall in the remainder of this paper speak of excitine and excitinase.

We do not know the chemical nature of the transmitter substance of the inhibitory neurons. We shall merely designate by the hypothetical transmitter substance which inhibitory neurons sendsacross the synaptic gap as inhibitine. We assume that inhibitine is destroyed by an enzyme which we shall designate as inhibitinase at the rate which is proportional both to the concentration of inhibitine and to the concentration of the enzyme inhibitinase.

The dendritic tree of any one neuron may be branched into several hundreds of dendrites and the axon of any one neuron may be branched into a correspondingly large number of fibres, each fibre ending in an endbulb that synapses with a dendrite of a neuron. Within such a neural network the level of excitation of a given neuron which receives an input through its dendrites from a large number of inhibitory as well as excitatory neurons depends on the rate at which excitine and inhibitine are produced and destroyed at the individual synapses. We may assume that the destruction of both substances is reasonably fast so that if the rate of production changes at one point in time from one value to another value the new stationery values is approached half way within about 5 or 10 milliseconds.

In these circumstances, each neuron may draw some sort of a balance between the excitatory and inhibitory impulses which reach it within any one given unit of time amounting to about 5 or 10 milliseconds.

We might for instance postulate that the firing frequency of the neuron is given by: (FORMULA)

where f is a monotonously rising function of the argument

(FORMULA)

We may assume that f is zero if all the frequncies (Formula) relating to excitatory impulses are zero (Formula).

We can, without losing too much flexibility assume that f is the same universal function, of the argument for all neurons involved in the network, that (Formula) is the same as the universal function of the firing frequency.

In this formula the firing frequency in the neuron is represented as a function of a quotient, the individual terms in the numerator relate to individual enbulbs of excitatory neurons which synapse with a dendrite of the neuron which we have singled out for attention and the individual terms in the denominator relate to the individual enbulbs of inhibitory neurons which synapse with the dendrite of the same neuron.

The coefficients (symbol) in the numerator are inversely proportionate to the concentration of the excitinase in the individual synapses of the excitatory neurons and the coefficients (symbol) in the denominator are inversely proportionate to the concentration of the enzyme inhibitinase.

In the individual synapses of inhibitory neurons we can, without too much loss of flexibility, assume, as we are doing here that (symbol) is the universal function of the frequency (symbol) of the volley of nerve impulses which reach the synapses from excitatory neurons and (symbol) is a universal function of the frequcnies of volleys which reach the synapses from inhibitory neurons. Similarly, we can, without too much loss of flexibility, assume that f is the same universal function of the argument, the quotient given above, for all neurons that we propose to consider.

We shall assume that (formula) increase monotonously with the argument of the function and that all three functions are zero if the value of the argument is zero.

As far as f is concerned the formula:

would obviously satisfy these conditions.

On the basis of assumptions made above, the frequency would be zero, which means that the frequency (symbol) is zero if the neuron does not receive an input

from excitatory neurons or if it receives an input from excitatory neurons but the concentration of excitinase at the synapse is very high.

Similarly, the frequency (symbol) will be low if the second term in the denominator of the argument of f is large. This would be the case if nerve impulses having a high frequency reach the neuron through a synapse from inhibitory neurons or if the enzyme inhibitinase has a low concentration in the synapse.

In our formula (symbol) stands for our unit of time which is about 5 or 10 millisenconc and (symbol) stands for the frequency of the nerve impulses reaching the synapse number i from an excitatory neuron and accordingly, the product (symbol) represents the number of nerve impulses reaching during one unit of time the individual synapse. Similarly, in the phenomenon the product (symbol) represents the number of nerve impulses which reach the individual synapse from the individual neuron.

We can, without too much loss of flexibility assume that f is the same inverse function of the argument, that it monotonously increases with increasing frequency and that it is zero if the value of the argument is zero. These conditions would, for instance, be satisfied if we wrote (FORMULA)

The value of (symbol) will be: (FORMULA)

The value of (symbol) is large if the coefficient (symbol) is large and if the frequencies (symbol) are large. All things being equal, the value of (symbol) is going to be small if the coefficients (symbol) are large and if the frequencies of the inhibitory impulses are high and if (symbol) the frequencies are large. At this point we are now ready to formulate our second postulate and to describe a biochemical model that would correspond to this postulate.

Our second postulate simply says that the concentration of the enzymes excitinase and inhibitinase in the respective synapses is proportional to the overlap numbers of the two neurons which are bridged by that synapse. From this postulate it follows that the frequency of firing of the neuron we have singled out for attention will be high if the overlap numbers of the excitatory synapses are high and the overlap numbers of the individual synapses are low.

In our formula (symbol) stands for a period of time of about 10 milliseconds. In the numerator (symbol) stands for the frequency of the nerve impulses reaching the individual synapse from an excitatory neruon. The product (symbol) represents a number of nerve impulses which reach an individual synapse during a period of time of 10 milliseconds and we assume that the amount of excitine produced at the synapse during such a period of time is proprtional to this product.

Simultaneously, the denominator (symbol) stands for the frequency of the nerve impulses which reach the individual synapse from an inhibitory neuron and we assume that the amount of inhibitine produced at the synapse during the period of time of 10 milliseconds is proportionate to the product (symbol).

We can, without too much loss of flexibility, assume that for all the neurons we shall consider here, f is the same universal function of the argument. We assume that f increases monotonously with the argument and that it is zero for argument zero.

Among the numerous functions that satisfy this condition would be for example:

FORMULA

all other things being equal, the value of (symbol) will be large if the coefficients (symbol) are large and if the frequencies (symbol) are large. All other things being equal, the value of (symbol) is going to be small if the coefficients (symbol) are large and if the frequencies (symbol) are high.

At this point we are ready to formulate our second postulate and we propose thereafter to describe a biochemical model that would correspond to this postulate. Our postulate assumes that the enzymes excitinase and inhibitinase are inactivated at the synapses at the rate which is proporational to their concentration and also proportional to the overlap numbers y of the two neurons which are bridged by the individual synapse. Since we may assume that these enzymes are produced at a constant rate in the cell body of the neuron from where they diffuse into the synapse, it follows that their concentration in the individual synapses will be proportionate to the overlap number of the synapse. Thus we will also formulate our second postulate by saying that in our formula (Formula) coefficients (symbol) and (symbol) are proportional to the overlap number of the individual synapse. This then means that the contribution to the excitation of a neuron to another

means that, all other things being equal, the contribution of the excitatory neuron to the excitation of another neuron will be large if the overlap number is large, and it will be small if the overlap number is small and the same postulate holds mutatis mutandis to the contribution to the inhibition of a neuron by the inhibitory neurons.

Even for man, verbal expression does not give us a quantitative measure of sensory signals and there is no verbal expression on which to rely in the case of animals. In these circumstances we could attempt to give our postulate meaning in a quantitative sense by defining the similarity of say visual signals in terms of the strength of instinct controlled response of the bird or the fish, however, it is much simpler to define similarity of sensory input by considering either the strength of a classical conditioned response or the strength of a response in operate conditioning by applying an input signal which is different from that to which the animal was conditioned and by observing the strength of the response. Thus, for instance, if say a pigeon has learned to peck in response to a visual signal without having learned to discriminate between this signal and other similar signals, then the reduction in pecking frequency when presented with the wrong signal instead of the right signal may be considered as a degree of the resemblance between the two signals. Our postulate can then be quantitatively formulated by saying that the overlap number of the two relevant neurons which are excited by the correct signal and the relevant neuron which is excited by the wrong signal have an overlap number which is all the greater the greater the similarity of the two responses..... that the greater the similarity of the two responses is the greater is the overlap number of these two neurons.

Let us now consider a class A of congenitally-determined neurons. If this class is sufficiently broadly defined then there will be a number of neurons within this class within one brain which differ in their chemical specificity. All the neurons within this class which have the same chemical specificity t h u s contain a smaller or larger number of sub-class Ai. The neurons which belong to this sub-class are characterized by the neuro-specific proteins which are maintained in these neurons at a high level.

In the following we shall designate with (symbol) the set of neuro-specific proteins composed of a number of (symbol) different proteins which characterize the class Ai. Let us now consider two neurons which belong to two different sub-classes Ai and Al. We propose then to designate as the overlap of the chemical specificity of these two neurons the number y of different neuro-specific proteins which are elevated in both of these neurons. Accordingly, the value of y is between zero and either (symbol) or (symbol) whichever is smaller. We shall be lead further below to assume that what we shall call an elementary sensory signal in contrast to a composite sensory signal may preferentially excite at a certain level all neurons in the brain which have all the same chemical specificty and that two elementary signals which are different will excite two groups of neurons which differ in chemical specificty. We shall be lead to assume, however, that there is such a thing as an orderly coding of the congenitally-determined neurons which respond to elementary sensory signals and that the overlap numbers of these two different neurons is large if the response of the animal to elementary sensory signals is smaller. Further below we shall discuss experiments which may furnish a quantitative measure of the similarity of the two sensory signals and only after that has been done is it possible to attach a clearly defined meaning to the notion that the overlap number of two neurons which preferentially respond to two different elementary sensory inputs is greater the greater the similarity of the two elementary sensory inputs.

Just what an elementary visual signal is depends very much upon the animal we have in mind. Thus, in the visual cortex of the cat there are neurons which preferentially respond to a minute slit in the visual field of an orientation defined between 5 or 10 degrees but located within a very wide limit anywhere within the visual field. In this case the illuminated slit is an elementary visual signal and two neurons which preferentially respond to two slits differ in orientation by say 20 degrees should have a substantial overlap number. In general the strength of a conditioned response with which an animal responds for the first time when the wrong signal is given may be regarded as a measure of the resemblance of this signal to the correct signal to which the animal was exposed during the establishment of the conditioned response.

If an animal is conditioned to respond to such an elementary sensory signal and is, thereafter, for the first time confronted not with the correct elementary signal but with a somewhat similar elementary signal, the itensity of his response may be taken as a measure of the similarity of the two elementary signals. We shall be lead to believe that the greater the similarity of the two signals, the greater is the overlap number of the two neurons which respond preferentially to these two signals

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The sets of the neuro-specific proteins which are elevated in the different neurons represent in a sense a code and I am anxious to avoid to give the impression that the coding of the congenitally-determined neurons which respond to sensory signals might be quite arbitrary. On the question of whether the coding of the congenitally-determined neurons which respond to sensory stimuli could be quite arbitrary, there is the following to be said.

Let us consider two neurons, say in the visual cortex, which respond preferentially to a different elementary signal. Just what the elementary signal is depends on the animal which is involved. Thus, in the visual cortex of the cat there are neurons which respond to an illuminated slit provided that the orientation of the slit is just right..... is correct within 5 or 10 degrees. Where in the visual space the slit is located does not matter, however, another neuron in the same part of the cortex responds preferentially to an illuminated slit with a slightly different orientation. In this case, the illuminated slit is an elementary visual signal.

The sets of neuro-specific proteins which are elevated in the different congenitally-determined neurons which respond to a sensory signal represent a code. It will be seen later that if this code were quite arbitrary then it would not be possible to account for the phenomenon which cats or dogs exhibit in the conditioned response. It might be just as well to say a few words here about the kind of irregularity of coding which we shall be forced to assume..

The sets and the neuro-specific proteins elevated in the different congenitally-determined neurons which respond to a sensory signal represent a code. If this code were quite arbitrary then it would be impossible for us to account for the phenomenon

which a cat or a dog exhibits in the conditioned response.

This point will be discussed later but it might be just as well to say a few words now about the regularity of the coding which we shall be forced to assume.

Let us then consider two neurons, say in the visual cortex, each of which responds preferentially to a different elementary visual signal.

The term " elementary visual signal" is used here in contra-distinction to a composite visual signal but just what may be regarded as an elementary visual signal depends on the kind of animal involved. Thus in the visual cortex of the cat, for example, there are neurons which respond preferentially to an illuminated slit, provided that the orientation of the slit is just right within 5 or 10 degrees.

The location of the slit in the visual space is, however, immaterial.

Any neuron located in the same region of the cortex responds preferentially to an illuminated slit with a slightly different orientation, etc. For the cat an illuminated slit is an elementary visual signal. Generally speaking, if an animal is conditioned to respond to a given elementary visual signal and is thereafter for the first time confronted with a different elementary signal then the response of the animal is likely to be weaker than his previous response to the correct signal. The strength of his first response to the wrong signal may be taken as a measure of the similarity of the two signals and we shall be lead to assume that the greater the similarity of the two signals the greater is the overlap of the two neurons in the visual cortex which respond preferentially to these two signals. This assumption reflects our belief in the orderliness and regularity of the coding system of the congenitally determined neurons which respond to sensory signals.

The biochemical model which, according to the notions here adopted, corresponds to this postulate, assumes that the neuro-specific proteins are located in the membrane which covers the cell body, the dendrites, the axon and the enbulbs of the branch fibres of the axon. We then assume, for the sake of simplicity, that the concentration of each neuro-specific molecule in the cell membrane is the same. We further assume that a molecule of any given neuro-specific protein located in the membrane covering the enbulb of a branch fibre can dimerize with a molecule of the same neuro-specific protein located in the membrane covering the dendrite or the cell body of another neuron. Fianlly, we assume molecules of the neuro-specific proteins undergo an allosteric transition when they are so dimerized and that in the dimerized form they inactivate the enzymes excitinase and inhibitinase. If, for the sake of discussion, we postulate that all neuro-specific proteins are contained in the membranes involved at the same concentration and that in their dimerized form all neuro-specific proteins inactivate the enzymes excitinase and inhibitinase at the same rate then our biochemical model corresponds to our first postulate sited above.

This biochemical model is not as far fetched as it might seem. The ability of neuro-specific proteins to dimerize and to bind in the dimerized state an unspecific protein like excitinase would be quite similar to the ability of antibody molecule when combined with its specific antigen molecule to bind complement.

Fig. 1 illustrates the notions here adopted. In this figure there is some schematically represented synapse consisting of two membranes, one covering the bouton of one neuron and the other covering the dendrite of another neuron, which are separated by a gap. The figure shows schematically a few molecules of neuro-specific proteins which are dimerized and a few others which are not dimerized, the idea being that they are present only if one of the two neurons ..... that they represent molecules of neuro-specific proteins which are present in one of the other two neurons but not in both. If a synapse bridges two neurons for which the overlap is zero, the corresponding figure would show no dimers.

Fig. 1 illustrates the notions here adopted; it is a schematic representation of a synapse and it shows two membranes which are separated by a narrow gap. One of these is supposed to be the membrane of an enbulb of a branch fibre of a neuron and the other is supposed to be a membrane of a dendrite of another neuron. The figure shows schematically a few molecules of neuro-specific proteins located in the membrane of the enbulb which are dimerized across the synaptic gap with their counterparts located in the membrane of the dendrite. The figure also shows a few molecules of other neuro-specific proteins which are not dimerized. They are supposed to represent molecules of neuro-specific proteins which are present in one neuron but lack their counterpart in the other neuron. The number of dimers one may expect to find in a synapse which bridges two neurons depends on the overlap number of the two neurons which are bridged by the synapse. If the overlap is zero the number of dimers would be zero.

We shall, for the sake of our discussion, here assume that a concentration of neuro-specific proteins in the cell membrane is the same for all neuro-specific proteins and accordingly the number of dimers present in a synapse bridging two neurons will be assumed to be proportional and accordingly we will assume the number of dimers present at a synapse to be proportional to the overlap number of the two neurons which bridge the synapse. If we make these assumptions our postulate will then conform to our biochemical model.

This seems to be as good a point as any to make a few remarks about antibodies which might be relevant to our topic in as much as the analogies which they afford might guide us in thinking about neuro-specific proteins.

In certain circumstances complement will manifest enzymatic activity, thus if antibody prepared against the rabbit is added to red sheep cells in the presence of a complement the sheep cells will rise. Just what role this phenomenon may play from the point of view of survival of the individual is not clear. It is conceivable, however, that the binding of complement or some other enzyme similar to complement by antibody molecules which are combined with their antigen plays a major biological role.

As pointed out earlier "L. Szilard - Proceedings National Academy of Sciences" - it is conceivable that the cells of the lymphatic system contain an enzyme S which inhibits cell division at a high concentration and that this enzyme resembles complement in as much as it gets bound by antibody or antibody molecules provided these are combined with their antigen. The possibility that this hypothetical enzyme S not only resembles complement but that it actually is complement cannot be ruled out at the present time.

If nature employs this mechanism in order to enable the antigen to evoke the selective proliferation of lymphatic cells which make the corresponding antibody then the ability of all antibodies unselectively to bind complement when the antibody is selectively bound with its antigen may play a fundamental role in the response.

Transprtined neurons

We postulate that there are in the nervous system of the neonatal animal cells which have not yet attained their full chemical specificity and which can be induced to differentiate beyond the spontaneous differentiation that they have undergone during embryon development in certain circumstances which we shall specify in detail.

We have assumed that in the case of congenitally-determined neurons a set of neuro-specific proteins is maintained at a high concentration and presumably the corresponding messenger RNA molecules are produced at a high rate. We do not know, however, what role the neuro-specific proteins themselves or the messenger RNA may play in the locking mechanism which is responsible for the persistence of the neuro-specific proteins once their concentration has been raised beyond a certain threshold.

INSERT:

According to the notions here adopted, memory and learning is possible because there are present in the nervous system of the neonatal animal neurons which have not yet attained their full chemical specificty when they have undergone spontaneous differentiation during the embryonal development and which can be induced to differentiate in certain circumstances during adult life. We shall use the term induced differentiation in contradistinction to the term spontaneous differentiation to denote differentiation which takes place during the lifetime of the adult.

Transprintable neurons

According to the notions here adopted, memory and learning is possible because there are present in the nervous system of the neonatal animal neurons which have not yet attained their full chemical specificity when they underwent spontaneous differentiation during embryonal development and which can further differentiate in certain circumstances during adult life under the influence of congenitally-determined neurons which are activated as a result of sensory stimulation. We shall designate these neurons which remain so to speak beyond the end of the neonatal period as transprintable neurons. These neurons which have remained, so to speak, plastic beyond the end of the neonatal period and may attain their full chemical specificity antytime during the adult life of the animal, as transprintable neurons. They attain their final chemical specificity through processes of differentiation to which we refer as induced differentiation in contradistinction to spontaneous differentiation by which we mean the differentiation which takes place during embryonal development or the very early nenatal period. Thus, all differentiation which takes place during the lifetime of the adult in the nervous system may be assumed to be induced rather thatn spontaneous. We shall assume that induced differentiation takes place once a transprintable neuron has undergone induced differentation.

We shall assumethat when a transprintable neuron undergoes induced differentiation it attains its final chemical specificity and, so to speak, ceases to be plastic. As we shall see below a transprintable neuron can undergo induced differentiation only at a time when its excitation is raised to the level where it begins to fire and send volleys of nerve impulses travelling down its axon. According to the notions here adopted, as a result of induced

differentiation,the set of neuro-specific proteins that are maintained at a high level of concentration in the transprintable neuron,may comprise the sets of neuro-specific proteins which characterize one or more of the congenitally-determined neurons are connected by synapses to the transprintable neuron, or, to be more precise, the only thing that can happen in induced differentiation is tantermount to transprinting in the sense that when the transprintable neuron undergoes.....

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.....For all we know N might be smaller than 10,000 but as we shall see later, there is some reason to believe that n is considerably larger than 10.

We are now ready to formulate our first postulate. In Fig. 1(a) is represented a neuron which has remained plastic. Four branch fibres of axons shown in the figure are assumed to come from four different neurons in the brain each of which responds to a different visual signal. One branch fibre comes from a neuron F in the brain which we assume is activated by a signal when food is squirted into the mouth of the dog. We shall assume that a memory neuron depicted in the figure..... We shall assume that in certain circumstances to be stated below, if such a memory neuron receives simultaneously signals all of these branch fibres contact the neuron E through an endbulb or bouton which is in loose contact either in the cell body of the neuron E itself - as represented in the figure - or as one of the numerous dendrites of the neuron E - which are not represented in the figure. The point of this loose contact is called a synapse. In certain circumstances, to be specified below, if nerve impulses reach the neuron E through one of the branch fibres of some neuron L and through the branch fibre of the neuron F depicted in the figure, the neuron F and neuron L, which is sending nerve impulses to the neuron E, causes the neuron E to fire and when that happens the neuron L and the neuron F induce differentiation of the neuron E so that the neuron E assumes its final chemical specificity. Thereafter the neuron E will cease to be plastic and cannot be induced any longer to further differentiation . When this happens, we shall see that the neuron F and the neuron L, which were simultaneously firing volleys, have transprinted neuron E.

Let us designate with (e) the set of n neuro-specific proteins that are elevated in the neuron E while it is has still remained plastic, and similarly we shall designate with (f) the set of n neuro-specific proteins which are elevated in the congenitally-determined neuron F and designate with (l) the set of neuro-specific proteins which are elevated in the congenitally-determined neuron L. After transprinting has taken place the chemical specificity of the neuron E will, according to our postulate, be characterized by three sets of neuro-specific proteins which are elevated, the sets (e), (l) and (f). Fig. A and B, indicate this. Fig. A represents the neuron E before transprinting and B depicts the

the same neuron after transprinting by the neurons L and F and in both cases the sets of neuro-specific proteins elevated in the neuron are shown inside the circle which depicts the cell body of the neuron.

In order to distinguish a memory neuron from a congenitally-determined neuron, the circle which symbolizes the outline of the cell body of the memory neuron is drawn in a dotted line whereas the same circle for the congenitally-determined neuron is drawn with an unbroken line.

In order to indicate in Fig. B that a memory neuron has been transprinted and is no longer plastic, an inner circle with an unbroken line is drawn concentrically with the dotted circle.

Further, branch fibres which come from neurons which are capable of transprinting are marked with a double arrow at the synapse as shown in Fig. 1(a) and B in the case of branch fibres coming from axons of the neurons F and L.

It is an essential feature of the notions here applied that a memory is not always laid down , i.e. transprinting does not always take place when a memory E is simultaneously reached by nerve impulses from two different neurons such as L and F. Rather, the simultaneous excitation of the neurons L and F is recorded by the memory neuron only if it is of significance. In our model, the fact that the event is of significance to the animal is represented by signals coming from a particular network of neurons which are designated by F*. A branch fibre of an axon into which volleys are fired when the network of the neurons F* is signalling, is depicted as having a synapse on the cell body of the neuron E in Fig. 1. According to our postulate, the memory neuron depicted in Fig. E will be transprinted only if it receives volleys from F* and from E. In such a case, if it receives volleys from L but not from F, the neuron E will be transprinted only by the neuron L so that its chemical specificity then becomes (e) plus (1) and, further, it will be also transprinted if in addition to F* it receives nerve impulses simultaneously both from L and F. In this case it will be transprinted both by the neuron L and the neuron F and its chemical specificity is then characterized by the sets (e), (1), and (f).

Shorthand Notebook 4 Transcribed posthumously

According to the notions here adopted, the unit of recorded memory which may be recorded within one neuron is not a bit but something that contains considerably more information than a bit. There is a class of dreams, first described by Freud and discussed by him in great detail which is centered on what he calls a "traumgedanke". In a dream of this type the sametraumgedanke appears in a number of differet representations and if, within one night, several dreams of this type follow each other the same traumgedanke is likely to be represented in every one of them.

It is conceivable that a Freudian dream is generated because one single neuron gets excited during the night and remains excited for an extended period of time. If the individual wakes up, becomes conscious and the dream enters his consciousness, the neuron involved may cease to be excited.

A traumgedanke is a gestalt in a meaning of the term defined by Wortheimer and Koehler..... We consider a traumgendanke to be a gestalt in terms of the concept initially introduced by Wortheimer and Koehler and according to our notions it is a most complex gestalt that can still be stored in a single neuron. Our model cannot account for a greater complexity of storage than one gestalt per neuron and one may ask whether this limitaion might not get us into trouble from the start.

If an individual were able to retain information of the complexity of a traumgedanke conveyed to him every few seconds, 24 hours a day over a period of one hundred years, then the units of recorded memory stored by such an individual would irreversably tie down just about 10^9 neurons of his brain. This would still be 10 times less than the number of neurons in the brain of man, which is usually qutoed to be 10^{10}.

It may be seen from the above that models which attribute to the neuron a storage capacity that is several orders of magnitude lower would not be able to account for the memory storage capacity of man. We shall not attempt here to devise any neural networks which could account for the higher mental functions of man. Rather, we shall go here only as far as to describe a simple neural network which, on the basis of the molecular processes here postulated, would account for the ability of a mammal to establish a classical (Pavlovian) conditioned response for the ability of the animal to achieve higher and higher degreees of discrimination in the cause of the establishment of the conditioned response

and the extinction of the conditioned response if it is not reinforced.

For the sake of concreteness, we shall base our discussions on detailed models since the details must of necessity be based on guesses and since we cannot expect for all of our notions to be correct it would be foolish to expect our models to be correct in detail. The best we can expect is to have guessed correctly the general nature of the molecular processes which the brain employs and that when we have hit on the correct general concepts in formulating our models. In this circumstance we may start out by describing the general concepts upon which the two main postulates of this paper are based. Both of these concepts have first cropped up in papers which dealt with the functions of the lymphatic system. The first of these concepts is the ability of certain cells of the lymphatic system to distinguish between self and non-self. This concept was, I believe, introduced by Sir ------MacFarlane Burton (?).

The fagocytes of an animal will ingest a variety of cells of an animal of a different species but will not ingest the same kind of cells of the animal itself. If it were true that this phenomenon is not embodied by specific antibodies ~~with~~-which are capable of coating the cells of the foreign species then indeed there would be such phenomenon of recognition of self and non-self then it will very well be an all or none process. This may or may not be true and fagocytes may or may not be able to discriminate between self and non-self. But, however, that may be and whether fagocytes are or are not able to discriminate between self and npn-self we shall postulate that such a recognition of self and non-self plays a major role in the nervous system. We shall not assume, however, this to be an all or non- process, rather we shall attribute ..... We shall not assume that this is an all or none process, rather we shall assume that it is a quantitative phenomenon in which the degree of selfness plays a determining role. Moreover, we shall present a biochemical model which could account for this phenomenon.

.....Roughly speaking, our postulate says that if a neuron contributes to the excitation or inhibition of any neuron, its contribution is proportional - all other things being equal - to the overlap of the chemical specificity of the two neurons. We propose to formulate below much more precisely just what we mean by chemical specificity and what we mean by overlap and we also propose to present on that occasion a biochemical model which could account for this postulate. The second major concept relates to the supposed ability of an antigen when injected into a rabbit to bring about an irreversible change in certain lymphatic cells and to induce these cells to differentiate in the sense that as a result of the exposure to the antigen these cells willthereafter produce a specific antibody to the antigen at a high rate. This concept of a post-neonatally induced differentiation which irreversibly alters the chemical specificity of the cell was introduced by me in a paper which appeared in 1960. I presented a biochemical mechanism which could explain how an antigen which penetrates into a lymphatic cell raises the concentration of an antibody molecule which is specific for this antigen above the threshhold beyond which a locking mechanism would go into effect. The antigen would thus induce an irreversible differentiation in a lymphatic cell and so that after the cell had been exposed to the antigen the concentration of the corresponding antibody would thereafter be maintained at a high level. If this were correct then the lymphatic system would process a certain kind of memory and this memory could account for the abundant production of the antibody if the antigen is injected into a pre-immunized animal for a second time, the socalled secondary response. Taking his departure from these considerations, H.S. Anker suggested in a letter to Nature, that a similar biochemical mechanism could conceivably account for long-term memory in the CNS and irrespective of whether or not antigens are capable of inducing this kind of differentiation in the lymphatic cells of the adult, I propose to postulate here that induced differentiation takes place in the CNS of the adult and is responsible for the long term memory in the CNS. Roughly speaking, our second postulate says that there are neurons in the CNS of the adult which have not reached their final chemical specificity when they have undergone differentiation during embryon development and the early post natal period. Such neurons which have remained in a sense plastic can in certain circumstances be induced to undergo further differentiation and to assume their final chemical specificity by other neurons which contribute to their

excitation. It is assumed that such induced differentiation takes place over a period of a few minutes and that thereafter the plastic neuron having attained its final chemical specificity ceases to be plastic. It is assumed that such an induced differentiation takes place only if the plastic neuron gets excited to the point where it begins to fire volleys into its axon and that what takes place in the process of differentiation is something that we may designate as transprinting. We propose to state more precisely further below just what we mean by the term of transprinting and all we needto say at the moment is that as a result of the process of transprinting the chemical specificity of the memory neuron will have a substantial overlap with some of the neurons which have contributed to its excitation at the time when differentiation was induced, thus roughly speaking, our second postulate says that a neuron of the CNS which was not as yet fully differentiated may be transprinted during the life of the adult by neurons which have attained their final chemical specificity,and these neurons may on such an occasion confer their chemical specificity on the memory neuron.

We will take it for granted that after a memory neuron acquires its final chemical specificity this chemical specificity will persist by virtue of the locking mechanism which operates in the neurons which have attained their final chemical specificity during embryonal development or in the early post natal period. This, however, does not tell us in what manner neurons which have attained their final chemical specifity can induce differentiation in neurons which have as yet remained plastic.

The phenomenon of enzyme induction does not provide us in this regard with any real clue, still we know in the case of enzyme induction in the case of bacteria, at least this much.

When the inducer is present in the growth medium the gene which is specific for βgalactosidase produces an RNA molecule - the messenger RNA - which is specific for βgalactosidase. The base sequence of this messenger RNA determines the amino acid sequence of the corresponding polypeptide chain and four of these polypeptide chains combine to form the enzyme βgalactosidase.

We may surmise that in a neuron which has attained its final chemical specificity and in which a set of n different protein molecules are maintained at a high level of

of concentration the set of n specific proteins is maintained at a high concentration and n corresponding messenger RNA molecules are produced at a high rate. We do not know, however, what role these specific protein molecules themselves or their messenger RNA may play in the locking mechanisms which are responsibile for the persistence of this high level.

The best we can do is to assume that there is a class of compounds which plays a key role in differentiation that takes place during the embryon development and in the ensuing persistence of the chemical specificity of the neurons which have attained their final chemical specificity during embryon development and that each of these key compounds is maintained at a high level of concentration if differentiation is taking place. We cannot say, however, whether the key compound is a protein molecule, an RNA molecule or some other kind of molecule, nor can we exclude the possibility that the key compound might be the specific protein molecule itself. On this basis, we may then say that one cell may induce the differentiaiton of another cell with which its in physical contact if, for one reason or another, the membrane of another cell which has not reached its final chemical specificity and which it is in physical contact..... if something happens that renders the membranes of both cells permeable to all relevant key compounds and providing these cells remain permeable for a sufficiently long period of time, a few minutes perhaps, so that there is enough time to permit the diffusion of the key compounds from the fully-differentiated cell into the cell that has as yet remained plastic. The description of the biochemical processes through involved transprinting will in these circumstances have to remain rather fragmentary.

Network involving Congenitally-Determined Neurons March 27,1964

While it may be true that an animal like a bird would be seriously handicapped if it could not learn and remember, it is also true that in comparison with mammals learning and memory plays a comparatively small part in a bird. Even if, through some magic, we could destroy the ability of a bird to remember, the bird would be still capable of a high degree of visual discrimination. Thus, it is known that migratory birds are guided in the long journey which their migration involves, not by memory, but by instinct, i.e. the degree of discrimination which a bird exercises on such an occasion is accomplished by means of networks which have not been modified during the lifetime of the bird is

is not to be modified by what the bird might have learned after its birth.

We shall limit this first part of our discussion to neurons and neural networks from which any neurons that may be modified through learning have been completely eliminated so that we are dealing with learning. I propose to start out by discussing the notions here adopted in so far as they relate to neurons and neural networks which perform in the manner as a bird performs when its response is guided by instinct..... I propose to start out discussing the notions here adopted by limiting the discussion to the application of these notions to networks of neurons which are not modified by the sensory experiences to which the animal is exposed during its lifetime. Thus, our discussion leaves out that part of the nervous system which is involved in learning, the recording and recall of memory or any other form of recording and recalling memory. In other words, we shall at first consider here only networks of, so to speak, non-plastic or congenitally-determined neurons. This rigid part of the nervous system develops to a large extent during the embryon development of the animal and to a minor extent during the early post natal period. By the end of the post natal period, the system is fully developed and we shall assume that it remains rigidly untouched throughout life after the early post natal period. The embryonal development of the rigid nervous system involves both differentiation and morphogenesis. The neural networks which involve a large number of neurons with different chemical specificities involved during the embryon development through differentiation and morphogenesis and, for the sake of clarity, we want to define these two terms and to separate them from each other as far as possible. We shall use the term "differentiation" in regard to neurons to denote changes in the chemical specificity and morphology, the meaning of which can be defined for a single neuron leaving other neurons out of consideration. This does not mean that other neurons do not play a part in bringing about the differentiation of the neuron in question. Rather, it means only that after differentiation has occurred the chemical specificity and morphology of the neuron in question has a definite meaning in itself and can be defined out of context of the neural network of each neuron may be a part. In contrast to this, differentiation as defined above plays almost certainly a major part in the morphogenesis which is responsible for the genesis of a great variety of neural networks during embryon development.

We shall refer to the differentiation of neurons which takes place during embryonal development as "spontaneous differentiation" and the neural networks here considered which involve only neurons which are congenitally-determined, we need not be concerned with. We know very little about how spontaneous differentiation of neurons acts during embryon development. There is a general belief that differentiation of cells within a tissue may in some way be influenced by cells of another tissue provided they are adjacent to and presumably in physical contact with each other.

This leaves it completely open to what extent other neurons may play a part in triggering the differentiation of the neuron in question, but while differentiation in its narrow sense here defined is likely to turn out to be a useful concept, it seems doubtful whether it would be useful to discuss morphogenesis in the nervous system except in context with differentiation.

As a result of the differentiation undergone during embryonal development, the congenitally-determined neurons attain their final chemical specificity by the end of the early post natal period at the lates. When we speak here of chemical specificity of a congenitally-determined neuron we have in mind a rather definite model which may be formulated as follows. There is in the neurons of the CNS, just as there is in other somatic cells of mammals, an amount of DNA which corresponds to about one million genes. This may be compared with the amount of DNA contained in the somatic cells of insects, say the fruit fly, which is about a hundred times less, just enough to account for about 10,000 genes. We assume that each gene contained in a neuron is capable of causing the production of one part protein and the base eequence of the gene determines the amino acid sequence of the polypeptide chain which consitutues that particular protein of the mammal. For the purposes of our discussion we assume that out of this one million genes there are a certain number N of genes, about10,000 perhaps, which, from the point of view here adopted, play a role in the neurons of the CNS. We shall refer to these N genes as the neuro-specific genes and assume that each one of them can somehow be programmed to produce its particular neuro-specific protein, once the level of concentration of such a neuro-specific protein has been raised beyond a certain threshhold during spontaneous differentiation in a given

neuron. Thereafter, this neuron will forever maintain this neuro-specific protein at a high level of concentration. If we consider a broad class of neurons of congenitally-determined neurons which attain their full chemical specificity at birth or soon thereafter, we may then say that different sub-classes of the neurons of Class A which may be designated by Ai, Al, etc., differ from each other in as much as in each of these sub-classes .....

Let us now single out at random one of these neurons and then consider all the neurons in the brain have the same chemical specificity as the neuron we singled out. All of them form a homogenous group which may be regarded as sub-class Ai of the neurons of class A. According to our postulate, the neurons which belong to sub-class Ai can be characterized by the different neuro-specific proteins which are maintained in these neurons at a high level. We shall assume that the number ni is between 10 and 100 and we may designate the set of neuro-specific proteins which are elevated in the neuron Ai by ai. If we postulate that the number of n of the different neuro-specific proteins which are elevated in different neurons of the brain is the same then the number of congenitally-determined neurons which differ from each other by chemical specificity would be given by the binomial coefficient (symbol), for N^{10} and for n = 10. This binomial coefficient would be of the order of magnitude of ------. This would be larger than the number of neurons contained in the CNS of man which is usually quoted to be about 10^{10}. As we shall see later, however, there is some reason to believe that while N should be considerably larger than 10,000 n may have to be assumed to be considerably larger than 10. There is no reason except perhaps the simplicity of the discussion for us to assume that the different neurons of the brain contain the same number of n of elevated neuro-specific proteins.

Let us now consider some rather broadly defined class of congenitally-determined neurons, neurons of a certain class A, if the class is sufficiently broadly defined then within the human brain there will be a number of neurons within this class which differ in their chemical specificity and all the neurons of Class A within the brain which have the same chemical specificity from one sub-class and the brain will contain a small or large number of sub-classes Ai. The neurons which belong to a given sub-class Ai are characterized by the different neuro-specific proteins which are maintained in these

neurons at a high level, we shall designate with ni the number of different neuro-specific proteins which are elevated in the neurons of the sub-class Ai and at this stage of the game we are free to imagine that ni might be a number between 10 and 100. Then the number of different congenitally-determined neurons which could exist would be given by the binomial coefficient:

(FORMULA)

for (symbol) for (symbol). This binomial coefficient would be of the order of magnitude of (FORMULA). This would be immensely larger than the number of neurons contained in the CNS of man.

N could be considerably less than 10000 but as we shall see later, if the number of different elevated proteins per neuron were the same for every neuron then there would be some reason to believe that this number may be considerably larger than 10.

In the following we shall designate with ai the set of neuro-specific proteins composed of ni different proteins which characterize the sub-class Ai. Let us now consider two neurons, a neuron Ai and a neuron Bk, which may either belong to the same broad class or to a different broad class. We shall define as the overlap of the chemical specificity of these two neurons (symbol) the number of different neuro-specific proteins which are elevated in both of these neurons. Clearly y could be anything between zero and either ni or nk whichever is smaller.

With these definitions we are now in possession of the terminology that makes it possible for us to formulate our first postulate regarding congenitally-determined neurons. It is easiest to make clear what that postulate means if we formulate first for man and limit ourselves to neurons in the brain of man which respond to some visual signal. Among these neurons there will be some which will preferentially respond to say a flash of light coming from a certain direction in the visual space provided the illumination is say in the red region of the spectrum. There will be other neurons in the brain of man which will preferentially respond to a light signal which comes from the same direction in the visual space. We may now ask which neuron in the brain will preferentially respond to a light signal coming from a certain direct point in the visual space if the illumination is in the

region ofthe spectrum. Let us designate these neurons as neurons of Class A. We can further ask which neurons will preferentially respond to a light signal irrespective of colour which comes from the same point in the visual space. Let us designate these neurons as neurons of Class B and finally we can ask what neurons will preferentially respond to a light signal if the illumination is in the red irrespective of the point in the visual space from where the signal is located. Let us designate these neurons as neurons of Class C. In the case of this special example our general postulate says that the neurons of Class A and B have a substantial overlap number, that the neurons of Class A and Class C have a substantial overlap number, and finally that the neurons of Classes B and C have an overlap number which is different from zero but is presumably smaller than the two overlap numbers referred to above. This is a special case of a more general postulate which can be formulated as follows: If two neurons which preferentially respond to different visual signals have a certain overlap number and this overlap number may be assumed to be larger than our postulate formulated for man.....

Our postulate formulated for man in this general form says that two neurons each of which respond to a different sensory signal have an appreciable overlap number if the two signals have something in common which can be expressed in fairly simple terms within the common usage of the language, the greater the similarity of the two signals again defined in terms of a verbal expression, the greater will this overlap number assume to be. We shall not beable to formulate this postulate more precisely in abstract butit would be possible to define the overlap number experimentally on the basis of ease or difficulty with which say a cat or a dog would have to discriminate between the two things in a classical conditioned response.

Our next postulate relates not to a single neuron but to a network of neurons and therefore we must say first about the kind of neural networks that we have in mind. We assume that each of the neurons involved in the kind of networks we are considering has its axon which ends in a large number of branch fibres and that each of these fibres ends in an endbulb or bouton. These enbulbs or boutons are located on the cell body of another neuron or one of the numerous fibres which emanate from another neuron. We assume that each neuron involved in the network sends volleys of nerve impulses along its axon and the

and the frequency of these impulses increases with increasing level of excitation of the neuron. The axon of each of the neurons involved has a certain large or small number of fibres each of which ends in an endbulb or bouton. The cell bodies of all the neurons involved do not have a small surface but rather they send out numerous branches. Each endbulb of a branch fibre of the axon of one neuron contacts the cell body or a dendrite of other neurons, each such point of contact is referred to as a synapse. There is always a gap of about one millionth of an inch between the cell membrane of the endbulb and the cell membrane of the cell body of the neuron or its dendrite.

April 7

Induced differentiation consists of the adoption by the transprintable neuron of the sets of neuro-specific proteins that characterize one or more of the congenitally-determined neurons which are connected through synapses with the transprintable neuron and which at the outset of induced differentiation are sending volleys of nerve impulses to these synapses. We shall assume that some of the congenitally-determined neurons can induce the set of neuro-specific proteins which is characteristic for them in the transprintable neuron which undergoes induced differentiation and we shall designate these congenitally-determined neurons as transprinting neurons.

A number of congenitally-determined neurons of different chemical specificities may be connected with a given transprintable neuron through synapses and may send volleys of nerve impulses to these synapses at the time when the transprintable neuron undergoes induced differentiation. This does not mean, however, that the transprintable neuron will necessarily adopt the neuro-specific proteins that characterize each of these congenitally-determined neurons, rather the congenitally-determined neurons may be different from each other in as much as that some of them may be capable of inducting their own set of neuro-specific proteins in the transprintable neuron during the processes of induced differentiation and other congenitally-determined neurons may not be capable of doing so. Accordingly, the congenitally-determined neurons may be divided into two classes depending upon whether they can or cannot transprint in the process. One may at this point ask just how induced differentiation might take place in the central nervous system and in what circumstances one could expect such a process which may result in the establishment of recording of a sensory experience to take place.

We may now assume that in the case of congenitally-determined neurons which are capable of transprinting the membrane covering the endbulbs of the branch fibres of the axon become permeable for the whole class of key compounds whenever the neuron fires volleys of nerve impulses of substantial frequency along its axon. This does not necessarily mean however, that these key compounds can diffuse across the synapses into a transprintable neuron from the congenitally-determined neuron into the dendrite of a transprintable neuron which is bridged by the synapse. For this to happen it would be necessary that

that the membrane covering the dendrite also become permeable for the class of key compounds at the synapse. According to the notions here adopted, this will happen only if the transprintable neuron is reached..... if neurons belonging to a certain class contact the transprintable neuron through synapses..... send volleys of nerve impulses into these sunapses. The firing of neurons belonging to this special class takes place only in case the sensory stimuli which reach.....

If volleys of nerve impulses reach the neurons of this special class as well as the transprintable neuron which we have singled out for attention, there is attached an appreciable significance and as will be presently seen, certain kinds of sensory stimuli have significance in the meaning of the term here employed either when the stimulus was not expected or when it was expected but did not materialize.

When food is squirted into the mouth of of a dog, the dog responds with salivation. This is the congenital or unconditioned response. In a classical Pavlovian experiment a dog may be presented with a certain kind of a light signal and this signal is then immediately followed with the squirting of food into the dog's mouth. After exposing the dog a number of times to such an experience, thereafter, the dog will respond with salivation to the light signal alone even if no food is squirted into its mouth. This is a conditioned response. Let us assume that the light signal consists of a flash of red light appearing in the upper right hand quadrant of the visual field and that a neuron Lk preferentially responds to this kind of light signal by sending volleys of nerve impulses along its axon. Let us further assume that another neuron designated by Fo preferentially responds to the squirting of food into the dog's mouth and sends volleys of nerve impulses along its axon when food is squirted into the dog's mouth. The chemical specificity of the neuron Lk is characterized by the set of neuro-specific proteins (lk) and the chemical specificity of the neuron Lo is characterized by the set of neuro-specific proteins (lo).

We postulate that both of these neurons are capable of transprinting. We assume that there are present in the central nerouvous system transprintable neurons E and that branch fibres of the axons of the neuron Lk and the neuron Lo are connected through a

a synapse with these neurons E. When the conditioned response described above is established neurons of Class E are transprinted by both the neuron Lk and the nueron Lo. Before being transprinted such a transprintable neuron E was characterized by a set of neuro-specific proteins (e). After being transprinted the same neuron E, no longer transprintable, will be characterized by a set of neuro-specific proteins which comprise in addition to the set (e) also the sets lk and fo.

The transprinting of the neuron E represents the establishment of the conditioned response. If, when the conditioned response is established, the dog is presented with a flash of red in the upper right quadrant of his visual field, the neuron Lk will fire and because the transprinted neuron E contains the set of neuro-specific proteins lk at a high level of conentration the neuron Lk will fire.

In order to illustrate what goes on when a conditioned response is established and when it is extinguished we shall consider pairs of neurons composed of an excitatory neuron E and an inhibitory neuron I and we shall assume that a number of these pairs of neurons, each of which is composed of one excitatory neuron E and one inhibitory neuron I , with the branch fibre of the excitatory neuron connected through a synapse to the inhibitory neuron so that when the excitatory neuron fires it causes the inhibitory neuron to fire also. We shall assume that a number of such pairs of neurons form a closed group, by which term we mean that each inhibitory neuron within the group has a branch fibre which is connected through a synapse..... that the axon of each individual neuron has many branch fibres and is connected through a synapse to every excitatory neuron within the group. We shall further assume that the neuron Lk as well as a number of other similar neurons of the primary visual cortex have branch fibres of their axons synapse with each one of the neurons E and similarly the neuron Fo has branch fibres synapsing with each of these neurons.

We shall assume that the squirting of food into the mouth of the dog causes salivation because the neuron Fo sends nerve impulses to a .....the neuron Fo has a branch fibre of its axon connected through a synapse with a neuron S which innervates the salivary gland. We assume the neuron S is characterized by the same set of (fo) of neuro-specific proteins

which characterize the neuron Fo. We assume that the conditioned response is established by the simultaneous transprinting of of an excitatory neuron E by the neurons Lk and Fo. Prior to the transprinting the transprintable neuron E was characterized by a set of neuro-specific proteins (e) and after transprinting the neuron E is characterized by a set of neuro-specific proteins which comprise the sets (e) (lk) and (fo).

We shall further assume that the establishment of the conditioned response assists in the change which takes place in a transprintable excitatory neuron E, to which a branch fibre of a neuron Lk and neuron Fo are connected through a synapse and branch fibre of which is connected through a synapse to the neuron S. The establishment of the conditioned response assists in the simultaneous transprinting of the neuron E by the neurons Lk and Fo. Prior to the transprinting the transprintable neuron E was characterized by a set of neuro-specific proteins and after transprinting the neuron E is characterized by a set of neuro-specific proteins which comprises the sets of (e), (lk) and (fo).

If, after the establishment of the conditioned response, the dog is presented with a light signal to which the neuron Lk will preferentially respond then because the neuron Lk and the neuron E now have an overlap number of lk which may be assumed to be substantial the firing of the neuron Lk will cause the firing of the neuron E. Because the transprinted neuron E and the neuron Fo have an overlap number of (fo) which may be assumed to be substantial the firing of the neuron E will cause the firing of the neuron FO and will thus cause salivation.

We assume that in the case of a congenitally-determined neuron which is capable of transprinting the membrane covering the enbulbs of the branch fibres of its axon of the neuron becomes permeable for all key compounds whenever the neuron sends nerve impulses at a sufficiently high rate into its axon. This does not necessarily mean, however, that these key compounds can diffuse across a synapse from the congenitally-determined neuron into a transprintable neuron on all such occasions. Rather, for this to happen it would be necessary that the membrane of the transprintable neuron also become permeable at the synapse for all compounds. According to the notions here adopted this will happen only if the level of excitation of the transprintable neuron is raised high enough to cause such a neuron to start to fire at a sufficiently high rate.

If after the establishment of the conditioned response, the dog is presented with a flash of red light located in the upper right hand quadrant of the visual field but if this is not followed within a short period with the squirting of food into the dog's mouth, then there may occur the transprinting of another transprintable neuron E but this time the transprinting is induced only by the neuron Lk and not by the neuron Fo. Accordingly this second transprintable neuron E will after being transprinted be characterized by a set of elevated neuro-specific proteins which comprise the set (e) of the set (lk) but will not comprise the set (fo).

Figure 1a represents the transprintable neuron E, in the form of a circle drawn with a broken line, of the branch of the axons of the various neurons which are connected with this neuron through a synapse. Those coming from a neuron that is capable of transprinting are marked with a double arrow in contra-distinction to the others which are marked with a single arrow. As indicated in Fig. A the transprintable neuron E is characterized by the set of neuro-specific proteins (e). Fig. b represents the same neuron after it has been transprinted by neurons Lk and Fo. This neuron is now no longer transprintable which we are indicating by having a circle drawn with an unbroken line concentric with the circle drawn with the broken line. As Fig B indicates, the neuron E thus transprinted is now characterized by neuro-specific proteins which comprise the set (e), the set (lk), and the set (fo).

Fig. 1C shows a second neuron E which has been transprinted by the neuron Lk but has not been transprinted by the neuron Fo. As the figure indicates the set of neuro-specific proteins in the neuron E which has been thus transprinted comprises the set (e) and the set (lk) but does not comprise the set (fo).

For a memory to be recorded in the case of the sensory stimulation of the animal in the conditioned response, the stimulation must have a significance attached to it. According to the notions here adopted, there is no significance attached to the presentation of the signal if its immediately followed by the presentation of food. There is significance attached to the presentation of food which has not been preceeded by a signal.....
For a sensory experience to be recorded in the sense that it will lead to a classical

conditioned response, it is necessary that the excitation level of a suitable transprintable neuron be raised to a level where this neuron starts to fire and we shall postulate that in order for this to happen, it is necessary, not only that the transprintable neuron receives nerve impulses from neurons such as neurons L which respond to a visual stimulus but also that it receive nerve impulses from a neural network which we shall designate with F*. As we shall presently see, the sending out of signals by the neural network F* represents the significance which is attached to the sensory experience. Once a conditioned response has been established there is no significance attached to the presentation of food if it is preceeded by a signal which leaves the conditioned animal to expect the presentation of food. The neural network F* is composed of neurons characterized by the set of neuro-specific chemicals (fo). The neuron Fo has branch fibres which are connected with synapses with the neurons of the neural network F* and also the neurons E have branch fibres..... the neuron Fo on the one hand and the neurons E on the other hand have branch fibres of their neurons which are connected with synapses with the neurons which compose the neural network F* and we shall assume that the neural network F* sends signals either if it receives nerve impulses from the neuron Fo or if it receives nerve impulses from neurons E which have been transprinted so that the set of neuro-specific proteins comprises the set (fo). The neural network F* does not send out signals if it receives an approximately equal input from the neuron Fo on the one hand and from one or more neurons E on the other hand. It is the peculiarity of the neural network which is located in the superior olive that it sends out signals if it receives signals from one ear alone, whereas contemporaneous signals from both ears cancel each other. By this cell network in the superior olive, we detect the directionality of sound and are able to hear a signal in one ear despite the large common background of noise in both ears. We assume here that the network of neurons F* sends out a volley of nerve impulses only if it receives a signal either from Fo or from one of several neurons E while signals of comparable strength arriving simultaneoulsy from neuron F and from the neurons E cancel out.

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The chemical specificity of an end organ may determine the chemical specificity of a neuron which innervates this end organ . This was fairly well substantiated by Paul Weiss and his experiment as well as subsequent experiments by Sperry lent considerable support to this notion. What takes place in cases which they have investigated can be considered as developmental transprinting since this relates to congenital differentiation and not the kind of induced differentiation with which we are concerned here. It should be noted, however, that while the induced differentiation which concerns us goes in the same direction as the nerve signals go, the developmental transprinting of Paul Weiss and Sperry would be retrograde, i.e. it would go in the direction opposite to those in which the nerve signals are propogated. It is quite possible that both of these phenomena occur but it would not be too surprising if induced differentiation in the adult moved in one direction and developmental differentiation in the embryo and the neonatal animal moved in the opposite direction. Particularly in view of the fact that there is such a thing as the retrograde nerve fibres. .....

Accordingly, this neural network can receive signals from neuron Fo. It also can receive signals from those of the neurons E which have been transprinted in such a manner that a set of neuro-specific proteins comprises the set (fo). We assume that the function fulfilled by the neural network F* resembles a function fulfilled by a neural network which is located in the superior olive. Fig. 2 shows one part of the model of the neural network to which we attribute the establishment of the extinction of the classical conditioned response. This neural network is composed of pairs of neurons; a neuron E which is excitatory and transprintable and a neuron I which is inhibitory and which we have so far no reason to assume to be transprintable. Whenever the neuron E fires it will raise the level of excitation of the inhibitory neuron I to the point where it will fire also. As the figure shows, when an as-yet-unconditioned dog is conditioned by a flash of red light coming/from the upper right hand quadrant of the visual field, followed immediately by the squirting of food, the neuron Fo will send nerve impulses to the neuron E and also into the neural network Fo*. Since we are dealing with a dog which is not yet conditioned, the neural network Fo* will receive no signals from any neurons E and accordingly, the neural

(PART II IS MENTIONED HERE)*

network Fo* will send out signals which will reach the neuron E depicted in Fig. 3. Under the influence of these signals and the signals which it receives from one of the neurons the neuron E will now begin to fire and will be transprinted by the simultaneoulsy firing neuron Lk and neuron Fo. We shall, in the following, assume for the sake of simplicity, that one such experience is sufficient to establish the conditioned response and we shall now discuss the extinction of this conditioned response which takes place if the conditioned dog is now repeatedly given the correct light signal but this is no reinforced by squirting food into the mouth of the dog immedialy following the signal. Fig. 4 shows the neural network we have assumed is composed of pairs of neurons E and I. We may mention that we have a hundred or several hundred such couples of neurons and in our idealized model we shall assume that this group of neurons is self-contained in the sense that every neuron I sends a branch fibre of its axon to every neuron E contained in the group.

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* In Part II we shall discuss in detail a simple neural network which can fully account for the ability of the animal to establish a classical Pavlovian response and the main phenomena which characterizes this type of response. In Part I of this paper I propose to discuss that part of the central nervous system .....to the extent as this can be done without introducing the molecular processes on which the recording of a memory is based. But, while I shall not discuss in the first part how a memory is recorded, which is the subject matter of the second of the two postulates upon which our model is based, the molecular mechanism which I am discussing in Part I forms the basis of our first postulate which is basic for the reading out of a memory in our model. As will be explained in Part II the recording of a memory may be regarded as a form of differentiation which is mentally induced. In contra-distinction to this kind of differentiation Part I of the paper will be conerned only with what may be called developmental differentiation. In Part I we shall be concerned only with neurons which owe their full chemical specificity to developmental differentiation. Most of this differentiation takes place during embryon development but part of it may be induced by the experience to which

which the neonatal animal is exposed by sensory experiences and to which the neonatal animal may be exposed in its animal environment. Thus, for instance, a neonatal cat which is prevented from moving about and turning its head will not undergo the developmental differentiation which appears to be essential. We need not concern ourselves here, however, with how much developmental differentiation may go on in the early post natal period. It is sufficient for us to know that developmental differentiation is completed by the end of the early post natal period and we shall assume that no such differentiation takes place during adult life. In part one of the paper we shall only consider neurons which fully achieve their chemical specificity through developmental differentiation and their chemical specificity does not change during adult life. We shall designate these neurons as congenitally determined neurons even though some of them may not have attained their full chemical specificity until the end of the early post natal period and sensory experiences during the early post natal period .....

If in developmental differentiation the differentiation of a neuron of the CNS is induced then the chemical specificity which such a neuron contains through such induced differentiation, is determined by the peripheral organ which the neuron innervates and towards which nerve impulses move down along the axon of the neuron. Thus, in contra-distinction to transprinting in mentally-induced differentiation, induced developmental differentiation - if it exists, would be retrograde. The notion of such a retrograde process in developmental differentiation was first put forward by Paul Weiss and his experiments as well as subsequent experiments by Sperry, gave considerable support to this notion, however, their experiments are relevant to our considerations only in as much as they seem to show that even neurons which fulfill their similar functions in the CNS must markedly differ from each other in their chemical specificity.

ON THE MOLECULAR BASIS OF LONG TERM MEMORY - PART I April 6, 1964

by Leo Szilard

Introduction

The subject matter of this paper is a hypotethical molecular process on which the capability of the central nervous system to record and to recall an experience might conceivably be based. The chances are that we do not know enough about the biological processes which may take place in living cells to be able to guess the molecular processes that the brain employs. We might, with luck, have succeeded here in presenting the model of a neural system but this would hardly permit us to conclude that our model represents the processes that the brain employs. The model can certainly not be expected to turn out to be correct in all of its details, in as much as many of these details had to be guessed and we shall have to consider ourselves lucky if it turns out that we have guessed correctly the general nature of the molecular processes which the brain employs.

All we can say in this regard at the moment is that our model cannot be apriori ruled out on the grounds that the molecular processes which it represents are biologically implausible and further that the model appears to represent an efficient system and we can add that, in our model, a unit of recorded memory consisting of information of a high complexity would tie down only one neuron or a few neurons and that our model represents in this regard an efficient system.....

The Classical Conditioned Response

I shall illustrate how a memory may be recorded through transprinting and how it may be read out by discussing in some detail the application of our model to the classical conditioned response which is exhibited by the autonomous nervous sytem.

According to our notions, the squirting of food into the mouth of the dog causes salivation because, as illustrated in Fig. 2, the neuron Fo has a branch fibre of its axon which is connected through a synapse to an effector neuron that innervates the salivary glands and this effector neuron is characterized by the same set (fo) of neuro-specific proteins as the neuron Fo. We may assume that the overlap number of neuron Fo is substantial so that whenever the neuron Fo fires the effector neuron inhibits the salivary gland.

We shall now consider the transprintable neurons in the Central Nervous System and among these we shall single out for our attention one class, Class E of excitatory neurons. The members of this class have two things in common. Everyone of them is contacted through a synapse by a branch fibre of the axon of the neuron Fo and every neuron E contacts the effector neuron through a synapse of a branch fibre of its axon. Another thing each of the neurons E have in common is that they are contacted through a synapse by branch fibres of the axons of different classes of neurons in the CNS each of which responds to say visual, auditory and tactile stimuli, respectively. In Fig. 2 the neuron represented happens to be one which is contacted only by a nerve fibre of the axon of a neuron Lk in the visual cortex which responds preferentially to say a light signal consisting of a flash of red light appearing in the upper right quadrant of the visual field

Because the overlap number (fo) of the neuron Fo and the Effector neuron is substantial, therefore, whenever the neuron Fo fires, the Effector neuron, which innervates the salivary gland, will fire also.

We shall now turn our attention to the transprintable neurons in the CNS and among these we shall single out a particular class, Class E, of excitatory neurons which have these things in common: Each of the neurons of Class E is contacted through a synapse by a branch fibre of the axon of the neuron Fo. A branch fibre of the axon of each neuron of Class E contacts through a synapse the Effector neuron. Further, all neurons E are contacted through a synapse by branch fibres of axons of different neurons in the CNS which preferentially respond to certain visual, auditory or tactile, stimuli. We shall first direct our attention to a sub-group of the Class E of neurons which are contacted through a synapse by branch fibres of the axons of neurons of the visual cortex, each of which responds preferentially to a different elementary visual signal.

The particular neuron E represented in Figure 2 is contacted through a synapse by a branch fibre of the axon of a neuron Lk in the visual cortex which we assume preferentially respondsto a light signal consisting of a flash of red light located in the upper right quadrant of visual field.

If now the dog is exposed to this light signal immediately followed by the squirting of food into its mouth then, in certain circumstances, which we shall discuss in detail below, the neuron E in Fig. 2 will be transprinted by the neurons Fo and Lk and after this happens this neuron will cease to be transprintable. After this transprinting, the set of neuro-specific proteins which are elevated will be composed of the sets (e), fo), and (lk). If the dog is exposed for a second time to this same light signal immediately followed by the squirting of food into its mouth another similar neuron E may be transprinted in the same way. If the number of such neurons E which are transprinted thus is large enough ..... if a dog which went through several such experiences is then exposed to the light signal but this signal is not followed by the squirting of food into the dog's mouth, the dog will salivate provided that sufficient number of such neurons E got transprinted in the preceeding combined exposures to light and food. This happens because these transprinted neurons E will be excited owing to the fact that.....

This comes about in the following manner. The transprinted neurons E and the neuron Lk in the visual cortex have an overlap number of (lk) and therefore, when the dog is exposed to the correct light signal these transprinted neurons E will be excited and further, because these transprinted neurons E will excite the Effector neuron which inhibits the salivary gland. Thus, in response to the correct light signal such a dog will salivate even though no food was squirted into its mouth. This is a conditioned response. We must now discuss in some detail in what circumstances the simultaneous exposure of the dog to food and light signal will lead to the transprinting of neuron E.

INSERT:

This comes about in the following manner; the transprinted neuron E and the neuron Lk in the visual cortex have an overlap number of (lk) which is substantial and, therefore, when the dog is exposed to the correct light signal this neuron will respond by sending out volleys of nerve impulses..... In as much as the transprinted neuron E and the Effector neuron have an overlap number of Fo which is substantial, a volley of nerve impulses sent out by the transprinted neuron E will substantially raise the level of excitation of the neuron which innervates the salivary gland. If a sufficient number of neurons E have been transprinted during the conditioning then when the dog is for the

for the first time exposed to the light signal in the absence of food being squirted into its mouth the dog will salivate. This is a conditioned response.

Let us now discuss in some detail the circumstances under which the exposure of the dog to the light signal immediately followed by the squirting of food into the dog's mouth will lead to the transprinting of a transprintable neuron E.

As we stated before, a necessary condition for a neuron to be transprinted is that the excitation level of that neuron should be raised to the point where it begins to send out volleys of nerve impulses. The transprintable neuron E represented in Fig. 3 can receive excitatory nerve impulses from one of four different neurons L from the neuron Fo, and from the neural network designated by F*. It can receive inhibitory impulses from neurons designated by I. We shall assume that in the absence of inhibitory impulses the neuron E can be excited to the point of sending out volleys of nerve impulses along its axon only if it receives nerve impulses of sufficiently high frequency both from the neural network F* and from one of several neurons of the visual cortex. We assume that the particular neuron E depicted in Fig. 3 does not receive any inputs from neurons in the cortex which preferentially respond to auditory or tactile stimuli, etc. Only when this neuron E receives nerve impulses in adequate strengths both from the neural network F* and from the visual cortex will its excitation reach the level where it sends out volleys and only then will the membrane covering the cell body of the neuron E or its dendrites become permeable to the key substances which we discussed above. The assumption made here, that the sending out of signals by the neural network F* is a necessary condition for a transprintable neuron E to begin to send out volleys of nerve impulses, is derived from the notion that, in this particular system of transprintable neurons, it is not enough for the dog to be exposed to a visual signal or for food being squirted into its mouth for the recording of an experience, rather an experience must carry attached to it a certain amount of signals. In our case the signal attached is represented by the neuron E receiving signals from the neural network F*.

As we shall presently see, the receipt by the neuron E of signals sent out by the neural network F* represents the significance which is attached to sendory input coming from the neuron Fo or from one of the neurons L in the visual cortex as far as the

phenomenon of classical conditioning involving the autonomous nervous system is concerned. As far as this phenomenon is concerned, there is no attached significance to the squirting of food into the mouth of the dog if it is preceded by the correct light signal to which the dog is fully conditioned.

The neural network F* is composed of neurons characterized by the set of neuro-specific chemicals Fo. Accordingly, this neural network is adapted to receive signals from the neuron Fo and also from those of the neurons E which have been transprinted in such a manner that the set of elevated neuro-specific proteins includes the set of Fo. We shall postulate that the network of neurons F* sends out a signal only if it receives a signal, either from the neuron Fo or if it receives a signal of an aggregate strength from a number of neurons E while signals arriving from the neuron Fo..... but that it will not send out signals after it receives signals of nerve impulses simultaneously from ..... if it is simultaneoulsy reached by volleys of nerve impulses from the neuron Fo and from transprinted neurons E, provided that the impulses coming from the neurons E have comparable aggregate strength. In other words, signals of comparable strength coming simultaneously from these two different sources cancel out. We attribute here to the neural network F* a function which is analogous to the function fulfilled.....

The transprintable neuron E represented in Fig. 3 can receive excitatory nerve impulses from the neuron L, from the neuron Fo, and from the neural network designated by F*. It can receive inhibitory impulses from the neurons designated by I. We assume that of these only the neurons Fo and Lk are capable of transprinting; the neural network F* and the inhibitory neuron I are not assumed to be capable of transprinting. The question is: Under what circumstances will the neuron E, represented in Fig. 3, be actually transprinted by both the neuron Fo and the neuron Lk?

(Here Dr. Szilard started to dictate a letter to several mathematicians, as follows:

A biological problem on which I am working has led me to the following problem:

Let us take n different objects (where n is about 10,000 or 20,000).....

We are interested in sets of n different objects picked out at random of which.....

th

- Dr. Szilard changed his mind about writing the letter and phoned about his problem).

We assume that it is quite generally true that for a transprintable neuron to be transprinted it is not sufficient that such a transprintable neuron receive signals from neurons of the cortex which preferentially respond to certain kinds of sensory.....

According to our notions, a transprintable neuron which is reached by nerve impulses from neurons of the cortex which may each respond preferentially to a certain kind of stimulus will be transprinted only if it receives signals which have significance attached to them or in other words, of a great multitude of sensory experiences only those which have "significance" attached to them will be recorded and will leave behind long term memory that can be recalled at a later time. Just what significance means will depend on what kind of mental function is under consideration.

As far as the classical conditioning of the autonomous nervous system is concerned there is, according to our notions, in the unconditioned dog, no significance attached to the light signal and there is no significance attached in the fully conditioned dog to the light signal which is immediately followed by the squirting of food into its mouth. There is, however, significance attached in the unconditioned dog, or not fully conditioned dog, to the light signal which is immediately followed by the squirting of food into the mouth and there is significance attached in the fully conditioned dog to the light signal which is not immediately followed by the squirting of food into the dog's mouth.

As we shall presently see, volleys of nerve impulses reaching the neuron E from cells of the visual cortex have or have not "significance" attached to them, depending upon whether the neuron E receives simultaneously signals from the neural network F* or, in other words, we shall assume that the transprintable neuron E will be caused to start to fire only if it receives signals simultaneously from one or several of the neurons L and if it receives simultaneously volleys of nerve impulses from the neural network F* and, as we stated below, only when the transprintable neuron E is caused to fire will its cell membrane become permeable for the key compounds and only if this happens can transprinting take place.

According to our postulate formulated above, when the neuron fires the membrane covering its body and its fibres becomes permeable for the key substances. If, at the time when the neuron fires, the neuron Fo and the neuron Lk fire also then, because the membranes covering the boutons of the branch fibres of these neurons which are connected through a synapse with the neuron E, the neuron E will be transprinted by the neurons Fo and Lk.

Fig. 3 represents the transprintable neuron E in the form of a circle drawn with a broken line to which branch fibres of the excitatory neurons Lk and Lo are connected through a synapse. This neuron can also receive excitatory nerve impulses from the fibre coming from the neural network F*, about which more is said below. Branch fibres of inhibitory neurons I are also connected to the neuron E through a synapse. The fibres coming from neurons that are capable of transprinting are marked with a double arrow in contradistinction to fibres coming from neurons which are not capable of transprinting, which are marked with a simple arrow. As indicated in this manner, the neuron Fo and Lk are assumed to be capable of transprinting while the neural network F*, as well as the inhibitory neurons I are assumed to be capable of transprinting.

According to our postulate formulated above, the transprinting of such a neuron will occur only when the neuron fires and the membrane covering its body and its dendrites becomes permeable for the key compounds. We shall define below in what circumstances such a neuron will be caused to fire and all we need to say here is that if, while such a neuron fires, the neurons Fo and Lk fire also, so that the membranes covering the boutons of the branch fibres become permeable for the key compounds, then the neurons Fo and Lk will transprint the neuron F; the neuron E will then have achieved its final chemical specificity and the neuron E which has been thus transprinted is no longer transprintable. We indicate this in Fig. 3b by a circle drawn with an unbroken line concentric with a circle drawn with a broken line. As Fig. 3b indicates, the neuron E which has been transprinted by the neurons Fo and Lk, is characterized by three sets of neuro-specific proteins (e), (lk) and (fo). If, at the time when a neuron E does fire it receives nerve impulses only from neuron Lk but not from neuron Fo then this neuron will be transprinted only by the neuron Lk. A neuron thus transprinted is shown in Fig. 3

As the figure shows, this neuron is characterized by the sets of neuro-specific proteins (e), and (1k), and its set of neuro-specific proteins does not comprise the set (fo).

In Fig. 4 there is represented an element of the neural network to which we attribute the capability of the central nervous system of establishing and extinguishing a classical conditioned response. The basic element of this neural network is composed of a pair of neurons and an excitatory neuron E which is transprintable and an inhibitory neuron E which is not transprintable. Whenever the neuron E fires it raises the level of excitation of the inhibitory neuron I to the point where it may also fire. The neurons E can send signals to the neural network F* and, as we stated above they can be raised to fire if they receive signals ~~from~~ simultaneously from the neural network F* and from the neurons of the visual cortex L.

We assume that there are fibres of the axon of each inhibitory neuron in contact through a synapse with every neuron E of the group. We need to examine now to what extent a neural network of this kind can correctly describe the basic phenomenon of the classical conditioned response of the autonomous nervous system. When the dog is exposed for the first time to a flash of red light coming from the upper right hand quadrant of the visual space and this is immediately followed by the squirting of food into its mouth, both the neural network F* and the neuron Lk will send signals to all the neurons E of the group. Thereafter one of the neurons E and the corresponding inhibitory neuron I will begin to fire and the neuron E will be transprinted by the neurons Lk and Fo. This transprinted neuron E will be characterized by the sets of neuro specific proteins (e), (1k) and (fo). If the dog is led for a second time through the same experience, the neural network F* will receive signals not only from the nueron Fo but also from the neuron E which has been transprinted by the neuron Fo. Assuming that the signals received by the neural network F* from the neuron E are substantially weaker than the signal it receives from the neuron Fo, the neural network F* will again send out signals even though these signals will now be weaker than they were on the occasion of the first exposure of the dog to the conditioning. In these circumstances, the second neuron E will be transprinted by the neurons Lk and Fo/ If This process is repeated, however, several times there will come a point when the

the greater strength of the signal reaching the neural network F* from the neurons E which have been transprinted by the neuron Fo will counterbalance the strength of the signal which reaches this neural network from the neuron Fo. From that point the neural network F* will no longer fire when the dog is exposed to the correct light signal immediately followed by the squirting of food into its mouth. Thus keeping on with the conditioned response because going rapeatedly through a routine does not lead to the transprinting of any further neurons E, and could not, therefore, contribute in any way to the strengthening of the conditioned response.

Extinction

Let us now examine what happens if a dog which is thus fully conditioned is now given the correct light signal without reinforcement, i.e. without following it with the squirting of food into its mouth. When the full conditioned dog is first given the correct light signal, unreinforced, the neurons E are transprinted during the preceeding conditioning and contain the set of neuro-specific proteins (lk) at a high level.... will fire in response to the light signal. Because these transprinted neurons E also contain the set of neuro-specific proteins (fo) at a high level, these neurons E will succesfully send signals to the neural network F* and since these signals are not counterbalanced by any signal coming from the neuron Fo, the neuron F* will fire and will cause one of the transprintable neurons E to fire also, and to be transprinted on this occasion by the neuron Lk. Since the neuron Fo did not fire on this occasion this transprinted neuron E will now be characterized by the set of neuro-specific proteins (eo) and (lk) but not by (fo). When the same dog is now for the second time given the light signal unreinforced the same thing will happen except that this time, due to the firing of the inhibitory neuron which is coupled to the last transprinted neuron, the neurons E which have been transprinted during the conditioning routine will send somewhat weaker volleys of impulses to the neural network F* and to the Effector neuron which inhibits the salivary gland. Still, presumably the second neuron E will be transprinted by the neuron Lk. If you continue the routine of giving the correct light signal unreinforced the point will be reached when, due to the increasing number of inhibitory neurons which fire in response to the light signal, the nerve impulses reaching the Effector neuron which innervates the salivary gland will no longer be sufficient to cause salivation..... where there might still be sufficient to cause the neural network F*

to fire. In these circumstances, continuing to expose the dog to the correct light signal unreinforced will lead to extinction, so to speak, below zero, until finally the nerve impulses reaching the neural network F* from the neurons E which have been transprinted with the character of 0 will no longer be strong enough to cause the neural network F* to send out signals.

Let us now condition the dog which is in such a super extinguished state regarding a specific light signal and condition this dog to respond with salivation to say a particular tactile stimulus immediately followed by squirting of food into the mouth of the dog. We may assume that neurons T in the cortex which preferentially respond to a particular tactile stimulus have branch fibres of their axons in contact through a synapse with many of the transprintable neurons E and accordingly the conditioning process is much the same when similar tactile stimulus is employed as the conditioning processes described above in connection with a visual stimulus. If the super extinguished dog is now fully conditioned to respond to a tactile stimulus and is then for the first time exposed to the tactile stimulus unreinforced, it will respond with the production of a certain amount of saliva but if, instead of giving tactile stimulus the tactile stimulus is given simultaneously with the light signal to which the conditioned response had been super-extinguished, then we should expect a substantial reduction in the magnitude of the salivary response because a substantial number of neurons I will be excited by the transprinted neurons E which, during the extinguishing routine have been transprinted with the set of neuro-specific proteins (1k) but not with the set (fo)

Let us now consider that we condition a previously unconditioned dog simultaneously to a visual signal and say an auditory signal. If the signals are chosen accurately and of the proper strength we shall succeed in conditioning the salivary response in such a way that after the simultaneous presentation of the two signals, reinforced by the squirting of food into the mouth of the dog, say 10 or 20 times, the dog will respond with an appreciable salivation to the unreinforced presentation of the auditory signal alone. It is an essential characteristic of our model that if the conditioned response to the light signal is fully established first, and then the auditory and the light signal are presented simultaneously, always reinforced by squirting food into the mouth of the dog, say 10 or 20 times, and

if now the auditory signal is given alone, unreinforced, there ought to be no appreciable salivary response, at least not if when the visual and auditory signals are given together the intensity of the light signal is..... This is so because when the dog, which has been fully conditioned to the light signal, is again presented with the light signal reinforced that even though the visual signal is accompanied by the auditory signal, the neural network F* is not going to send out signals and therefore no transprinting of neurons E takes place.

Our model predicts that if the conditioned response to the light signal was first fully established, and then the auditory and the visual signals were presented 10 or 20 times simultaneously, always reinforced, we would not obtain an appreciable conditioning of the dog to the auditory signal, or in other words, if the auditory signal is given alone unreinforced, our model leads us to expect that there will be no appreciable salivary response.

Our model leads to this expectation because when a dog which has been fully conditioned to the light signal continues to be presented with the light signal reinforced, either alone or accompanied by the auditory signal, the neural network F* would not respond by sending out signals and, therefore, there could be no transprinting of neuron E by the auditory signal.

Discrimination

If the dog has been conditioned to give a salivary response to the flashing of red light in the upper right hand quadrant of the visual space and after having been fully conditioned, is exposed either to the flashing of light in the upper right hand quadrant of the visual space which is not red but has a different colour, or to the flashing of red light which is not located in the upper quadrant of the visual space but is located somewhere else, the dog will show a conditioned salivary response at a diminished strength but still at a substantial strength. This is what we will expect if we assume that a set of neuro-specific proteins of the neuron of the visual cortex, which preferentially responds to the correct signal, has an overlap with the set of neuro-specific proteins which characterizes the neuron, which preferentially responds to a red signal irrespective of location of that signal in the visual space, and the neuron located in the visual cortex which may

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Text runs from P. 78 to P. 80

preferentially respond to a light signal coming from the upper right hand quadrant of the visual space irrespective of colour. As is easy to see, our model would lead us to expect that when the wrong signal is presented unreinforced again and again, a certain number of neurons E will be transprinted with the wrong set of neuro-specific proteins since these neurons E are not transprinted with the set of o repeated in reinforced exposure of the dog to the wrong signal, will lead to weakening of the conditioned response to the correct signal. Our model demands this because when the right signal is again unreinforced the neurons E, which have been transprinted with the wrong signal but not with the set of o, will be excited and will excite the inhibitory neurons coupled with them. Accordingly, the nerve impulses sent out by neurons which were transprinted with the correct visual signal and the set of o will fire only weakly. In other words, the conditioned response to the correct signal has been partially extinguished by the unreinforced presentation of the wrong signal. If we now again present the dog with the correct light signal reinforced, the neural network F* will fire and if the process is repeated for a number of times a certain number of additional neurons E will be transprinted with the correct visual signal and the set of o. By the time the conditioned response to the correct visual signal is again fully established, there are more neurons E transprinted with the correct visual signal and the set of o than there had been at the end of the first series of forced exposures to the correct signal which was carried to full conditioning to the correct visual signal.

If one wants to explain some function of the nervous system on the basis of the molecular processes here postulated, then it is necessary to invent the neural network

which is based on the molecular processes here postulated/is capable of fulfilling that function. The only case which is simple enough and which has been investigated enough to venture to invent such a network seems to be the case of the classical conditioned response of the autonomous nervous system. We shall in the following attempt to invent a neural network that will exhibit the phenomenon that characterizes the classical conditioning but even in this simple case we cannot be sure of guessing correctly. While the neural network described below seems to exhibit a number of the characteristics of the conditioned response, it does not explain all the characteristics that have been claimed..... There are exceptional cases where it does not explain phenomena that have been reported. If, upon repeating the experiments, these examples stand up, the neural network here proposed will have to be either modified or amplified.

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A transprintable neuron is not going to be transprinted just because it is reached by nerve impulses from neurons in the cortex which respond to a certain sensory signal; rather of the great multitude of sensory experiences only those with attached significance are going to be recorded in the form of a long term memory that can be recalled. This means that for such a transprintable neuron to be transprinted it is also necessary that the neuron receive signals from some neural network F* . Just what is the significance will depend on what kind of mental function is under discussion. In the case of the conditioned response we may imagine that some neural network F*, which fires only if the experience of the dog is significant.....We can imagine, for instance, there is a particular neural network F* which sends out signals only when in the cause of an experiment related to the conditioned response, the dog is subject to an experience which is significant from the point of view of the conditioned response and we would then have to assume that a transprintable neuron which may play a role in the establishment of a conditioned response can be transprinted only during periods of time when it receives signals from the neural network F*.

We assume that the transprintable neuron E can be caused to fire only if it receives signals not only from one or several of the neurons L but also from the neural network F*. If, at the time when the transprintable neuron is caused to fire, the neurons Fo and Lk fire also, and the membranes covering the boutons of their branch fibres become permeable for the

key compounds then the neurons Fo and Lk transprint the neuron E. Thereafter, the transprintable neuron will no longer be transprintable; it will have achieved its final chemical specificity.

The Efficacy of a Synapse

We shall assume that the neurons in the CNS which fulfill different functions differ from each other in their chemical specificity and we shall divide these neurons into two broad classes, the neurons which achieve their full chemical specificity through differentiation that takes place during embryonal development or during the early post natal period, and we shall refer to these neurons, somewhat misleadingly, as congenitally-determined neurons, and neurons which have not attained their full chemical specificity as developmentally-determined. To the other broad class of the neurons which have not achieved their full chemical specificity during development, and the chemical specificity of which can be modified during the life of the adult..... rather they can undergo mentally-induced differentiation during the lifetime of the adult and attain their full chemical specificity on such an occasion through a process which we shall designate as transprinting. To these neurons we shall refer as transprintable neurons before they achieve their full chemical specificity and as transprinted neurons after they have attained their full chemical specificity.

At this point it is necessary for us to say what exactly we mean when we speak here of chemical specificity. In contrast to the fruit fly which has..... the amount of DNA per cell in the fruit fly is just about enough to account for 10,000 genes. The amount of DNA per somatic cell of the mammal is about a hundred times larger. We assume that each of these genes is capable of producing a specific protein and we assume as a result of differentiation during development, in the developmentally-fully-determined neurons, there will be certain genes to which we shall refer as neuro-specific genes which, as a result of differentiation that takes place during development, are produced at a high rate and are maintained at a high level of concentration.

In mammals the amount of DNA per somatic cell is about 100 times larger. We assume that each gene is capable of producing a specific protein molecule and that as a result of the differentiation which a somatic cell undergoes during development by the end of the post natal period.....

Our unit of recorded memory may contain information of a fairly high complexity and one unit of memory would have to tie down one neuron only. Moreover, it seems likely that one can devise neural networks requiring a reasonably small number of neurons that can mimic all of the simplest functions of the CNS..... Moreover it seems that it will not be difficult to devise a neural network requiring a reasonably small number of neurons that will mimic the complexities of the simplest functions of the CNS. Our model thus appears to describe a rather efficient system for the recording and recalling of an experience.....

INSERT:..... will contain a different set of neuro-specific genes which produce their specific protein molecules at a high rate so that in the different neurons a different set of neuro-specific proteins will be produced at a high rate and will be maintained at a high level of concentration.

We assume that the number of neuro-specific genes is somwhere between 10,000 and one million. If we were to assume, if we could without losing too much flexibility at this point, that the sets of neuro-specific proteins which are elevated is the same in all the congenitally-determined neurons and if we designate this number with n then there could exist congenitally-determined neurons which differ from each other in their chemcial specificity. If we assume n = 30 or n = 50 this binomial coefficient would fall inside the total number of neurons in the human brain which is generally estimated to be about -----. This apparant abundance disappears, however, when we consider that many of these different sets of n neuro-specific proteins would be related in the sense that several neuro-specific proteins contained in one set would be contained in other sets also. If we define two sets as related to the nth degree if the number of neuro-specific proteins which are contained in both is n or larger than n, then we may ask how many different congenitally-determined neurons could exist if we demand that no two of them shall be related to the nth degree. At the time of this writing I do not know the solution of the mathematical problem which this question represents but it is obvious that for reasonable numbers of N and m the number of sets which are not related to the nth degree is very much smaller than the binomial and if we were to demand that these sets are not related even to the nth degree, i.e. that no two sets have one neuro-specific protein in common, then for $N = 10^6$ and m = 50 we have only 20,000 different congenitally-determined neurons. This would appear to be insufficient for explaining the function of the CNS system on the basis of neural

networks. This number would presumably be too small to be able to account for the functions of the CNS on the basis of the notions here adopted. Even if we assumed N = 1, i.e. if each neuron contained only one neuro-specific protein, we could have only one million congenitally-determined neurons of different chemical specificities..... This might be perhaps a sufficiently high number but it would be impossible to have an efficient system for recording and recalling on the basis of notions here adopted by assuming N to be smaller than 10 and for N = 10 we could have only 100,000 congenitally-determined neurons of different chemical specificities. It would seem more reasonable for this and other reasons to ask how many congenitally-determined neurons of different chemical specificities we can have if either sets of neuro-specific proteins of N = 30 which are not related to the 4th degree..... For this and other reasons it seems more reasonable to assume for n the value of 30 or 50 and, instead of asking that the sets of neuro-specific proteins of two different neurons shall not be related even to the first order, to permit two congenitally-determined neurons which are supposed to function as if they were unrelated, to have in common up to 10% of their elevated neuro-specific proteins. This means that if n = 30 ..... On this basis we may ask how many different congenitally-determined neurons we can have for n = 30 which are unrelated to the 4th degree or we may ask how many different congenitally-determined neurons we can have for n = 50 which are not related to each other to the 6th degree.

In spite of the simplicity of its formulation the mathematical question which this problem seems to be a rather..... the mathematical question seems to be a rather difficult one ..... Neither I nor the experts I have consulted have so far come up with the solution. I am inclined to think, however, that the latitude which we have in choosing N, n and m, is sufficient to allow for a sufficiently large number of congenitally-determined neurons of different chemical specificity .....

HERE DR. SZILARD DICTATED LETTERS TO Professor Mark Kac, Professor Leo Goodman to this effect:

"This morning Bruno Bronowski of this Institute came up with a solution to the problem which I am enclosing. Any comments?"

In the fruit fly the amount of DNA per somatic cell is just about enough to account for 10,000 genes. In mammals the amount of DNA per somatic cell is about 100 times larger. Each gene is capable of producing a specific protein molecule as a result of differentiation which takes place during development results in a variety of somatic cells and different somatic cells contain a different set of genes..... Each gene is capable of producing a specific protein molecule and we assume that, as the result of the differentiation which the neurons of the CNS undergo during development, those congenitally-determined neurons which differ from each other in as much as they respond preferentially to different sensory signals will contain a different set of genes which produce their specific protein molecules at a high rate.

We assume that somatic cells differ from each other because a different set of the genes they contain produce in them their specific protein molecules at a high rate. We assume in particular that as a result of the differentiation which the neurons of the CNS undergo during development, those congenitally-determined neurons which differ from each other in as much as they respond preferentially to different sensory signals, contain a different set of genes which produce their specific protein molecules at a high rate, i.e. in those neurons a different set of neuro-specific proteins will be maintained at a high level of concentration.

If we were to assume, as we could for the moment without losing too much flexibility at this point, that the number of neuro-specific proteins which are elevated is the same in all congenitally-determined neurons and, if we designate this number with n, then the number of possible congenitally-determined neurons which will differ from each other in their chemical specificity, would be given by the binomial coefficient (symbol) where N designates the number of neuro-specific genes each of which is capable of producing a neuro-specific protein.....

For a number n = 10,000.....

For n = 30 and $N = 10^4$ the binomial would amount to (symbol). This number would far exceed the total number of neurons in the human brain which is generally estimated to be about 10^{10}. This overlap number disappears, however, when we consider than many of these would have a number of elevated neuro-specific proteins in common. We shall define as the overlap numbers y of two neurons the number of neuro-specific proteins which the sets of elevated neuro-specific proteins have in common. As we shall see later, there may be a certain amount of cross-talk

between neurons if their overlap number is high and one may thus ask how many.....

We shall designate two sets as having an overlap of the nth degree if their overlap number is m.

One is, therefore, led to ask how many neurons exist whose chemical specificity is different in the sense that their overlap number m is small, perhaps 3 or 4. The mathematical problem which is involved may be formulated as follows:

Let there be N different objects. How many different sets composed of n objects.... how many are there if no two sets must have an overlap number of m or larger than m. The solution of this problem will be reported elsewhere by Dr. Jacob Bronowski of this Institute.

If we assume (FORMULA) for values of (FORMULA) the number of possible sets is (FORMULA).

As we shall see below, according to the notions here adopted, signals coming from two neurons which have an appreciable number of elevated neuro-specific proteins in common can in certain circumstances be confused. We shall define as the overlap number m the number of neuro-specific proteins which their sets of elevated neuro-specific proteins have in common. As we shall see below, signals coming from two congenitally-determined neurons each have a substantial overlap number in excess of m = (symbol) can in certain circumstances be confused. Let us now designate two congenitally-determined neurons which respond to two different sensory signals between which the individual can <u>easily discriminate</u> as substantially different and assume that this means that they have an overlap number which is a fairly small number.....

As we shall see below, the signals coming from two congenitally-determined neurons can be fairly easily confused if the number of the neuro-specific proteins which their sets of elevated neuro-specific proteins have in common is substantial. Let us then define the number of neuro-specific proteins which the sets of elevated neuro-specific proteins of two neurons have in common as the overlap number m of the two neurons. We shall assume that the overlap number of two congenitally-determined neurons which respond to two different sensory signals between which the individual can easily discriminate does not exceed a certain percentage, perhaps 10% of m so that thus, for instance, in the case of n = 30, we would have (formula). If we designate two congenitally-determined neurons for which the overlap

number does not exceed some such limit as being substantially different then we can ask how many substanitally different neurons are possible for say (formula). The mathematical problem which is involved may be formulated as follows:

Let there be n different objects, how many different sets composed of n objects are there if no two sets must have an overlap number of m or larger than m. This problem, which does not seem capable of a solution has,been solved by Dr. Bronowski of this Institute, and will be reported elsewhere.

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We shall make an attempt to test the notions here adopted by inventing a neural network which is capable of performing one of the simpler functions of the CNS. The CNS is capable of performing a great variety of different functions; some rather simple. One may attempt to test the notions here adopted by constructing models of neural networks which are capable of performing some of the simple functions of the CNS and then ask whether these models mimic.....

The relevance of the notions here adopted may then be judged by seeing whether or not such models mimic,not only the performance of the CNS for which they would be the model, but also the shortcomings which the CNS exhibits in connection with these performances. The question to what extent a simple neural network can mimic the phenomena observed in classical Pavlovian conditioning of the autonomous nervous system will be discussed elsewhere. If we want to discuss models for neural networks which mimic the higher mental functions, for instance, the mental functions which a mammal can perform with ease but a bird cannot, or mental functions that a man can perform but a monkey cannot,..... It would be of great help to carry out a similar discussion for higher mental functions but when it comes to mental functions which a mammal can perform with ease but a bird cannot or the mental functions which man can perform with ease but a monkey cannot, then it would be first necessary to invent the kind of neural networks which the CNS of a bird does not possess but that of the mammal does,and the kind of neural network which the CNS of the monkey does not posess but man does. It might turn out that such neural networks are very difficult to invent or alternatively, it might turn out that such neural networks are too easy to

invent and that a variety of different networks could be devised which could all be capable of fulfilling the mental function under discussion.

The overlap number of two neurons, which are connected through a synapse, is a measure of the efficacy of the synapse.

As we shall also see below, we assume that when a memory neuron is transprinted by other neurons it adopts the sets of these neuro-specific proteins which are elevated.... of these other neurons and thereafter the synapses of these other neurons with the memory neuron ..... and accordingly, after such a transprinting the overlap number of a neuron which has transprinted the memory neuron is at least as great as the number of elevated neuro-specific proteins of the transprinting. This means that through the processes of transprinting the efficacy of the synapse between the transprinting neuron and the transprinted memory neuron is likely to become substantial.

Since there exist both excitatory and inhibitory neurons we shall have to distinguish between two kinds of "transmitine" - "Transmitine I", which is excitatory , and "Transmitine II" which is inhibitory. Similarly, we shall have to distinguish between two enzymes, - "Transmitinase I" and "Transmitinase II".

The dendritic tree of any one neuron has a large number of branches and the axon of any one neuron may have a very large number of branch fibres with each fibre ending in a bouton connected through a synapse with a dendrite of some neuron. A neuron which receives an input through its dendrites from a large number of excitatory as well as inhibitory neurons, depends on the concentration of Transmitine I and Transmitine II which are produced and destroyed at the individual synapses. We assume that the rate of destruction of Transmitine II is proportional to their concentration and that the factor of proportionality is such that if the rate of production of this substance changes at one point in time over some lower value to another higher value, the new stationery value of this concentration may be approached halfway within a period of time of about 10 milliseconds. We further assume that the amount of Transmitine I and Transmitine II produced during this period of time (symbol) at an excitatory or an inhibitory synapse, is proportional to (symbol) where

where (symbol) is the frequency of the nerve impulses reaching the synapse from the excitatory neuron and (symbol) is a frequency of the nerve impulses reaching a synapse from an inhibitory neuron. We do not loose much flexibility if we further assume that the boutons of all excitatory neurons produce Transmitine I at the same rate if the frequency of the nerve impulses (symbol) is the same and that all inhibitory neurons produce Transmitine II at the same rate. We assume that Transmitine is destroyed in the bouton at a rate which is proportional to its concentration and also proportional to the concentration of the enzyme transmitinase. This means that if we increase at one point in time the frequency of the nerve impulses reaching a bouton from some lower value to any higher value the concentration of transmitine will rise from a lower value to a higher value and the increase in the concentration of transmitine will be proportional to the increase of the frequency of the nerve impulses. The time which it takes for the concentration of transmitine to approach halfway the new level of concentration will be, however, independent of the change of the frequency of nerve impulses and will depend only on the concentration of transmitinase. If, on the other hand,.....for a given change in the frequency, on the other hand, the rising concentration of transmitine for a given amount of increase in the frequency of the nerve impulses will be inversely proportional with the concentration of transmitinase, i.e. if the concentration of transmitinase is low in the bouton the efficacy of the synapse will be high so that we may regard the concentration of transmitinase ..... i.e. the efficacy of the synapse is a measure of the efficacy.....

We shall assume that the transmitinase is produced in all boutons at the same rate but that it is inactivated at different rates. In these circumstances the concentration of transmitinase in the boutons will be inversely proportionate to the rate at which it is inactivated and accordingly the efficacy of the synapse will be proportional to the rate at which transmitinase is inactivated. The hypothetical biochemical process described below demands that the rate of inactivation of transmitinase be proportional to the overlap number of the two neurons which form the synapse and we shall be thus lead to the postulate formulated above which says that the efficacy of the synapse is measured by the increase in the concentration of transmitine which is brought about by the increase in the frequency of the nerve impulses reaching the bouton being proportional to the overlap number of the two neurons which form the synapse.

The rise in concentration of transmitine in the bouton that results from a change in the frequency of the nerve impulses reaching the bouton will be inversely proportional to the concentration of transmitinase prevailing in the bouton and, accordingly, we may regard the concentration of transmitinase mentioned in the bouton as a measure of the efficacy of the synapse in the sense that when the concentration of transmitinase is low, the efficacy of the synapse is high. We assume that transmitinase is produced at the same rate in all boutons and all neurons but is inactivated in different boutons of the same neuron at rates which are proportional to the overlap number of two neurons bridging the synapse. Since the concentration of transmitinase prevailing in the bouton is .....
The hypothetical biochemical process described below leads us to assume that the rate of inactivation of transmitinase is proportional to the overlap number.....

We assume that transmitinase is produced at the same rate in all boutons of all neurons but that it is inactivated in different boutons of the same neuron at different rates. The hypothetical biochemical process described below leads us to assume that the rate of inactivation of transmitinase in a given bouton is proportional to the overlap number of the two neurons which forms a synapse. Accordingly, the concentration of transmitinase maintained in the bouton will be inversely proportional to the overlap number of the two neurons bridged by the synapse from which follows that the efficacy of the synapse is proportional to the overlap number of two neurons bridged by the synapse.

Let us now assume, for the sake of argument, that Transmitine I raises the level of excitation of the neuron because molecules of Transmitine I combine with certain specific sites located on the cell membrane within the cell body of the neuron and that Transmitine II antagonizes the action of Transmitine I.....
....that molecules of Transmitine I can combine with the same sites, i.e. we assume that Transmitine I antagonizes the action of Transmitine I by being a competitive inhibitor of Transmitine I and let us further assume that molecules of Transmitine II compete with molecules of Transmitine I for these sites of the cell membrane, i.e. we assume that Transmitine II antagonizes the action of Transmitine I because it acts as a competive inhibitor. On the basis of these assumptions we may regard the expression: (FORMULA) as a measure of combined excitatory action of the combined excitatory and inhibitory impulses which reach the neuron where the coefficients (symbols) represent the efficacy

of the inhibitory synapses. On this basis we may then assume that a firing rate (symbol) of the neuron is given by (formula) where F might be the same function for all neurons with which we are here concerned. We may assume f to increase monotonously with increasing argument and to have a value of zero if the argument is zero.

The hypothetical biochemical mechanism which would account for our postulate that the overlap number of two neurons which are bridged by the synapse determines the efficacy of the synapse, assumes that the neuro-specific proteins resemble antibodies in as much as they are allosteric proteins which have two combining sites. A molecule of each neuro-specific protein has a combining site where it can combine with any molecule of the same neuro-specific protein and if so dimerized it undergoes an allosteric transition so that it now can combine at any site with a molecule of transmitinase, causing the inactivation molecule of transmitinase which it inactivates.

The biochemical model from which the notions here adopted are based on assumptions that the neuro-specific proteins are located in the membrane of the neuron which covers the cell body of the dendrites of the neuron, as well as the axon of the neuron including all branch fibres of the axon and boutons at the end of these branch fibres. We assume that a molecule of a given neuro-specific protein located in the membrane covering the bouton of a branch fibre of the axon can dimerize across the synapse with a molecule of the same neuro-specific protein located in the cell membrane covering the body or the dendrite of the neuron. We assume that a molecule of a neuro-specific protein undergoes an allosteric transition when it is so dimerized and that in the dimerized form it can combine and inactivate molecules of the enzyme transmitinase. Accordingly, the neuro-specific proteins would be similar to antibodies in as much as an antibody molecule when it is combined with the corresponding antigen molecule undergoes an allosteric transition and is then capable of binding complement. We assume that the molecules of neuro-specific proteins are located in the membrane.

INSERT:

We shall assume that two neurons which preferentially respond to two very different sensory signals between which the CNS can discriminate with ease, have a small overlap number m whereas two neurons which respond to sensory signals between which the CNS can

discriminate with ease, have a small overlap number m, whereas two neurons which respond to sensory signals between which the CNS can discriminate only with a great amount of difficulty, have a large overlap number m. According to the notions here adopted, if the firing of one neuron contributes to the excitation of another, to which it is connected through a synapse, its contribution will be large for a given firing frequency if the overlap number m is large, and the contribution will be small if the overlap number is small. We shall discuss below a hypothetical biochemical model which would account for this basic postulate and our theory. As we shall see, we further assume, that if a memory neuron is transprinted by another neuron it incorporates the set of elevated neuro-specific proteins of the other neuron. This is the second basic postulate. It follows from this postulate that if a neuron transprints a memory neuron thereafter the overlap number of the neuron with the transprinted memory neuron is given by the number of neuro-specific proteins contained in the set of elevated neuro-specific proteins of the transprinting neuron. Accordingly, the efficacy of a synapse between a neuron and a transprintable memory neuron can be substantially raised through the processes of transprinting.

Insert: We shall assume that the concentration of all neuro-specific proteins is the same in all synaptic membranes and that the area of all synapses is the same and may then ask what is the number of dimerized neuro-specific proteins contained in the synapse..... We may then ask what is the number of neuro-specific protein molecules located in the pre-synaptic membrane contained within the synapse which have their counterpart present in the post-synaptic membrane within the synapse. This number is either given by the overlap number m of the two neurons which are bridged by the synapse or it is given by the synapse or by the ratio (symbol) where n designates the number of elevated neuro-specific proteins either in the pre-synaptic or in the post-synaptic neuron whichever number is larger, depending on whether we assume that: (a) the concentration of any elevated neuro-specific protein is the same in the membrane of all neurons, or (b) the total concentration of all elevated neuro-specific proteins is the same in all neurons. Depending on whether we adopt the assumption (a) or (b) we shall find a somewhat different calculation especially between the coefficients (formula) and the overlap number. Depending on what we assume in this regard, the overlap number m will determine in a

a different manner the efficacy of the synapse. Nevertheless, it will be generally true that the efficacy of the synapse may be assumed to be small if m is small and that it may be assumed to be large if m is large.

Let us now consider a group of transprintable memory neurons E which have been selected as follows: Each neuron E receives through a synapse an input from an excitatory neuron F in the CNS which preferenitally responds to a signal of food in the mouth and each neuron E can send a signal (presumably through an inner neuron) to an Effector neuron which innervates the salivary gland. Assuming that the neuron F contacts the neurons E through two comparably small number of synapses each..... We shall further assume that the great majority of the neurons E receive an input through a comparatively large number of synapses from neurons A in the auditoy cortex which preferentially respond to the particular auditory signal using these experiments. While they receive an input throughonly a small number of synapses from neurons in the visual cortex which preferentially respond to our visual signal. In contrast to this we assume that there is a small minority of the neurons E for which the situation in regard to input from the auditory and the visual cortex is just the reverse. We may designate the sets of neuro-specific proteins elevated in the neurons F, L and V with (symbols) respectively, and the transprintable neurons A and the congenitally-determined neurons with (symbols) respectively. We assume there is no substantial overlap between any of these sets. In these circumstances we assume that even a strong signal from the neuron A will be insufficient to cause the transprintable neuron to fire and that signals coming from the neurons A and that for the transprintable neuron E to fire it has to receive, in addition to signals from neurons A, a signal from one or another of a very specific kind of neuron, which belong to the responses to food system, are connected to the neurons E through a comparatively large number of synapses and which fire only if the stimuli to which the dog is exposed are significant from the point of view of food response system. In a paper to be published elsewhere, we shall discuss a simple neural network which mimics all the essential phenomena observed in the classical conditioned response of the autonomous nervous system and on that occasion it will be possible to state just what are the terms of the excitinase generated in such a neural network.

We may designate the sets of neuro-specific proteins elevated with (symbol) respectively, in the transprintable neuron E and the transprinting neurons F, L and V with (symbol) respectively and we assume that there is no substantial overlap between any of these sets. Accordingly, the efficacy of the synapses which bridge and the synapses which form a bridge between the transprintable neuron E with the neurons F, L and V will have a low efficacy and accordingly, we assume that even the auditory signal which is assumed to be strong..... We assume that signals coming from any of these three neurons will be unable to cause the transprintable neuron to fire. Rather, for the transprintable neuron to be caused to fire it will be necessary for it to receive strong signals from the auditory neuron A..... It is necessary for a dog to be exposed to a strong auditory signal/in addition for this neuron to receive signals from certain neurons which belong to the food-salivation system, and which fire only if the stimuli to which the dog is exposed are significant from the point of view of this particular system. In a paper to be published elsewhere, we shall present a simple neural network which appears to mimic all the essential phenomena observed in the classical conditioned response of the autonomous nervous system of the dog and on that occasion it will then be possible for us to state just what the term "significant" means in terms of excitation generated in a particular part of this network.

In anticipation of this discussion we can only say on this occasion that in a dog in which the conditioned response to the stimulus has not yet been fully established, the firing of the neuron A leads to the firing of the "significance" part of the neural network but that in a dog which is already fully conditioned the firing of the neuron A does not lead to the firing of this particular part of the network. Similarly, in a dog which has been fully conditioned the presentation of the signal, not followed by the squirting of food into the mouth of the dog, leads to signals emanating from the "significance" network..... When an as yet unconditioned dog is exposed to the compound signal described above and this is immediately followed by the squirting of food into the mouth of the dog, the neurons E receive simultaneously volleys of nerve impulses from the neuron Fe and the neuron A.....

The neurons E may be assumed to receive volleys of impulses of neurons Fe and A in sufficient strength to cause one of the neurons E to start to fire. Because this happens at a time when the neurons F and V are also firing, this neuron E will then be transprinted on such an occasion and the neuron E which has been thus transprinted..... this neuron will then incorporate the set of elevated neuro-specific proteins. If the dog is repeatedly exposed to the same experience there will be a number of neurons E which will be thus transprinted. If we now expose the dog to the compound stimulus, these transprinted neurons E will be excited because the set of elevated neuro-specific proteins has a substanital overlap with the neurons A and V and because a substantial number of boutons belonging to the neurons A may be assumed to be reached by volleys from other nerve impulses. If a number of neurons thus transprinted are excited they may be assumed to excite the Effector neuron which is characterized by the set of elevated neuro-specific proteins f and the dog will salivate.

Let us now consider a group of transprintable excitatory neurons E which have the following in common. Each of these neurons E can receive input from an excitatory neuron F in the CNS which preferentially responds to the signal "food in the mouth" and each neuron E can send volleys of nerve impulses..... each of these neurons E can receive volleys of nerve impulses through an excitatory neuron F in the CNS which preferentially responds to the signal "food in the mouth" and each of these neurons E can in turn send volleys of nerve impulses (through an inner neuron) to an effector neuron which innervates the salivary gland. The neuron F in the nervous system can also send volleys of nerve impulses to this effector neuron. We assume that the effector neuron F* and the neuron F in the CNS are characterized by the same set (f) of elevated neuro-specific proteins. The set of elevated neuro-specific proteins in the transprintable neuron E is distinguished by (e) and we assume that the sets (e) and (f) have no substanital overlap. On this basis we may then say that if we excite a transprintable neuron E ~~to~~ the excitation cannot be efficaciously transmitted to the effector neuron and accordingly, the excitation of such a transprintable neuron E will not cause salivation. On the same basis we may say that excitation of the neuron F in the CNS can be effectively transmitted to the effector neuron F* and will, therefore, cause salivation. If, however, a transprintable neuron E is transprinted in such a manner that the transprinted neuron has a set of elevated neuro-

-specific proteins which comprise a set (f) then the excitaion of such a transprinted neuron E will cause salivation.

For the sake of simplicity of discussion we shall now assume that the great majority of the neurons E can receive an input from a number of neurons A in the auditory cortex which preferentially respond to our auditory signal, and can also receive an input through a small number of synapses from neurons V in the visual cortex which preferentially respond to our visual signal.

If the dog is repeatedly exposed to the same experience there will result a number of neurons which will be thus transprinted. If we now expose a dog which has been thus conditioned once to the strong auditory stimulus the transprinted neurons E will be excited because their set of elevated neuro-specific proteins has a substanital overlap with the set of neuron A and because a substantial number of boutons belonging to the neuron A are reached by volleys of nerve impulses from the neuron E which responds to the strong signal. Accordingly, the dog may be expected to salivate even though on this occasion no food is squirted into his mouth. If, however, instead of exposing this dog to the strong auditory stimulus, we expose it to the weak visual stimulus the dog may not be expected to salivate if the visual stimulus is not strong and if no food is squirted into his mouth.

Further, if we repeatedly expose such a dog to the weak visual stimulus unreinforced by the squirting of food into his mouth, we shall, for a while, on each such occasion transprint one or several neurons E when this time the transprinted neurons E will be characterized by the set of neuro-specific proteins (e) and (v) and the set of elevated neuro-specific proteins will not include the sets (a) and (f). The neurons E which have been thus transprinted can be excited by exposing the dog to the weak visual signal but the excitation of the effector neuron and, as may be seen by examining the neural network to be presented on another occasion, it will lead to an inhibition of the salivary response. Such inhibition can, however, be obtained by exposing this same dog to the auditory signal. The reason for this paradox result is the fact that the auditory signal will excite the neurons E which have been transprinted during the conditioning period and these transprinted neurons E can in turn, because of their overlap with the neurons E, which have been transprinted during extinguishing series of exposures, which as we said before have an inhibitory effect.

We shall assume that there also is a minority of neurons E for which the situation with regard to input from auditory and the visual cortex is just the reverse.

Insert: We can always adjust the strength of the visual component of the compound stimulus which we used during the conditioning procedure to be just below the level above which the dog conditioned to the compound stimulus would respond with salivation to the presentation of the visual stimulus alone and let us assume that this is what we have done and then let us assume that the strength of the visual component of the compound stimulus which we used during the conditioning of the dog to the compound stimulus was so adjusted.

Insert on P. 26: We shall designate the exposures as extinguishing exposures. It follows from the behaviour of the neural network to be presented that while carrying out such a series of extinguishing exposures neurons A will be reached by volleys from neurons Fe and simultaneously also from the neurons F and, therefore, on the occasion of each exposure one of several neurons E will be transprinted.

Let us now repeatedly expose this dog to the weak visual stimulus, unreinforced by the squirting of food into its mouth. We shall subsequently refer to these particular exercises as "extinguishing exposures". During these extinguishing exposures the neurons E will be reached by volleys from the neurons Fe and those of the neurons E which belong to the minority group defined above will be reached at the same time also by volleys of nerve impulses from the neurons V in the cortex which preferentially respond to our visual signals. Accordingly, one may assume, one or several neurons E belonging to the minority group will be transprinted on such occasions. The neurons E transprinted will be characterized by.....

Insert on P. 26: When we say this we mean, by inhibition of the salivary response..... we mean two different things:

(a) we mean that a dog will not respond with salivation upon being exposed to the compound stimulus, and

(b) we mean that a dog will not respond with salivation upon being exposed to the auditory component of the compound stimulus.

The statement (a) is easy enough to understand because when we expose the dog to the compound stimulus the visual component will excite the neurons E which were transprinted during the series of extinguishing exposures. The statement under (b) can be explained, however, only by saying that the auditory stimulus excites one of the neurons E which were transprinted during the conditioning series and which comprise the set of elevated neuro-specific proteins and which comprise (a) as well as (1). This transprinted neuron in turn can effectively transmit the excitation to the neurons E which were transprinted during ..... which the set of neuro-specific proteins of ..... the set of neuro-specific proteins of which consist of the set (1) alone. This explanation emphasizes the characteristic feature of the notions here adopted, according to which the transprinting is an all or none phenomenon. Let us assume that the neurons V contact the neurons E which were transprinted during the conditioning series of exposures only through one or two synapses. This is not enough to excite this transprinted neuron upon exposure of the dog to this visual signal to a sufficiently high level to cause salivation yet one or two synapses..... these few synapses were sufficient to cause a transprinting of the transprintable neuron during the conditioning exercises by the neurons V in the cortex.

Insert on P. 21

The case which is of particular interest to us is one in which the magnamity of a salivary response is no greater to a compound stimulus than to the auditory (the strong) component to the compound stimulus. In order to explain the conditioning of the dog to the compound stimulus or the stronger compound stimulus.....

We are particularly interested in the case which has been conditioned to a compound stimulus, which is a strong auditory and a weak visual component, and which responds with the same degree of salivation to the compound stimulus or to its stronger component, the auditory stimulus alone.

If such a dog is then repeatedly exposed to the weaker visual stimulus and if such an exposure is never coupled with squirting food into the mouth of the dog, i.e. if the exposure to the weaker stimulus is never reinforced, after a number of such exposures to which we shall refer as extinguishing exposures, the conditioned response which has been previously established may be abolished. By saying this we mean not only that the dog will

now no longer respond with salivation upon being exposed to the compound stimulus but also that it will not respond with salivation after being exposed to its stronger component of the auditory stimulus.

I propose to discuss the significance of this phenomenon from the notions here adopted. When a dog, which has been fully conditioned to the compound stimulus is exposed to the weaker component of the compound stimulus during the early exposures..... ....The neurons which have been transprinted during the conditioning will be excited and as a result of this a number of transprintable neurons E will be reached by volleys from the neurons Fe mentioned before. Accordingly, one may assume that one or several of these transprintable neurons will be induced to fire by the simultaneous arrival of volleys from the neuron Fe and the neurons V in the cortex which preferentially respond to the visual signals. The neurons E which will be transprinted on such an occasion will be characterized by the set of neuro-specific proteins (e) and (v) and therefore the set of neuro-specific proteins will not include the sets (a) and (f).

The neurons E which have been thus transprinted during the extinguishing exposures and thereafter by exciting ..... by exposing the dog to the visual signal but since these transprinted neurons E do not contain the set (f) their excitation will not lead to the excitation of the effector neuron, i.e. it will not cause the dog to salivate, rather the excitation of the neurons which were transprinted during the extinguishing exposures will have an inhibitory effect on the salivary response.

On the basis of the notions here adopted we can understand why a dog which has been exposed to the weak visual signal without reinforcement, after a number of such exposures will not respond with salivation if presented with a stronger component of the compound stimulus, the auditory signal.

April 15, 1964

In a paper to be published elsewhere we shall discuss to what extent a simple neural network could describe the classical Pavlovian conditioning in the autonomous nervous system of the dog. We shall have to defer a detailed discussion of how a memory may be recorded and read out in the conditioned response to that occasion and shall indicate here only rather sketchily how transprinting takes place during conditioning. When food is squirted into the mouth of the dog, the dog responds with salivation. This is the inborn response.

Let us now present a dog simultaneously with an auditory and a visual stimulus (compound stimulus) and let us squirt food into the mouth of the dog where the compound stimulus is still maintained. If, after being exposed to several such conditioning exposures the dog is then on one occasion presented with a compound stimulus, it may be expected to salivate even though no food is squirted into its mouth on this occasion.

We assume that there is a neuron F in the CNS which preferentially responds to the signal "food in the mouth" which is characterized by the set f and which is connected to an Effector neuron also characterized by the set (f) which innervates the salivary gland and this is the reason why the dog salivates when food is squirted into its mouth. Let us now focus our attention on a group of transprintable excitatory neurons E characterized by the set (e) which has no overlap with the set (f), which have the following in common: Each of these neurons is weakly connected to the neuron F and is in turn connected through an inner neuron to the Effector neuron which innervates the salivary gland. If such a neuron E has been transprinted with the set (f) then thereafter the excitation of this transprinted neuron will cause salivation.

We assume that the neurons E are connected medium strongly to neurons A in the CNS which respond preferentiallyto the auditory component of our compound signal and they are also medium strongly connected to neurons V which respond preferentially to the visual component of our compound signal. We assume that there is no substantial overlap between the neurons E, F, A, and V, which are characterized by the sets (space) respectively and we assume there is no substantial overlap between any two of these four sets. Accordingly, the efficacy of a synapse which connects the neurons F, A, and V to the transprintable neurons E is low and signals sent by the neurons F, A, and V during a conditioning exposure are not sufficient to cause the transprintable neuron E to fire. A transprintable neuron E which receives such signals will, however, fire if it also receives a signal from a neural network F*, to which it is strongly connected and the neurons of which are characterized by the set (f). We attribute to this neural network F* the key role in classical conditioning. We assume that it receives an input from the neuron F and from neurons E but it can receive a signal only from those neurons E which have been transprinted with a set (f). We postulate that this neural network F* will send out signals only if the signals it receives from the neuron F or if the aggregate strength of the signals which it receives from neurons

substantially exceed the strength of the signal which it receives from neuron F.

If the unconditioned dog is for the first time presented with a compound stimulus and food the neural network F* will send out signals and one or several of the neurons E will be caused to fire and will be transprinted on that occasion with the sets (f), (a) and (v). If the conditioning exposure is repeated several times, more and more neurons E will be so transprinted on each subsequent exposure. The aggregate strength of the signals sent by the neurons E which have been previously transprinted with the set (f) will increase and therefore the signals sent out by the network F* will decrease. After a number of such conditioning exposures the signals sent out by the neural network F* will be so weak that no further neurons will be caused to fire.

We attribute to this neural network F* a key role in classical conditioning. We assume that it receives an input from the neuron F and from neurons E but it can receive a signal only from those neurons E which have been transprinted with a set (f). We postulate that this neural network F* will send out signals only if the signals it receives from the neuron F are substantial or if the aggregate strength of the signals which it receives from neurons substantially exceed the strength of the signal which it receives from the neuron F.....

If the unconditioned dog is for the first time presented with a compound stimulus and food the neural network F* will send out signals and one or several of the neurons E will be transprinted on that occasion with the sets (f), (a) and (v). If the conditioning exposure is repeated several times,more and more neurons E will be so transprinted but on each subsequent exposure, the aggregate strength of the signals sent out by the neurons E which have been previously transprinted with the set (f) will increase and, therefore, the signals sent out by the network F* will decrease after a number of such conditioning exposures..... the signals sent out by the neural network F* will be so weak that no further neurons will be caused to fire.

If such a fully-conditioned dog is now, on one occasion, exposed either to the compound stimulus alone or to the auditory component of the compound stimulus, but is not presented with food on that occasion, the neural Network F* will fire and will cause one of several transprintable neurons E to fire also which will be transprinted on that occasion with the sets (leave space) respectively. We designate exposures of the dog to stimulus which is unreinforced as "extinguishing exposures" and as the dog is subjected to more and more such extinguishing exposures, using the compound signal, the auditory component of the compound signal or the visual component of the compound signal, neurons which are transprinted with (leave space) respectively, will accumulate as may be shown on another occasion..... an accumulation of these transprintable neurons which do not contain the set (f), which is responsible for the extinguishing of the conditioned response.

As extinguishing progresses at some point the dog will no longer respond with salivation to the presentation of the stimulus. If the extinguishing processes continue beyond this point, i.e. if we are extinguishing below zero, there will be reached a point

when, upon the exposure to the stimulus, the aggregate strength of the signals sent by the neurons E, which have been transprinted with (f), is no longer sufficient to cause the network F* to fire. Continuing the extinguishing procedure beyond this point thus then would no longer lead to the transprinting of any transprintable neurons E. In another
* paper I intend to discuss in the near future in detail to what extent a simple neural network, which includes inhibitory neurons as well as excitatory neurons, can account for most if not all of the basic phenomena of classical conditioning of the autonomous nervous system of the dog.

If such a fully-conditioned dog is now exposed either to the compound stimulus or to its auditory component or to its visual component, but is not presented on this occasion with food, a number of neurons E which have been transprinted during previous conditioning procedures, with the set (f), as well as the sets (a) and (v), will be caused to fire. This, in turn, will cause the neural network F* to fire and the firing of this neural network will, in conjunction with the firing of neurons A or V or both, will cause one or several transprintable neurons E to fire. These neurons E will be transprinted on such an occasion with the sets (a) or (v) or both, depending on the stimulus used but they will not be transprinted by the set (f).

We designate such an exposure of the dog to the stimulus which is not reinforced by food as an "extinguishing" exposure. As the dog is subjected to more and more such extinguishing exposures, using either the compound signal or the auditory or the visual component of the compound signal.....

If the unconditioned dog is, for the first time, presented with "food" as well as the compound stimulus, the neural network F* will send out signals and one or several of the transprintable neurons E, will be caused to fire. These neurons E will be transprinted on this occasion with the sets (f), (a) and (v). If this conditioning exposure is repeated several times more, more and more neurons E will be so transprinted. Thus, as conditioning progresses, there will be an increase in the number of neurons E which are transprinted with the set (f). As conditioning progresses, the number of neurons E will increase and thereafter

on subsequent occasions..... subsequent conditioning exposures of the dog, the signals sent out by the network F* will decrease in strength. After a number of such conditioning exposures, the signals sent out by the neural network F* will be so weak that no fruther transprintable neurons E will be caused to fire. When this point is reached the dog is fully conditioned.

Insert: We assume that in the CNS the neurons which respond preferentially to different stimuli differ from each other in their chemical specificity. We may divid the neurons in the CNS into two broad classes. The class of congenitally-determined neurons and the class of memory neurons.

The congenitally-germined neurons attain their full chemical specificity through differentiation which they undergo during development of the individual, mostly during the embryonal life and at the latest during the early post natal period.

The memory neurons may attain their full chemical specificity anytime during the life of the adult, through a process which is induced by some of the congenitally-determined neurons on an occasion when these are activated by the proper stimulus. We shall designate this process as transprinting. Accordingly, up to the time they attain their full chemical specificity, we shall refer to the memory neurons as transprintable neurons and thereafter we shall refer to them as transprinted neurons.

Definition of chemical specificity

We assume that somatic cells in general differ from each other because a different set of genes they contain is active and, accordingly, the different specific proteins are produced at a high rate. We assume in particular that as the result of differentiation which the neurons of the CNS undergo during differentiation of the individual .... those congenitally-determined neurons which preferentially respond to different sensory signals contain a different set of neuro-specific genes which are active and, accordingly, in the neurons which differ from each other in their response specificity, a different set of specific proteins will be maintained at a high level of concentration. We shall refer to these specific proteins as the transmission specific proteins.

We shall designate as the overlap number m of two neurons the number of elevated transmission specific proteins which are contained in the set of elevated transmission specific proteins of both of them.

As we shall see below, according to the notions here adopted, the signals coming from two congenitally-determined neurons, can be easily confused by the CNS if their overlap number is a substantial fraction of the number of transmission specific proteins which are elevated in either of the two congenitally-determined neurons.

Let us now consider a broad class A of congenitally-determined neurons and distinguish within this class sub-classes in such a way that all the neurons of given sub-class Ai are characterized by the set (symbol) of elevated transmission specific proteins. We shall designate the number of specific proteins contained in the set (symbol) by (symbol).

We shall be lead to assume that two congenitally-determined neurons which preferentially respond to two very different sensory signals between which the CNS can discriminate with ease have a small overlap number m, whereas the two congenitally-determined neurons which espond to sensory signals between which the CNS can discriminate only with a great deal of difficulty, have a large overlap number m.

Neural Network

The neural network models which we shall employ have the following characteristics: Each neuron has an axon and may send nerve impulses along its axon have a frequency which increases when the level of excitation of the neuron increases. The axon of each such neuron branches into a smaller or larger number of fibres and each of these branch fibres ends in a bouton. Each such bouton contacts a dendrite (through a synapse) or the cell body of some other neuron.

At the synapse there is a gap between the pre-synaptic membrane of the bouton and the post-synaptic membrane of the dendrite..... membrane covering the bouton of the pre-sunaptic neuron and the membrane covering the dendrite (cell body)of the post-synaptic neuron. We assume that nerve impulses which reach the bouton cross the synaptic gap on a chemical carrier. Each nerve impulse reaching a given bouton is assumed to trigger the release of a certain amount of transmitter substance which diffuses across the synaptic gap into the post-synaptic neuron. We assume the neurons involved in our network models to be of two

kinds : (a) excitatory neurons whose boutons release in the vicinity of the pre-synaptic membrane an excitatory transmitter bustance which we shall designate "acetylcholine", which diffuses across the synaptic gap and raised the level of excitation of the post-synaptic neurons,

(b) inhibitory neurons whose boutons release an inhibitory transmitter substance we shall designate "inhibitine" and which diffuses across the synaptic gap and lowers the level of excitation of the post-synaptic neuron.

We assume in the case of excitatory synapses that there is an appreciable concentration of an enzyme in the vicinity of the synaptic membrane of the post-synaptic neuron that inactivates "acetylcholine" and we shall designate this enzyme "cholinesterase" - (in quotes)and we assume that similarly, in the case of inhibitory synapses, the presence in appreciable concentration of an enzyme which we shall designate as "inhibitinase" which destroys the hypothetical inhibitory transmitter substance.

The dendritic tree of a neuron may have a very large number of branches and the xonaof any one neuron may have a very large number of branch fibres with each fibre nding in a bouton and contacting through a synapse the dendrite of some other neuron. The contribution of an excitatory neuron to the excitation of another neuron is determined by three factors, by the frequency of the nerve..... When an excitatory neuron fires its contribution to the excitation of another neuron is determined by three factors:

(a) the frequency of the nerve impulses it sends out which we may designate as the intensity of the signal

(b) the number of synapses through which it contacts the other neuron. If this number is large, we shall say that the pre-synaptic neuron is strongly connected to the post-synaptic neuron and..... Depending on whether this number is small, medium or large, we shall say that the pre-synaptic neuron is weakly, medium strongly or strongly connected to the post-synaptic neuron.

(c) the efficacy of the individual synapse through which the pre-synaptic neuron is connected to the post-synaptic neuron.

We shall assume here that all the synapses with which a pre-synaptic neuron is connected to a given post-synaptic neuron, have the same efficacy but that efficacy of

of the synapses connecting the same pre-synaptic neuron to other post-synaptic neurons can differ greatly and is determined by the "cholinesterase concentration" or "inhibitinase concentration" that prevails at the post-synaptic membrane.

(New P. 3)

We assume the neurons involved in our network models to be of two kinds and two kinds only. Excitatory neurons and inhibitory neurons.

At an excitatory synapse there is a gap between the membrane covering the boutons of the pre-synaptic neuron and the membrane covering the dendrite (or the cell body) of the post-synaptic neuron. Each nerve impulse reaching a given bouton progresses the release of a certain quantity of excitatory transmitter substance which diffuses across the synaptic gap into the post-synaptic neuron and riases the level of excitation of the post-synaptic neuron. We shall designate this excitatory transmitter substance as "acetylcholine" - in quotes.

We assume that there is an appreciable concentration of an enzyme in the vicinity of the post-synaptic neuron in the vicinity of the synaptic membrane which inactivates "acetylcholine". We shall designate this enzyme as cholinesterase - in quotes.

Inhibitory neurons , which we shall assume, are exactly like the excitatory neurons except that the inhibitory transmitter substance which diffuses across the synaptic gap in the post-synaptic neuron does not raise but lowers the level of excitation of the post-synaptic neuron. We shall designate the inhibitory transmitter substance as inhibitine and the corresponding enzyme "inhibitinase".

(New P. 4)

When an excitatory neuron fires, its contribution to the excitation of a given post-synaptic neuron is determined by three factors:

(a) the frequency of the nerve impulses which the pre-synaptic neuron sends out to which we shall refer as the intensity of the signal -

(b) the number of synapses through which the presynaptic neuron contacts a given post-synaptic neuron. Depending on whether the number of these synapses is small, medium or large, we shall

we shall say that the pre-synaptic neuron is weakly, medium strongly, or strongly connected to the post-synaptic neuron,

(c) the efficacy of the synapse through which the pre-synaptic neuron is connected to a given post-synaptic neuron.

We assume that all these synapses have the same efficacy for the same post-synaptic neuron but the efficacy of the synapses through which the same pre-synaptic neuron is connected to a different post-synaptic neuron can be very different. We shall be lead to assume that the efficacy of a synapse is determined by the rate at which cholinesterase is destroyed at the post-synaptic membrane and we shall be further lead to assume that this rate depends on the overlap number of the pre-synaptic and the post-synaptic neuron.

(New P. 4)

..... in the vicinity of the post-synaptic membrane in the post-synaptic neuron which inactivates acetylcholine. We shall designate this enzyme as cholinesterase - in quotes - and we shall be lead to assume that it is destroyed at the post-synaptic membrane within the post-synaptic neuron.

We assume that the inhibitory neurons are just like the excitatory neurons except that the inhibitory transmitter substances which diffuse across the synaptic gap into the osp-synaptic neuron does not raise but lowers the level of excitation of the post-synaptic neuron. We shall designate the inhibitory transmitter substance as inhibitene and the enzyme which destroys it as inhibitinase.

Insert: Biochemical interpretation of the significance of the overlap number: We need to make a few remarks at this point about antibodies.

4(a) It is determined by the number of nerve impulses which the presynaptic neuron sends out within a period of time (symbol). (Symbol) depends on the overlap number of the presynaptic and post-synaptic neuron and is large if this overlap number is large. We shall refer to the number of nerve impulses which the pre-synaptic neuron sends out over a period of time (symbol) as the signal strength.

Let us now consider two neurons A and B; A being characterized by a set of elevated transmission specific proteins (leave space) and B being characterized by another set of elevated transmission specific proteins. If the sets (symbol) have any transmission specific protein in common..... the sets may have a set of transmission specific proteins.... might both contain some of the same transmission specific proteins so that there might be a sub-set (symbol) which the sets (symbol) have in common.

We shall designate the number of transmission specific proteins contained in the sets (symbols) with (symbol) respectively to the number m which tells us how many of the transmission specific proteins the neurons A, and B have in common. We shall refer to this as the overlap number of the sets (symbol) or as the overlap number of the neurons A & B.

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Footnote: As pointed out earlier, the binding of a protein resembling complement, or conceivably complement itself, by antibody molecules which are combined with their specific antigen molecules might account for the fact that the injection of antigen into a pre-immunized rabbit leads to the proliferation of lymphatic cells which contain the antibody which is specific for the antigen at a high concentration.

The biochemical model on which the notions here adopted are based assumes that the transmission specific proteins are located in the membrane of the neuron and in particular they are located in the pre-synaptic and post-synaptic membranes. It further assumes that a transmission specific molecule which is located in the post-synaptic neuron can dimerize with a molecule of the same transmission specific protein if such a molecule is located in the post-synaptic membrane.

(7)

The biochemical model on which the notions here adopted are based assumes that the transmission specific proteins located in the membrane of the neuron.....
assumes that a transmission specific molecule which is located in the post-synaptic membrane can dimerize, across the synaptic gap with a molecule of the same transmission specific protein which is located in the post-synaptic ..... Our model assumes that molecules of the transmission specific proteins resemble the molecules of antibodies just as an antibody molecule undergoes an allosteric transition when it combines with its antigen molecule so a transmission specific protein located in the pre-synaptic membrane undergoes an allosteric transition when it dimerizes across the synaptic gap with any molecule of the same transmission specific protein. We assume that a transmission specific molecule located in the post-synaptic membrane can combine and inactivate cholinesterase. We may now ask how many such dimers may be expected to be present per unit area of synaptic membrane. We shall for the purposes of this discussion assume that a concentration of each transmission specific protein in a membrane of a neuron is the same and that there are N_o molecules of equal size per unit area in the cell membrane which are not transmission specific proteins. If we then have two neurons A and B, which are bridged by the synapse, the number of dimers per unit area of the post-synaptic membrane will then be given by either the ratio (symbol) or the ratio (symbol) whichever is smaller. If we now assume, for the sake of simplicity, that all synapses have the same active area, then the number of dimers per synapse willbe proportional to the ratio sited above. If we further assume that the rate of production of cholinesterase is the same in all synapses while the rate of destruction is proportional to the smaller of the ratios (symbol) then we may also say that the concentration of the enzyme cholinesterase in the synapse may be proportional to.....

(8)

.....If we assume for the sake of simplicity of discussion that each elevated transmission specific protein is contained in the membrane of a neuron at the same concentration and that the active area of the post-synaptic membrane is the same for each synapse then the number of dimers per synapse is given by the overlap number of the presynaptic and post synaptic neuron and if we further assume that cholinesterase is produced at the same rate at the post synaptic membrane in every synapse, then the cholinesterase concentration at the post-sunaptic membrane will be inversely proportional to the overlap number of the pre-synaptic and post synaptic neuron.

The rate of cholinesterase production is given by the signal strength while the rate at which cholinesterase is produced in the bouton is given by the signal strength..... the rate at which acetylcholine is destroyed at the post-synaptic membrane is proportional to its concentration as well as the concentration of cholinesterase. If at one point in time, the signal strength is increased so it is double the acetylcholine concentration will begin to increase and it will asymptotically approach a high concentration. It will get half way towards this concentration at a time (symbol) which is proportional to the concentration of the enzyme cholinesterase. Accordingly, the total rise in acetylcholine concentration which is produced by a given change in the signal strength will be proportional to the concentration of cholinesterase which in turn will be inversely proportional to the number of pre-synaptic and post-synaptic neurons and since the concentration of cholinesterase is inversely proportional to the overlap number we see that the efficacy of the synapse is proportional to the overlap number.

(9)

If at one point in time the signal strength is increased , then the concentration of aceytlcholine in the vicinity of the post-synaptic membrane will begin to rise and it will assymptotically approach a high value. The increase in acetylcholine concentration will be proportional to the signal strength and inversely proportional to the concentration of the enzyme cholinesterase. If we designate this/efficacy of the synapse the rise in acetylcholine concentration is obtained for a fixed rise in signal strength then we may say that the efficacy of the synapse is inversely proportional to the cholinesterase concentration prevailing at the post-synaptic membrane, i.e. it is proportional to the overlap

number of the presynaptic neuron and the post synaptic neuron.

(10)

Transprinting of neurons

According to the notions here adopted, an adult can remember and learn because there are present in his central nervous system neurons which have not attained their full chemical specificity during the development of the individual and which attain their full chemical specificity during the lifetime of the adult through a process which we here designate as "transprinting". One might regard transprinting as a certain kind of differentiation through which the transprinted neuron attains its full chemical specificity or through the intervention of certain key compounds where each key compound would have to be specific for a given transmission specific protein. We cannot say just what this key compound is.. but we can assume for each transmission specific protein which is present at a high concentration in a given neuron, the corresponding key compound is also maintained at a high level of concentration.

We assume that the congenitally-determined neuron is capable of transprinting if the transprintable memory neuron to which it is connected through a synapse..... if the presynaptic membrane of the congenitally-determined neuron becomes, for a short period of time, permeable for the key compounds whenever the congenitally-determined neuron fires..... We assume that the post synaptic membrane of the transprintable neuron becaomes for a short period of time permeable for key compounds whenever the neuron fires. If the periods of time during which the presynaptic membrane and the postsynaptic membrane are permeable for key compounds overlaps then the key compounds which are maintained at a high level of concentration in the pre-synaptic neuron will diffuse into the post-synaptic neuron and the post-synaptic neuron will incorporate the set of transmissions specific proteins of the pre-synaptic neuron. Accordingly, the ..... This is a process of transprinting..... Accordingly, the process of transprinting requires the simultaneous or the nearly-simultaneous firing of the transprinting neuron and the transprintable neuron.

In order to illustrate how transprinting might take place I shall use as an example the classical Pavlovian conditioning of the salivary reflex of the dog. Because of the limitation of space I shall be able to indicate here only rather sketchily what takes place during conditioning on this occasion.

(12)

Transprinting

If, whenever the neuron fires, its presynaptic membranes become permeable for the key compounds for a certain period of time..... In the case of transprintable memory neurons, we assume that in any such neuron the post-synaptic membranes become permeable for key compounds for a certain period of time, whenever the neuron fires. Let us now consider if both of these neurons fire simultaneously in such a manner that the period of time during which the presynaptic membrane is permeable for the key compounds, overlaps with the period of time during which the postsynaptic membrane is permeable for the key compounds, then those key compounds which are contained at a high level of concentration in the presynaptic neuron will diffuse across the synaptic gap into the postsynaptic neuron. If this happens the post synaptic neuron will incorporate the full set of transmission specific proteins of the presynaptic neuron . This is the process of transprinting.

In order to illustrate how transprinting takes place we shall use as an example the classical Pavlovian conditioning of the salivary response of the dog. Because of the limitation of space, we shall be able to indicate rather sketchily only on this occasion.

When food is squirted into the mouth of the dog, the dog responds with salivation. This is the inborn, or unconditioned response. Let us now expose the dog to a compound stimulus which has an auditory and a visual component and let us further - before the compound stimulus is switched off - squirt food into the mouth of the dog. If, after several such conditioning exposures, the dog is then presented for the first time with a compound stimulus, unreinforced by the squirting of food into its mouth, the dog may be expected to salivate. This is the conditioned response.

We assume that there is a neuron F in the CNS which preferentially responds to the signal "food in the mouth" and that this neuron is characterized by the set (f). Let us further assume that this neuron is connected to an Effector neuron, also characterized by the set (f) which innervates the salivary gland. These two assumptions would account for the inborn, unconditioned response.

In order to account for the conditioned response, we need to assume that there exist a group of transprintable excitatory neurons E characterized by a set (e) which has no overlap with the set (f) and that these neurons E have the following in common. The

At least one bouton of a branch fibre of the axon of the neuron F contacts through a synapse, each of these neurons E and, in turn, each neuron E contacts through a synapse the above mentioned Effector neuron which innervates the salivary gland. It follows from the above that once a sufficient number of neurons E has been transprinted with the set (f) then thereafter the excitation of these transprinted neurons E may cause salivation even in the absence of any firing by the neuron F. We assume that neurons A and V in the CNS which respond preferentially to the auditory and to the visual component of the compound stimulus referred to above are connected through synapses to the neurons E. The neurons A & V are characterized by the set of transmission specific proteins (a) and (v) respectively and we assume that the number of transmission specific proteins contained in the sets (a) and (v) respectively are very large compared to the number of neuro-specific proteins contained in the set (e) which is given by (e). Regarding the neurons A and V, we assume that their overlap is zero in contra distinction to the neuron F. We assume that both the neurons A and V have a small overlap with the neuron E. Accordingly, the efficacy of the synapses which connect the neuron F to the transprintable memory neuron E is so low that the firing of the neuron F does not make an appreciable contribution to the excitation of the transprintable memory neuron. The firing of the neurons A and V will on the other hand make an appreciable contribution to the excitation of the transprintable neuron E but we assume this contribution to be insufficient to excite the transprintable memory neuron to the point where it would begin to fire. Rather, for the transprintable neuron E to fire it would have to receive signals in addition to signals which it receives from either neuron A or V, from a neural network F* via an inter neuron designated by FE. We assume that the neurons of the neural network F* to be characterized by the set (f) and the inter neuron FE to be characterized by both the set (f) and the set (e). According to the notions here adopted, the neural network F* plays the key role in classical conditioning. We assume that all neurons FE are connected to the neural network F* but only the synapses of those neurons E will have an appreciable efficacy and only ~~of~~ neurons E which have been transprinted with the set (f) will make an appreciable contribution if they fire to the excitation of the neurons contained in the neural network F*.

The neuron F is also connected to the neural network F* and we postulate that

that the neural network F* will send out signals only if the strength of the signals which penetrate into it from the neuron F substantially exceed the aggregate strength of the signals which penetrate into to it from the neurons E or, alternatively, if the aggregate strength of the signals which penetrate into it from the neurons E substantially exceed the strength of the signals which penetrate into it from the neuron F. If the aggregate strength of both signal is not very different a signal sent out by neural network F* will be weak and if the strength of both signals are about equal they will cancel out and the neural network F* will not send out a signal.

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* In another paper we shall discuss in detail to what extent a simple neural network can, on the basis of the moleculr processes here postulated, can account for Pavlov's*experiment on the conditioning of the salivary reflex of the dog.

Footnote: I.P. Pavlov "Conditioned Reflexes", 1927, Oxford University Press.

Our discussion will include the establishment and the various modes of extinction of the conditioned response and the phenomena which Pavlov call generalization, differentiation, and inhibition and negative induction.

Alternative Model

An alternative which is closely related to our model discussed above and which..... There is an alternative model which is no less plausible than the model discussed above and which could equally well account for.....

There is indeed an alternative which may deserve to be taken seriously and which is as follows: We assume that for every transmission specific protein there is a complementary transmission specific protein and that any transmission specific protein can combine with its counterpart much the same as an antigen molecule can combine with its antibody.

A congenitally-determined neuron can contain any transmission specific protein at a high level of concentration or it can contain its counterpat at a high level of concentration but it cannot contain both at a high level of concentration. If a transprintable memory neuron is transprinted by congenitally-determined neuron it incorporates not the set of transmission specific proteins which characterize the congenitally-determined neuron but the

set of the counterparts of these elevated transmission specific proteins. The overlap number of a presynaptic and postsynaptic neuron which determines the efficacy of the synapse is defined in this model as the number of the transmission specific proteins contained in the set that characterizes the presynaptic neuron which have their counterparts contained in the set of transmission specific proteins which characterizes the post synaptic neuron. This model is, in a sense, biologically more plausible than the model we have used but, in as much as a neural network based on it would operate in much the same manner as the neurons which operate on the basis of our first model.....

Insert on P. 2

We assume that all neurons which attain their full chemical specificity during development ..... and in equal numbers which have complementary sets of transmission specific proteins. If, however, we look at a network such as the network represented in Fig. 1 and if we assume that the neuron F is characterized by the set F, then when the neuron E is transprinted by the neuron F, it will incorporate not the set (f) but the complementary set $\bar{f}$. Accordingly, we would have to assume that an inter-neuron Fi is characterized by the set fi which has an overlap with $\bar{f}$. Similarly, we would have to assume that the Effector neuron and the neurons of the neural network F* are characterized by the set $\bar{f}$..... Similarly, we have to assume that the neuron FE is characterized by a set ($f\bar{e}$) and that the neuron I is characterized by the set $\bar{e}$, i and c.

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7 (a)

We assume that the active area of each post synaptic membrane has the same size for each synapse. We further assume that each elevated transmission specific protein.... that the concentrations of the elevated transmission specific proteins in the cell membrane is the same for all of them and that the concentration of each elevated non-transmission specific proteins present in the cell membrane is the same also. The number of dimers per synapse is then given by the ratio of the overlap of the two neurons which are bridged by the synapse. ... In order to obtain the number of dimers per synapse, we have then to consider two ratios, the ratio of the overlap number of two neurons which are bridged by the synapse and the ratio of the total number of elevated transmission specific

and non-transmission specific proteins of the presynaptic neuron. We shall designate the smaller of these two ratios as the overlap fraction of the two neurons which are bridged by the synapse and the number of dimers per synapse is given by this overlap fraction.

Insert on P.2.

This second model is biologically hardly less plausible than the first model but the neural networks based on it would operate in much the same manner as the networks which are based on the first model.

We must assume that if the central nervous system contains a certain number of a certain kind of neuron which attains its full chemical specificity during development, it contains an equal number of neurons which have the complementary set of elevated transmission specific proteins.

If we assume that the neuron F in a network such as that represented in Fig. 1 is characterized by the set (f) then the effector neuron would be characgerized by the set $(\bar{f})$ where $\bar{f}$ designates the set which is complementary to the set (f).

If the number of elevated non-transmission specific proteins present in the cell membrane were the same for all neurons and if this number were large compared to the number of elevated transmission specific neurons contained in all of our neurons, then the overlap fraction of two neurons which are bridged by the synapse becomes proportional to the overlap number of thw two neurons and accordingly, the number of dimers per synapse also becomes proportional to this overlap number.

Insert on P.11.

H.S. Anker* suggested in 1960 that this kind of locking mechanism might represent a biochemical basis for memory.

Footnote: *H.S. Anker, Nature, Vol. 188; P.938, 1960.

We may look upon the neural network F* as a part embodiment of a general principle for it must be generally true that the sensory experience is not recorded in a form in which it may be recalled unless there is somehow "significance" attached to this experience. In our model, the firing of the neural network F* represents the significance which is attached in the system involving the salivary reflex of the dog to the signal "food in the mouth" or to the sensory signal which has become associated through conditioning with the signal of food in the mouth.

Fig. 1 shows an essential part of our model of a simple neural network which could be involved in the conditioning of the salivary reflex of the dog. There is a neuron F in the CNS of the dog which responds to the signal "food in the mouth" and which is characterized by the set (f). We shall in part assume that the signal for the firing of the neuron F is the onset of the stimulus food in the mouth. As the figure shows, the neuron F is connected through a synapse to an effector neuron, also characterized by the set (f) which innervates the salivary gland. At the onset of the stimulus, food in the mouth, the neuron F sends out a volley of nerve impulses which excite theeffector neuron which innervates the salivary gland and this results in salivation. This is the inborn, unconditioned response.

In order to account for the conditioned response, we postulate that there is a group of transprintable excitatory neurons E characterized by the set (e) which has no overlap with the set (f) and that these neurons E (of which one example is shown in the Fig. 1), are characterized by the set (e) which has an overlap with a set (f) and all the neurons E have the following in common.

The neuron F contacts through a synapse each of these neurons E and, in turn, each neuron E contacts through at least one synapse the Effector neuron which innervates the salivary gland.

There are neurons A and V in the CNS which respond to the auditory and to the visual component of the compound stimulus, receiving.....

April 18, 1964

<u>The efficacy of a synapse bridging two neurons</u>:

Our neural network involves both excitatory neurons and inhibitory neurons, each of one particular kind. Let us consider an excitatory neuron which contacts through a synapse another neuron. If the excitatory neuron sends one volley of nerve impulses to the synapse a certain quantity of excitatory transmitter substance is released in the vicinity of the presynaptic membrane which diffuses across a gap - the synaptic cleft - into the post-sunaptic neuron and raises the level of excitation of the post synaptic neuron by a certain amount. We shall designate this transmitter substance "acetylcholein" - in quotes.

The acetylcholine which is released is destroyed in the post synaptic neuron in the vicinity of the post synaptic membrane by an enzyme which we shall designate "acetylcholine" - in quotes.

The rate at which acetylcholine is released in the vicinity of the presynaptic membrane when nerve impulses of a certain frequency reach the synapse is a function of this frequency and we shall designate this rate as a signal intensity. The acetylcholine released in the vicinity of the presynaptic membrane at the rate which is given by the signal intensity is destroyed at the post synaptic membrane at the rate which is proportional to the acetylcholine concentration of the enzyme cholinesterase revealing in the post synaptic neuron in the vicinity of the post synaptic membrane....
From this it follows that if at some point in time the excitatory neuron begins to send out nerve impulses which reach the synapse..... From this it follows that if, at a given point in time, nerve impulses at a certain frequency begin to arrive at the synapse the acetylcholine concentration in the vicinity of the post synaptic membrane will betin to rise and will assymptotically approach a concentration which is proportional to the signal intensity and inversely proportional to the concentration of the enzyme cholinesterase in the vicinity of the post synaptic membrane.

We shall here assume that the signal intensity is the same function of the frequency of the nerve impulses for all synapses, i.e. for any given frequency of the nerve impulses, the signal intensity would be the same for all synapses. On this basis we may then say that acetylcholine concentration, which is assymptotically approached, is ∝ proportional to the frequency of the nerve impulses reaching the synapse and is inversely proportional to the concentration of the enzyme cholinesterase in the vicinity of the post synaptic neuron. We shall also assume that the enzyme cholinesterase is produced at the same rate in all post synaptic neurons but is inactivated at the post synaptic membrane at different rates in different synapses, the rates being determined by the chemical specificities of the two neurons which are bridged by the synapse. We may define as the efficacy of a synapse the acetylcholine concentration which is assymptotically approached at the post synaptic membrane when a synapse is reached by nerve impulses of a given frequency which extends between a (arbitrary) unit of signal intensity. On the

basis of the above we may then say that the efficacy of the synapse is inversely proportional to the rate at which cholinesterase is inactivated at the post synaptic membrane which, in turn, is determined by the chemical specificity of the two neurons which are bridged by the synapse.

The biochemical model for the inactivation of "cholinesterase".....
We assume that neurons which differ from each other in their response specificity contain in the cell membrane a different set of certain specific proteins at an elevated concentration to which we shall refer as transmission-specific proteins.

We assume that a molecule of a transmission specific protein located in the post synaptic membrane at such a point of contact can dimerize across the synaptic gap with a molecule of the complementary transmission specific protein which is located in the presynaptic membrane with its compementary counterpart which may be contained in the pre-synaptic membrane. The number of such dimers contained within the active area of the post-synaptic and presynaptic membrane will then determine the rate at which the enzyme cholinesterase is inactivated at the post synaptic membrane. Let us now consider two neurons A and B which are bridged by the synapse; the neuron A will be characterized by a set of elevated specific proteins designated by (a) and the neuron B will characterized by a set designated by (b). We shall designate as the overlap number of these two neurons (space) the number of transmission specific proteins contained in the set (a) which have their complementary counterpart contained within the set (b) (or vice versa). From this overlap number, we may now compute the efficacy of the synapse which bridges these two neurons. In order to make this computation simple we shall assume that synapses bridging another two neurons have the same active area, and also that for any given neuron with the concentration of each neuro-specific protein which is present at a high concentration in the cell membrane is the same.

On the basis of these simplifying assumptions we may then say that the number of dimers contained within the active area of a synapse which bridges a neuron A and a neuron B is given either by the ratio of the overlap number to the total number of specific proteins which are present at a high concentration in the cell membrane of the neuron A or by the ratio

ratio of the overlap number of the total number of specific proteins which are present at a high concentration in the cell membrane of neuron B - whichever ratio is smaller.

We shall designate the smaller of these two ratios as the overlap fraction of the neurons A and B and, accordingly, we may then say that the efficacy of a synapse bridging two neurons is proportional to the overlap fraction of the two neurons. This is the first basic postulate of our model.

Our model could not account for the experiments of Pavlov to .....for the ability of the individual to learn to discriminate (differentiate) in the conditioned response if we were to assume that the signal sent out by a post synaptic neuron is a linear function of the input signal intensities. In our model of a neural network one neuron may receive simultaneously input signals from a number of different excitatory neurons, each of which contacts the neuron through one of several synapses. What we assume here is that the output signal of a post synaptic neuron is an S shaped function of the sum - extended over all synapses of the product of the input signal intensity x, the overlap fraction of the individual synapse or if we refer to this sum as the integrated input, we may then say that the intensity of the output signal of the post synaptic neuron is an S shaped function of the integrated input. To put it in other words, the post synaptic neuron behaves as if it had a threshhold which the integrated input must exceed in order to evoke an output signal of substantial intensity.

Insert on P. 6

We assume that the same holds mutatis mutandis for the synapses of inhibitory neurons except that in this case the transmitter substance which diffuses across the synaptic gap into the post synaptic neuron does not raise but lowers the level of excitation of the post synaptic neuron.

Were we to assume that the intensity of the signal sent out by a post synaptic neuron a is/linear signal of the intensities then our model would be unable to account for the ability of the individual to demonstrate by Pavlov to learn to discriminate (differentiate) in the conditioned response of the autonomous nervous system.

If all the neurons of the CNS were of this sort then the individual would not be able to learn and his behaviour would be wholly governed by "extinction", i.e. inborn reflexes.

According to the notions here adopted, an individual can learn and remember what he has learned because his CNS is equipped with memory neurons which remain, so to speak, plastic beyond the end of the individual's development. We postulate that all these memory neurons can, once in the lifetime of the individual, acquire a set of transmission specific proteins through a process ..... an additional set of transmission specific proteins through a process which we designate as transprinting.

That discussion will cover the establishment as well as the experimental extinction of the conditioned response to compound stimuli including the phenomena of inhibition and learning of discrimination (differentiation).

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(10)

The occurrence of transprinting, as a general phenomenon constitutes our second postulate. We shall refer hereafter to memory neurons, before they are transprinted as transprintable neurons and thereafter we shall refer to them as transprinted neurons. It should be kep in mind that memory neurons themselves may be of two kinds, those capable of transprinting and those not capable of transprinting. It should also be noted that no neuron may contain in its cell membrane both a given neuro-specific protein and its counterpart. Accordingly, a transprintable memory neuron which contains a set of neuro-specific proteins could not be transprinted to contain the complementary counterpart of any of the neuro-specific proteins contained in that set.

In order to illustrate how transprinting takes place, we shall utilize as an example the classical (Pavlovian) conditioning of the salivary reflex of the dog. We shall indicate on this occasion only rather sketchily what takes place during conditioning and shall present a more detailed discussion in our second paper.

We shall assume that there is a neuron F in the CNS characterized by the set (f) which preferentially responds to the signal "food in the mouth". This neuron is connected through synapses to an Effector neuron F* which is charac terized by the set (f) where (f) denotes the set of transmission specific proteins which are complementary to the set of

transmission specific proteins which constitute the set (f). The Effector neuron F* innervates the salivary gland. Because the two neurons F and F* have a large overlap fraction, the synapses which bridge the neurons F and F* have a high efficacy and, therefore, the excitation of the neuron F causes the dog to salivate. This is a manner in which our model accounts for the inborn unconditioned response.

In order to account for the conditioned response, we postulate that exist a large number of transprintable excitatory neurons E, characterized by the set (e) which has no overlap with the set (f) and that these neurons E have the following in common: The neuron F contacts through a synapse each of these neurons E and in turn each neuron E contacts through a synapse an inter neuron $\bar{FI}$ which is characterized by the set $(i\bar{f})$, the above mentioned Effector neuron F*.

In the CNS there is a neuron AE and there is a neuron VE which respond preferentially ot the auditory and to the visual component respectively, of the compound stimulus used in the experiment, which are connected through synapses to the neurons E. The neurons AE and VE are characterized by the sets of (a) + (e) and (v) + (e) respectively.

We assume that the number of transmission specific proteins contained in the neurons AE and VE which are given by (leave space) and (leave space) respectively, are large compared to the number of neuro-specific proteins contained in the neuron E which is given by (leave space).

Because the neurons F and E have no overlapping set of transmission specific proteins, volleys of nerve impulses emanating from the neuron F will not make an appreciable contribution to the excitation of any of the transprintable memory neurons E and thus the firing of the neuron F will not in itself cause any neurons E to fire also.

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(12)

In contradistinction to this, the firing of the neuron AE and VE will make a contribution to the excitation of the transprintable neurons E because these two neurons have an appreciable even though small overlap fraction..... Because this overlap fraction is small we assume that the excitation of the neurons AE or VE or both, will not make a sufficient contribution to the excitation of any of the transprintable neurons E to cause any of these neurons to fire, rather for a transprintable neuron E to fire,in addition to

PART II IS MENTIONED HERE*

receiving signals from either neuron AE or VE or both, it would also have to receive signals from the neural network FG via the inter neuron G which is characterized by the set (g)+(e).

Both the neuron F and each one of the neurons E is connected through a synapse to the neural network FG, which is characterized by the sets (f)+(g), and to which we shall attribute here a key role in the conditioning of the salivary reflex of the dog.

We postulate that the neural network FG sends out strong signals only if the integrated input signal which it receives from the neuron F substantially exceeds the integrated signal input which it receives from the neurons E or, alternatively, if the opposite is the case. If the integrated signal inputs which the network FG receives from the neuron F and from the neuron E are not very different,then this network will send out only signals of weak intensity and if the integrated signal inputs which this network receive from the neuron F and from the neurons E is about equal, then these two integrated inputs will cancel out and the neural network FG will not send out any signal.

Let us now expose such a fully conditioned dog to the compound stimulus - unreinfroced on this occasion by the squirting of food into its mouth. A number of the neurons E which have been, during the previous conditioning exposures, transprinted with the set (f)..... whereas the sets (a) and (v) may be caused to fire on this occasion. Because of the substantial overlap of the neurons E which have been transprinted and which contain the set (f), with the inter-neuron FI, the firing of the neurons E will lead to the firing of the inter-neuron FI and this, in turn, will lead to the firing of the Effector neuron F*. Accordingly, on the occasion of this exposure to the compound stimulus, the dog will salivate. This is a conditioned response.

Incidentally, when the transprinted neurons E fire on this occasion, this will cause the neural network FG to send out signals because on this occasion, this neural network does not receive any siganls from the neuron F. Accordingly, we one or more neurons E, may be transprinted with the sets (a) and (v) but not with the set (f). As we shall show

* in the detailed discussion of the conditioned response to be presented in our second paper, if the dog is repeatedly exposed to the compound stimulus without reinforcement, the number of neurons E which are transprinted with the sets (a) and (v) bur are not transprinted with the set (f) will increase and the neurons E which have been thus transprinted will be excited

by the compound stimulus and it is the excitation of these neurons E which do not contain the set (f) that leads to the extinction of the conditioned response.

The presence of a large number of neurons E which are transprinted with (a) and (v) but not with (f) extinguishes the previously established conditioned response, lies in the circumstances that when these neurons E are excited, they will excite the inhibitory neuron E but will not excite inhibitory neurons IE which contacts through a synapse the inter-neuron FI but because these transprintable neuron E do not contain the set (f) they will not excite the inter neurons FI.

On the basis of the foregoing the reader should be in a position to tell to what extent the neural network model represented in Fig. 1 would mimic..... any reader who prefers not to await the publication of our second paper should be able to figure out to what extent the neural network model represented in Fig. 1 will mimic the phenomena exhibited by the conditioned salivary reflex of the dog.

Our model can be simplified if we assume that every transmission specific proteins is complementary to itself, leaving, for the moment aside whether or not this is biologically plausible, the neural networks which are adequate from the point of view of the first model will also be adequate from the point of view of the second model and all one has to do is to take into account that, on the basis of the second model each elevated transmission specific protein is identical with the complementary set.

It should be noted that, on the basis of the model described above, one must assume, that the CNS contains in about equal number..... As will be shown in our next paper, in order to have our model of neural networks mimic some of the phenomena exhibited by the conditioned responses which appear to be fairly well established, we must assume that if the CNS contains a class of identical congenitally-determined neurons in a certain number, it also contains about the same number of neurons which are characterized by the complementary set of elevated transmission specific proteins.

Any reader who wishes to determine to what extent the neural network represented in Fig. 1 will mimic the phenomena exhibited by the conditioned salivary reflex of the dog, should be in a position to do so on the basis of the foregoing - without having to wait for publication * of our second paper.

It seems to be established fact that, if we establish a conditioned salivary response in the dog to a compound stimulus composed of an auditory and visual stimulus, and if we subsequently extinguish the response to one component of the compound stimulus, say the visual component alone, we thereby also automatically extinguish the conditioned response to the auditory component also. It should be noted that in order to account for this fact we are forced to assume that for any class of identical neurons which the CNS contain, there must be about an equally large number of neurons which are characterized by the complementary set of transmission specific proteins. Accordingly, the CNS must contain, in addition to a large number of neurons E characterized by the set (e) and about an equally large number of neurons E characterized by the set (e) and the neurons E belonging to one set must contact through synapses, the neurons E, characterized by the complementary set.

April 21, 1964

The Efficacy of a Synapse

Our neural network model involves both excitatory neurons and inhibitory neurons, each of one particular kind. Let us now consider an excitatory neuron which contacts through a synapse another neuron. If such an excitatory neuron sends a volley of nerve impulses to a synapse a certain quantity of an excitatory transmitter substance is released in the vicinity of the presynaptic membrane, which diffuses across a gap - the synaptic cleft - into the post synaptic neuron and raises the level of excitation of the post synaptic neuron by a certain amount. We shall designate here this excitatory transmitter substance as "acetylcholine".....

Acetylcholine is destroyed in the vicinity of the post synaptic membrane by an enzyme which is located there and which we shall designate as "cholinesterase" - in quotes. The rate at which acetylcholine is released in the vicinity of the preseynaptic membrane is a function of the frequency of the nerve impulses which reach the synapse and we shall designate this rate as the signal intensity. The rate at which acetylcholine is destroyed in the post synaptic neuron is proportional to the product of the concentration of acetylcholine and the concentration of the enzyme cholinesterase in the vicinity of the post synaptic membrane. From this it follows that if nerve impulses of a certain frequency begin to arrive at a synapse at a given point in time, the acetylcholine concentration

will begin to rise and will, in the vicinity of the post synaptic membrane, assymptotically approach a concentration which is proportional to the signal intensity and inversely proportional to the concentration of the enzyme cholinesterase prevailing in the vicinity of the post synaptic membrane.

We shall designate the acetylcholine concentration which is assymptotically approached at the post synaptic membrane as the excitatory input.

For the sake of sim plicity, we shall assume here that the signal intensity is for all synapses the same function of the frequency of the nerve impulses which are fed into the synapse., i.e. for any given frequency of the nerve impulses we have the same signal intensity for all synapses involved. On this basis, we may then say that the excitatory input of the synapse is inversely proportional to the cholinesterase concentration prevailing in the vicinity of the post synaptic neuron for any given signal intensity.

We assume that the enzyme cholinesterase is inactivated at the post synaptic membrane at different rates in different synapses, the rate of inactivation being determined by the chemical specificity of the two neurons which are bridged by the synapse. We assume, however, for the sake of simplicity, that the enzyme cholinesterase is produced at the same rate in all excitatory neurons. On the basis of the above assumptions, we may then say that the excitatory input per unit of signal intensity is inversely proportional to the rate at which cholinesterase is inactivated in the post synaptic membrane..... Accordingly, it is determined solely by the chemical specificity of the two neurons which are bridged by the synapse. We assume that neurons which differ from each other in their response specificity contain in the cell membrane a different set of certain specific proteins at a substantial concentration. We shall refer to these proteins as transmission specific proteins.

NOTE: "Specific membrane"protein instead of "transmission specific "

We assume that the same holds also, mutatis mutandis, for the synapse of inhibitory neurons, except that in this case the "transmitter substance" - in quotes - which diffuses across the synaptic gap into the post synaptic neuron lowers, rather than raises, the level of excitation of the post synaptic, excitatory or inhibitory, neuron.

PART II MENTIONED HERE *

In our models of neural networks one excitatory neuron may receive simultaneously input signals from a number of different excitatory neurons, each of which contacts the neuron through one or several synapses each. Were we to assume that the intensity of the signal sent out by a post synaptic neuron is a linear function of the intensities of the input signals, then our model would be unable to account for the ability of the dog - demonstrated by Pavlov - to learn to discriminate (differentiate) in the conditioned salivary reflexes between the compound stimulus, that has say an auditory and a visual component on the one * hand, and on the other hand auditory and visual components. This compound stimulus will be discussed in our second paper.

In the meantime, we shall in any case assume hereafter that the output signal intensity of a post synaptic neuron is an S shaped function with the assumption of the sum extended over all synapses of the excitatory input of the individual synapses. If we designate this sum as "integrated excitatory input" then we may say that the intensity of the output signal of the post synaptic neuron is an S shaped function of the integrated excitatory input. We may, accordingly, say roughly , that the post synaptic neuron has something like a threshhold which the integrated input must exceed in order to evoke an output signal of a substantial intensity.....

We assume that there is a neuron F in the CNS, characterized by the set (f).... which preferentially responds to a stimulus represented by the stimulus of food which is intorudced into the mouth of the dog. We shall assume that the signal to which the neuron F responds is the <u>onset</u> of the stimulus "food in the mouth". As shown in Fig. 1, this neuron is connected through a synapse to an Effector neuron which innervates the salivary gland. This effector neuron is characterized by the set $(\bar{f})$, where $(\bar{f})$ denotes a set of specific membrane proteins which is complementary to the set (f). Because the overlap fraction of the neuron F and the Effector neuron is 1 the synapses which bridge these two neurons have a high efficacy and therefore by placing food into its mouth we may cause the dog to salivate.

Footnote: No neuron may contain in its cell membrane both a given specific membrane protein and its complementary counterpart, accordingly a transprintable neuron which contains a set of specific membrane proteins cannot acquire through being transprinted the complementary counterpart of any of the specific membrane proteins which it contained before it was transprinted.

We shall nottry to indicate in what manner a conditioned salivary response may be established to a compound stimulus which has a visual and auditory component. To this end we assume there is a neuron $A\bar{E}$ in the CNS and another neuron $V\bar{E}$, which respond preferentially to the auditory and to the visual component respectively, of the compound stimulus employed in the conditioning processes and that these two neurons are each connected through a synapse to many of the neurons E. The neuron $A\bar{E}$ and $V\bar{E}$ are characterized by the sets $(a)+(\bar{e})$ respectively.

We assume that the number of specific membrane proteins contained in the neurons $A\bar{E}$ and $V\bar{E}$, by (symbol) and (symbol) respectively, are large compared to the number of specific membrane proteins contained in the neurons E, designated by (symbol). Because the neurons F and the transprintable neurons E have have a zero overlap, signals emanating from the neuron F will not make an appreciable contribution to the excitation of any of the transprintable memory neurons E. Therefore, the firing of the neurons F will not cause any transprintable neuron E to fire, even when these neurons are not inhibited by the firing of the inhibitory neuron $\bar{E}^*$. In contrast to this..... to the neuron F the neurons $A\bar{E}$, as well as $V\bar{E}$ and the neurons E have an appreciable, even though small, overlap fraction.

We may assume that if either the neuron $A\bar{E}$ or $V\bar{E}$ or both fire, at a time when the neurons E are not inhibited by the firing of the inhibitory neuron $\bar{E}^*$, then one or more transprintable neurons E will be caused to fire. If this occurs, eith of two things will happen, depending on whether the neuron F does or does not fire simultaneously with one of the neurons AE or VE or both.

Incidentally, when on this occasion, the inter neuron $F\bar{I}$ fires, it will cause the derepressor network to send out a strong siganl because this network does not receive on this occasion a signal from the neuron F. Accordingly, on this occasion, one or more neurons E will be transprinted with the sets (a), or (v), or both, but none of them will be transprinted with the set (f). Therefore, if the dog is repeatedly exposed to the compound stimulus in such a fashion, i.e. without reinforcement then the number of neurons E which are transprinted with the sets (a) or (v) or both, but not with the set (f), will increase on each such occasion.....

If one wants to see whether higher mental functions can be expanded on the basis of our two postulates then one first has to invent the neural networks which might be adequate. Thus, if one wanted to explain the mental functions which man could perform but primates could not, one would have to invent the neural networks which the brain of man contains but the brain of the primates does not. Clearly, this would be no mean task/. At this time it is difficult to set a limit for the functions which suitable neural networks which operate on the basis of our two postulates might be capable of performing.

There is no reason to believe that information of the complexity corresponding to that of a simple sentence would need to tie down more than one transprintable neuron. If an individual were given every four seconds, 24 hours a day, over a period of 100 years, information of this complexity and if on each such occasion a transprintable neuron were tied down, then over a period of 100 years one would tie down just about 10^9 neurons. This is about 1/10 of the number of neurons believed to be contained in the human brain.

The orderliness of the natural code

According to the notions here adopted, we assume that two neurons in the CNS which preferentially respond to two different sensory stimuli.....

Postcript

If our two basic postulates are correct then it ought to be possible to devise a neural network which would fully mimic the conditioning of the autonomous nervous system. The network described by Fig. 1 represents a first attempt in this direction and we shall

discuss in our second paper to what extent it accounts for the phenomena of inhibition and the learning of differentiation (discrimination) between the related stimul8. If one wanted to see, however,whetherhigher mental functions could be explained on the basis of our two main postulates, then one would have to invent a neural network which is adequate. Thus, if one wanted to to explain the mental functions which man can perform but the primates cannot one might have to invent the neural networks which are contained in the brain of man but not in the brain of the primates.....

TITLE: PREPRINT OF AN ARTICLE SCHEDULED TO APPEAR IN THE JUNE ISSUE OF THE PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES - April 22, 1964.

On Memory and Recall* by Leo Szilard

The Salk Institute for Biological Studies
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*This work was supported by a research grant administered by the University of Chicago of the General Medical Division of the National Institutes of Health.