VOLUME XXIX

UNIVERSITY OF MINNESOTA

Medical Bulletin

OFFICIAL PUBLICATION OF THE
UNIVERSITY OF MINNESOTA HOSPITALS
THE MINNESOTA MEDICAL FOUNDATION
AND THE MINNESOTA MEDICAL ALUMNI
ASSOCIATION

IN THIS ISSUE:

Experimental Epilepsy

Isotope Circulation Studies

University of Minnesota Medical Bulletin

Editor
N. L. GAULT, JR., M.D.

Associate Editors

E. B. BROWN, Ph.D.
GILBERT S. CAMPBELL, M.D.
BYRON B. COCHRANE, M.D.
ROBERT B. HOWARD, M.D.
WILLIAM F. SCHERER, M.D.
WESLEY W. SPINK, M.D.
EUGENE L. STAPLES
ROBERT A. ULSTROM, M.D.

Copy Editor
ELLEN Y. SIEGELMAN

University of Minnesota Medical School

J. L. MORRILL, *President, University of Minnesota*
HAROLD S. DIEHL, M.D., *Dean, College of Medical Sciences*
ROBERT B. HOWARD, M.D., *Associate Dean*
N. L. GAULT, JR., M.D., *Assistant Dean*
H. MEAD CAVERT, M.D., *Assistant Dean*

University Hospitals

RAY M. AMBERG, *Director*

Minnesota Medical Foundation

WESLEY W. SPINK, M.D., *President*
R. S. YLVISAKER, M.D., *Vice-President*
N. L. GAULT, JR., M.D., *Secretary-Treasurer*

Minnesota Medical Alumni Association

VIRGIL J. P. LUNDQUIST, M.D., *President*
SHELDON M. LAGAARD, M.D., *First Vice-President*
CHARLES J. BECK, M.D., *Second Vice-President*
NEIL M. PALM, M.D., *Secretary*
JAMES C. MANKEY, M.D., *Treasurer*

UNIVERSITY OF MINNESOTA

Medical Bulletin

OFFICIAL PUBLICATION OF THE UNIVERSITY OF MINNESOTA HOSPITALS, MINNESOTA MEDICAL FOUNDATION, AND MINNESOTA MEDICAL ALUMNI ASSOCIATION

VOLUME XXIX *December 1, 1957* NUMBER 4

CONTENTS

Published semi-monthly from October 15 to June 15 at Minneapolis, Minnesota

Staff Meeting Report

Effects of Experimental Epilepsy on Conditioned Electrical Potentials*†

Frank Morrell, M.D.‡

Introduction

The purpose of this investigation was to study the effect of a chronic focal epileptogenic lesion on day-to-day cerebral function. In the past a great deal of work has been devoted to clinical and electrophyisological abnormalities associated with seizure states, both in human epileptic patients and in experimental animals. Moreover, the human electroencephalogram (EEG) taken in periods between seizures has been studied quite thoroughly, and a more or less clear pattern of abnormality has been noted.[10,11,15,16] However, surprisingly little attention has been devoted to the functional correlates of these inter-seizure electrographic disturbances.

Clinically it is well known that patients with convulsive disorders often show various degrees of mental impairment and behavioral abnormality in the interval between seizures. Children frequently have considerable difficulty in school, and despite many exceptions there is an overall correlation between the degree of these disturbances and the frequency and severity of the seizures.[8] In an effort to refine our knowledge of the nature of these disturbances a large literature on psychological testing in epileptic patients has accumulated.[6,12,19,27] Evidence has been presented showing clear intellectual deterioration[1,17] and prominent memory deficits.[3,4,9] Although some support has been found for the distinction between large groups of organic or symptomatic epileptics and the so-called idiopathic variety, more recent work[6] has shown much greater differences between all epileptics and non-epileptics. This study revealed significant evidence of "organicity" among so-called idiopathic epileptics.

Except for this gross breakdown into broad diagnostic categories, there has been virtually no work related to the specific location within

*This report was given at the Staff Meeting of the University of Minnesota Hospitals on November 15, 1957.

†These and immediately related studies have been supported by the Teagle Foundation, the Graduate Faculty of the University of Minnesota, and the USPHS (B-1185).

‡Assistant Professor, Division of Neurology

the brain of the discharging lesions and the resultant disturbance in cortical function. With the advent in 1942 of the alumina-cream technique,[18] however, it became possible to study experimentally-induced chronic focal epilepsy in animals. Behavioral observations were carried out by Pribram,[26] Chow and Obrist,[5] and Henry and Pribram[14] on monkeys with alumina-cream lesions in the visual and in the frontal cortex. All studies involved retention of previously learned visual discriminations or delayed responses; none were concerned with learning of new material after an epileptogenic focus had been established. Nevertheless, Pribram[26] was able to demonstrate transient impairment in one monkey's performance on delayed-response tests and in visual discrimination following seizures induced by application of alumina-cream to the prefrontal cortex. Chow and Obrist[5] could not find any deficit in retention of visual discriminations in three monkeys with bilateral prestriated cortex disc placements. As the latter authors point out, the EEG's were not taken during the period of actual testing, and therefore it is not known whether the lesion was actually firing at that instant. Henry and Pribram[14] noted some lability in performance in monkeys with alumina-cream lesions but found that they performed at or near criterion levels on visual discrimination in delayed alternation problems even within minutes after a major seizure. Morrell[20,21] also noted no impairment of conditioning performance immediately following petit mal attack with unconsciousness. It is quite likely, however, that these negative findings reflect our inability to measure the particular function of a given area in the instantaneous presence of a discharging lesion in that area. A generalized seizure may affect all regions equally, or—as in petit mal—it may affect the cortex only secondarily. The recovery time required to permit criterion function is also unknown.

Clearly, what was needed was a means of investigating functions in a specific area with simultaneous recordings of the electrical activity in the same region. In order to examine further the intimate relationship between the specifically epileptiform quality of a lesion and disturbance in cortical function, a technique was developed by which the EEG tracing and the formation of conditioned connections could be simultaneously observed.

The conditioned connection, or "temporary" connection, has been defined by Pavlov as the link that occurs, for example, during the establishment of a conditioned salivary secretion in response to a nonspecific stimulus between the auditory "center" and the center responding to the unconditioned stimulus, i. e., the "food center." Since

stimulation of the food center results normally in salivation, this same response may be produced by a stimulus which in turn activates the food center. A connection so formed is, in the true sense of Pavlov's term, conditional. It is formed by the chance or experimental juxtaposition in time of two stimuli, one of which always (innately) results in a given response. The second stimulus acquires the ability to elicit this response and maintains this ability only as long as it is more or less persistently related to the original or unconditioned stimulus. Such a reflex is therefore conditional upon the continuation of a set of circumstances that initially produced the temporary linkage. The survival value of such a system is quite obvious: The temporary connections is the necessary, though not perhaps the sufficient, substrate of learning. Its conditional character provides for the equally important "unlearning," the dropping out of reactions no longer suitable to the situation. This temporary connection, therefore, is not an inborn neural link but an adaptive acquired coupling, responsive both in its establishment and its maintenance to the requirements of the environment. As the basis of the organization of behavior,[13,7,28] it probably participates in some form in all cerebral activity.

The existence of conditioning or of temporary connection can be investigated in a wide variety of behavioral situations by means of a diversity of stimulus-response measures. In recent years a technique has been devised for conditioning cerebral activity itself. This technique derives from the observation that the normal resting occipital rhythm responds to visual stimulus by depression in amplitude and increase in background frequency. This is the so-called "blocking" reaction. Ordinarily the occipital alpha rhythm does not "block" in response to stimulation from other sensory modalities, provided these are not of sufficient intensity to be startling. For example, a low intensity tone stimulus ordinarily will not produce a blocking of the alpha rhythm, but if this ineffective tone is repeatedly paired with an effective light stimulus, the blocking of the alpha rhythm soon occurs in response to the tone even when the light stimulus is omitted. Once the auditory stimulus has acquired the attribute of producing alpha blocking, a temporary connection must be assumed to have been formed between the auditory receiving area and the visual area (or the area responsible for generating the alpha rhythms). The capacity to form such linkages presumably depends upon the functional integrity not only of the area responsive to the unconditioned stimulus (in this case, the visual receiving area), but also of the sensory receiving area responsive to the conditioned stimulus. This technique

therefore gives a quantitative means of estimating the effect of discharging lesions on the functional integrity of sensory receiving areas. Furthermore, since the responses are those of the cortical rhythms themselves, the technique provides for simultaneous evaluation of the degree of activity and the localization of epileptogenic discharges.

Method and Materials

For these studies monkeys (*macacus rhesus*) were used, and the parameters of conditioning of the alpha rhythm were measured in eight normal animals as a preliminary to the study of the effects of epileptic lesions. The experimental procedure consisted in placing an alert unanesthetized monkey in a soundproof room with his head fixed in a comfortable holder. A photic stimulator with no auditory component was placed 1½ feet in front of the monkey's eyes. This photic stimulator provided the intermittent retinal illumination that served as the unconditioned stimulus. Alpha blocking was the unconditioned response. The conditioned stimuli were 1) pure tones of 500 or 200 cycles/sec.; 2) touch applied to right or left foot; and 3) increase or decrease in background illumination of the experimental room. These conditioned stimuli were presented two or three seconds before the unconditioned stimulus. The latter then came on and overlapped the conditioned stimulus for three to four seconds, after which both stimuli were shut off. Stimuli were delivered by hand, the key simultaneously activating a circuit to a signal marker on the EEG tracing; both simple and differential tracing procedures were used. The EEG examiner and the signal controls were outside the room.

Examples of the kinds of response observed may be seen in Figure 1, which shows the EEG of a normal, very relaxed but alert unanesthetized monkey. The signal line has a downward tip at the onset and an upward tip at the cessation of the stimuli. A of Figure 1 illustrates three successive presentations of a 200 cycles/sec. tone before conditioning has begun; there is no cortical response to the tone alone. B shows the first of the paired trials with no response to the tone but with clear blocking to the flickering light, which is the unconditioned stimulus (second signal pip). In C, Figure 1, the blocking appears in response to the tone, i. e., is conditioned, but note that the alpha suppression is present in all head regions as a generalized process. If the paired trials are continued, a contraction of the process takes place, manifested in localization of the blocking to the occipital regions (see D), and the frontal areas cease to re-

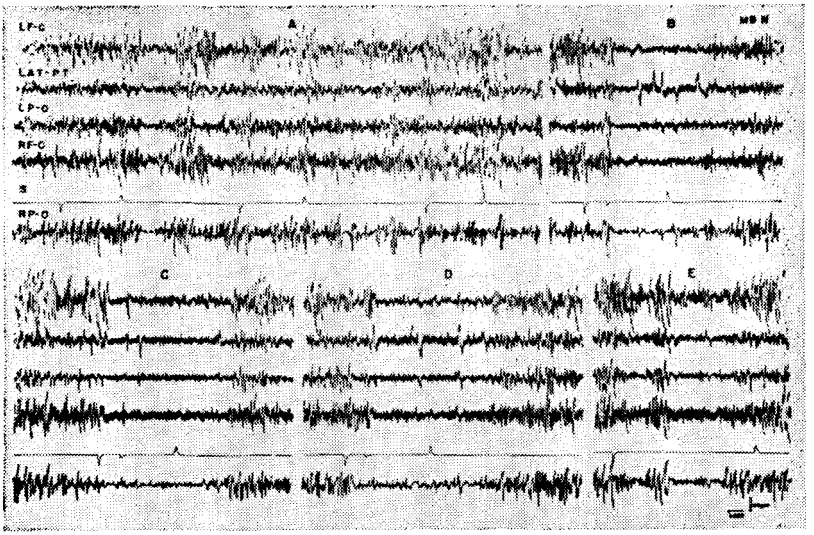

Fig. 1. Normal monkey, very relaxed, slightly drowsy but not asleep. Sequence of conditioning to tone. *A:* Lack of effect of tone stimuli (500 c/sec.) before conditioning and after adaptation has taken place. *B:* First conditioning trial in which no response is seen to the tone (first pip in signal line) but the expected blocking occurs in response to the UCS-flicker at 500/sec., (second pip on signal line). The third pip is the "off" signal for both tone and flicker. This convention is followed throughout all figures. *C:* First stage in the development of conditioned blocking. Note that the desynchronization appears, in response to the tone (CS), from all head regions. *D:* Final stage of conditioning when desynchronization is restricted to the occipital zones. *E:* Response to tone stimulus when presented without reinforcement after conditioning. Note biphasic blocking, one immediate and one again shortly after flicker would have appeared.

spond at all. This was the final and most stable form of the electrocortical conditioned reflex. E indicates blocking to the tone alone after conditioning.

There were two phases then to the conditioning procedure. Initially there was no response to the conditioned stimulus and a clear unequivocal blocking to the unconditioned stimulus. As paired trials were presented, the conditioned response appeared first as a diffuse desynchronization seen in all head regions (Phase 1). If trials were continued beyond this point, the anterior head regions then ceased to respond to the conditioned stimulus, but the desynchronization persisted in the occipital derivations (Phase 2). This latter response was sufficiently stable to be used as a measure of the achievement of the conditioned response, or temporary connection.

Figure 2 illustrates the same kinds of conditioned response to a

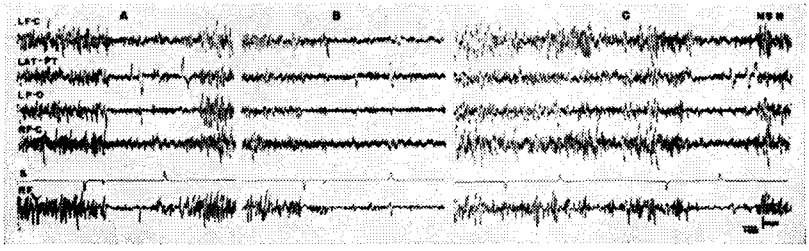

Fig. 2. Same animal as Fig. 1. Sequence of conditioning to touch. *A:* First conditioning trial showing response to UCS (flicker 500/sec.) but none to CS (touch to right leg). *B:* Fully developed CR to touch with blocking localized to occipital regions. *C:* Differential response to touch after conditioning. The first stimulus (touch to left leg) has been negatively conditioned, i. e., never paired with flicker, while the second stimulus (touch to right leg) is that used in B and has been reinforced.

touch stimulus. In this figure, A is the first of the paired trials showing no response to the touch but the typical blocking to the light signal. B indicates the well-established localized blocking response to touch. (In this instance touch to the right leg was always paired with the light stimulus, but touch to the left leg was repeatedly presented without pairing with the light.) From C, Figure 2, it is evident that following this series of trials the negatively conditioned stimulus (the first of the signals) does not cause alpha blocking, while the positively conditioned stimulus (second stimulation) does. The fact that both these conditioned stimuli are of sufficient intensity to reach cortical levels is evident in Figure 3, which again illustrates a differential conditioned response to touch. A of Figure 3 shows the positively conditioned touch to the right leg reinforced by the flickering light. (If the flicker frequency of the light is in the range of 5-12/sec., an occipital "driving" occurs, instead of the blocking response as an unconditioned stimulus. The conditioned blocking response persists, however.) A typical conditioned blocking is seen. Figure 3,B illustrates the presentation of the negative touch, which in this case elicits a marked evoked potential from cortical derivations but does not produce the conditioned blocking response. It is clear then that the negative stimulus is reaching cortical levels but has not acquired the alpha-inhibiting properties.

Table 1 indicates the number of trials required to establish these conditioned responses in the group of normal controls. The criterion for simple conditioning was the first trial with four successive positive responses; for differential conditioning, the first trial in a series of nine out of ten correct responses. Figures are divided into those for

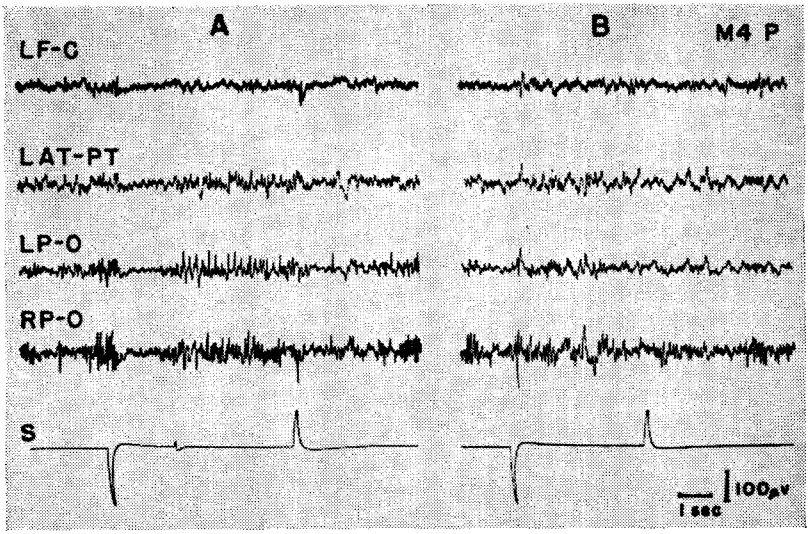

Fig. 3. Differential conditioned response to touch. *A:* Localized desynchronization to positively conditioned touch (right leg). In this experiment the unconditioned photic driving response appears poor because the flicker is at 5/sec. and the response is a mixture of 5 and 10 c/sec. frequencies. *B:* No desynchronization to the negatively conditioned touch (left leg), despite the fact that a cortical evoked potential can be seen in response to the stimulus.

simple conditioning and those for differential conditioning. Generally speaking, it is clear that conditioned responses are established most quickly to touch and to tone and somewhat less quickly to light stimulation. Differential conditioning requires approximately three times as many trials to establish as does simple conditioning. The mean for this group of animals is shown in the last line. Scores for one animal (M8), which was ill and died shortly after beginning the trials, were far above the standard deviation for the rest of the group and do not represent a normal finding. Although the "mean" in the first two columns includes this animal, a separate "mean" in parentheses is that calculated without M8. Number of trials required to establish conditioning was the basic measurement used to determine the impairment of physiologic function which resulted from the presence of chronic focal epileptogenic lesions in primary sensory receiving areas and in "association" cortex.

Our experimental series consisted of a total of 15 macaque monkeys. Eight animals were studied prior to operation and served as controls regarding the normal development, time course, and latency

TABLE 1

NORMAL CONTROLS: NUMBER OF TRIALS TO CONDITION

Animal	Simple			Differential		
	Tone	*Touch*	*Light*	*Tone*	*Touch*	*Light*
M8	31	25				
M9	9	7	12	28	26	39
M10	7	8	12	25	21	36
M11	6	5	11	19	21	31
M12	7	11	15	21	20	32
M13	9	5	11	22	14	38
M14	14	10	17	30	19	34
M15	6	5	15	21	20	34
Mean Normal	11.1 (8.2)	9.5 (7.2)	13.2	23.7	20.1	34.8

of the conditioned alpha response. Two of these were later subjected to craniotomy and placement of alumina-cream discs. In addition to these two, alumina-cream lesions were made in seven monkeys which had not had any testing prior to the onset of seizures. One of the normal monkeys was first tested with each modality and then subjected to "blank" craniotomy. This consisted of opening skull and dura, recording evoked auditory potentials, and closing without placement of alumina cream. Of the nine epileptic animals, six had lesions in the primary sensory cortex: two of them with lesions in the auditory cortex (one unilateral and one bilateral), two with lesions in the post-central leg area (both unilateral, left-sided), and two with left occipital placements. These sensory areas were identified by recording evoked potentials to the appropriate stimulus and placing the disc over the area of maximum evoked response. Of the other three epileptic animals, two had 0.1 cc. of alumina cream placed stereotactically in the left amygdaloid hippocampal region, and one had a left frontal placement anterior to the motor cortex. Thus unilateral lesions were produced in all but one monkey, and only one sensory receiving area was involved in any one animal. There was no post-operative physical defect.

Results

Between four and six months after disc placement, electrographic seizure foci were well developed in all animals. The two with amygdala injections had spontaneous seizures consisting of staring, contraversion, and contralateral facial twitching. Clinical seizures could be induced in the other animals only with prodding or by administration of metrazol. Testing in the epileptic animals was begun when serial

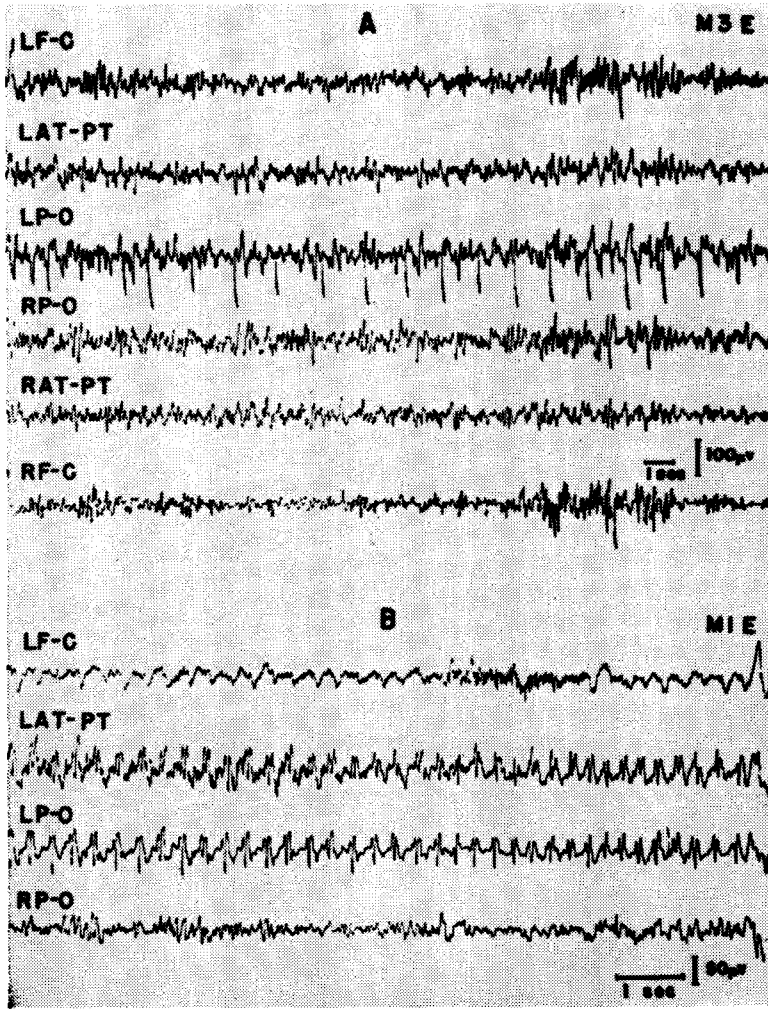

Fig. 4. Typical electrographic focus produced by local application of aluminum hydroxide. *A:* Sharply localized left occipital focus, actively firing but without spread to surrounding areas. *B:* Another animal with left temporal disc placement. At the beginning of a clinical seizure the EEG shows active spiking in left temporal and parietal regions with spread of slow waves, but not spikes, to frontal area. The right hemisphere at this moment is completely normal.

EEG's showed clear foci and when clinical seizures could be provoked.

Figure 4 indicates the kind of electrographic focus induced in two animals. A reveals a sharply localized left occipital spike discharge, not extending to other head regions on the same or opposite hemisphere. B shows the localized seizure discharge from a left superior temporal gyrus placement. The spike activity extends to the parietal region on the same side but not to the opposite hemiphere.

Table 2 discloses the results in number of trials required to establish a stable conditioned response, for both simple and differential forms and for each modality, in each of the epileptic animals. The mean of the control series is shown on the last line.

All animals except M2 and M5 showed a deficit when compared with the normal. Both animals with temporal placements had impaired conditioning to tone. Both monkeys with occipital placement showed deficit to light conditioning. One with post-central leg area placement had impairment to touch. Somewhat to our surprise, the animals with amygdaloid lesions revealed marked deficits to both tone and light, and one of them exhibited impairment to all three modalities.

Note that in all animals modalities not involved by the focus showed no deficit when compared with normal. Therefore it was possible to use each animal as his own control.

Our results indicated that a chronically discharging lesion involving a specific sensory representation, caused impairment of the conditioned alpha response to stimuli to that specific sense. Except in the animals with the amygdala lesions, only the modality implicated by the epileptogenic focus showed impairment. Discharging lesions of

TABLE 2

EPILEPTIC ANIMALS: NUMBER OF TRIALS TO CONDITION

Area of Lesion	*Simple*			*Differential*		
	Tone	*Touch*	*Light*	*Tone*	*Touch*	*Light*
Left Temporal (M1)	81	7	13	400nc	28	41
Left Post-Central (M2)	4	10	7	24	34	15
Left Occipital (M3)	9	8	112	18	16	400nc
Bilateral Temporal (M4)	200nc	3	8	400nc	21	31
Left Frontal (M5)	3	4	11	21	12	29
Left Amygdaloid (M6)	70	25	143	400nc	400nc	400nc
Left Amygdaloid (M7)	57	7	110	400nc	24	400nc
Left Occipital (M10)	9	7	200nc	27	31	400nc
Left Post-Central (M13)	10	200nc	13	29	400nc	33
Mean Normal	11.1 (8.2)	9.5 (7.2)	13.2	23.7	20.1	34.8

nc = not conditioned

the amygdala and mesial surface of temporal lobe resulted in impairment to both visual and auditory stimuli, with vision most involved. The monkey with a frontal lobe focus showed no deficit on any test-

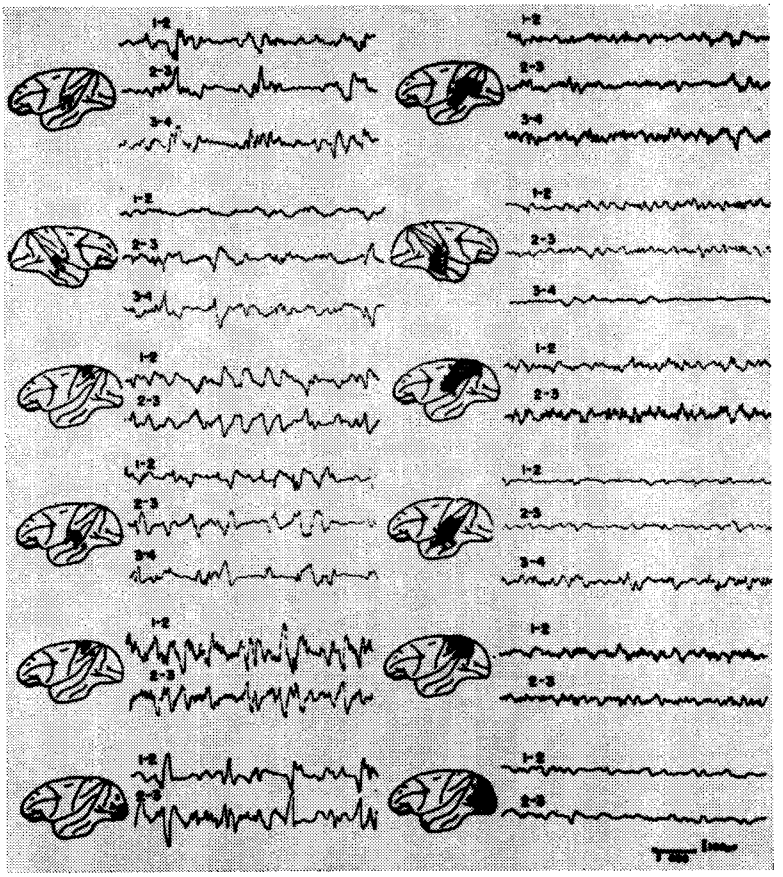

Fig. 5. Disc placements, electrocorticograms, and reconstructions after ablation for monkeys with lesions of the primary sensory receiving area. To the left is shown the disc placement as confirmed at the second operation and the electrocorticographic focus. Numbers on the diagram refer to electrode positions and correspond to those designating the tracings. The right side of the figure shows the total extent of ablation, as reconstructed from serial sections after sacrifice, together with the final electrocorticogram. The first two tracings are the left and right sides of the animal (M4) with bilateral temporal lobe lesion. Next is M13 with left post-central ablation. The fourth tracing is that of the unilateral temporal (M1), the fifth is another post-central (M2), and sixth is an occipital lobe placement (M10)

ing, and one of the animals with post-central disc placement also showed no impairment.

How then was this disturbance in formation of conditioned connections brought about? Was it simply due to destruction of cortical tissue by the reactive scar, or was it related to the specifically epileptogenic (discharging) quality of the lesion? To investigate this aspect of the problem we subjected all monkeys to reoperation and, under electrocorticographic control, to subpial resection of all actively firing tissue.

Figure 5 demonstrates the electrocorticograms of all animals with primary receiving area lesions. The diagrams on the left show the disc placement as confirmed at reoperation and those on the right show the total extent of ablation as reconstructed after sacrifice from serial sections of the brain (method of Blum, Chow, and Pribram). It is quite clear that the spike foci present before ablation have completely disappeared. In all cases the disappearance of electrographic abnormality was confirmed by postoperative serial EEG's. It will be noted that only one animal with an occipital ablation is shown; the other had died of intercurrent disease.

Figure 6 contains photographs of the brains of the animals with the primary sensory area lesions just shown. The ablated area is dotted. Note in monkey M2 that in addition to an ablated area there

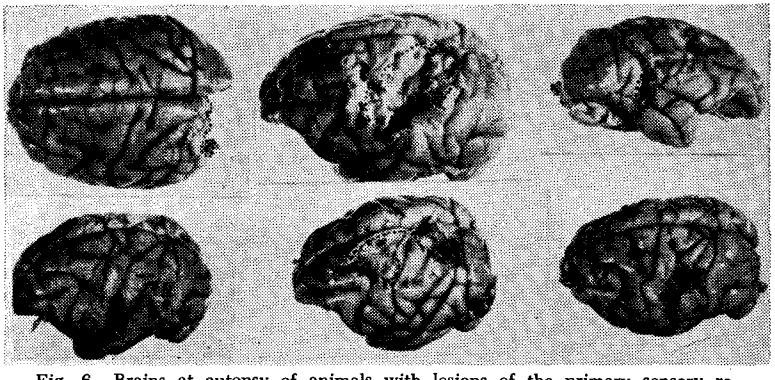

Fig. 6. Brains at autopsy of animals with lesions of the primary sensory receiving area. Dotted lines mark the limits of excision. Upper row includes, from left to right, the animals with the following ablations: occipital (M10), post-central leg area (M13), and right hemisphere of the bilateral auditory (M4). Lower row includes ablations of the unilateral auditory (M1), the second post-central leg area, (M2), and the left hemisphere of the bilateral auditory. In monkey M2 an area of infarction anterior to the rolandic fissure was found at autopsy; this is outlined by a broken line. The anterior depression near the vertex on the right hemisphere of M4 is an artifact of the autopsy procedure.

is an infarction of the superior portion of the precentral gyrus; this will be referred to again in the discussion of results.

Successful ablation of the focus was also accomplished in the monkey with a frontal lesion (Fig. 7) and in one of the two which had received the amygdala placements. (In the other with an amygdaloid lesion we were unable despite two operative attempts to remove completely the discharging tissue. This was the only monkey that continued to have seizures after the ablation.)

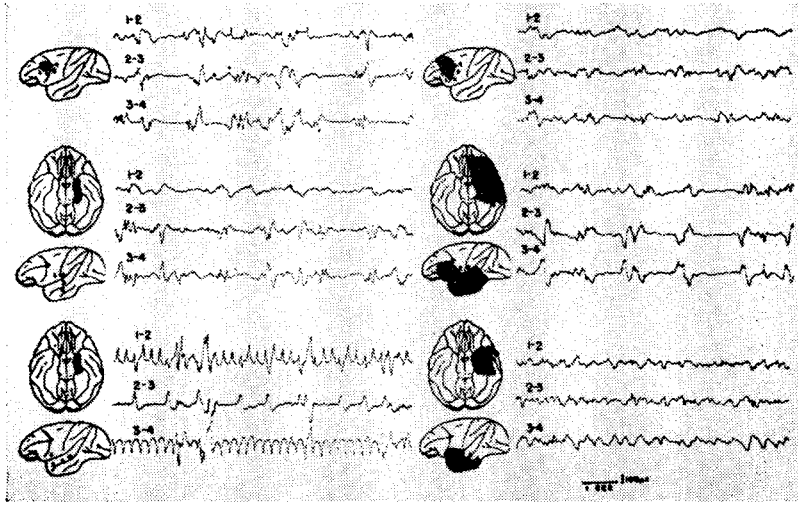

Fig. 7. Disc placements, electrocorticograms, and reconstructions after ablation in animals with lesions of the "association" cortex. Same convention as in Fig. 4. Upper tracing is from the monkey with the frontal excision (M5). Middle tracing is from a monkey with an ablation of the amygdaloid-hippocampal area (M6), and lower tracing is from the other monkey with ablation of the amygdaloid-hippocampal area (M7). Note that despite very extensive extirpation, an electrographic focus persists in M6. In the latter two animals, the aluminum hydroxide was placed stereotactically and the site rechecked at operation for removal of the focus. The ink spot represents the surgeon's estimate of the maximum extent of reactive scarring, and is therefore not exact, but we believe it is a fairly accurate approximation.

Figure 8 shows the brain of these two animals. Despite the extensive ablation in M6 (left hand side of figure), seizures continued.

Four to six weeks following excision of discs and epileptogenic foci, the latter confirmed by serial EEG's, the monkeys were again subjected to the conditioning procedure. Now let us compare results in terms of trials required to condition before and after ablation of epileptic foci: The first two animals in Table 3 had lesions of the

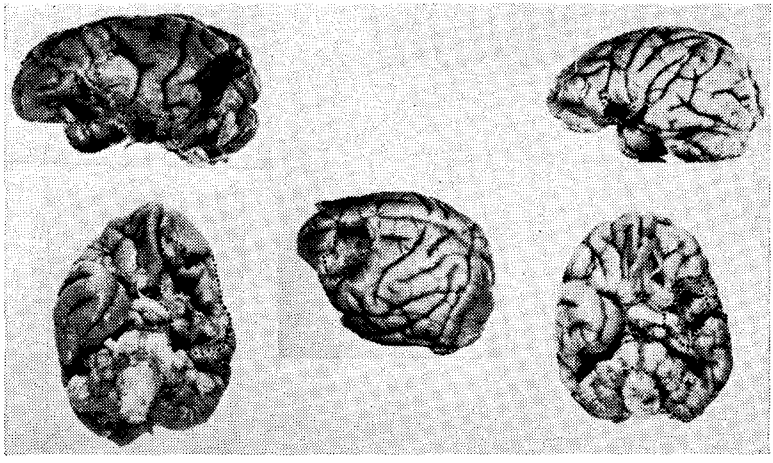

Fig. 8. Brains at autopsy of animals with lesions of the "association" cortex. Dotted lines mark the limits of excision. At the left are lateral and basal views of the temporal and frontal opercular removal (M6, amygdaloid-hippocampal implantation); center is the frontal ablation; and on right are lateral and basal views of the second animal with left temporal removal (M7, amygdaloid-hippocampal implantation). Note the extensive ablation in M6. Despite this, seizures, both clinical and electrographic, continued. The gap in the occipital region of M6 is an artifact of the autopsy procedure.

auditory cortex. Both, when epileptic, showed impairment on simple and differential conditioning to tone, no deficit when tested with touch or light. After the excision these animals showed marked improvement, returning almost to normal (except that the animal which had had bilateral lesions continued to show impairment to differential conditioning). The monkey with the left occipital disc placement returned to normal after the excision.

The two animals with left side post-central leg area lesions demonstrate a further interesting result. The first, M13, had a deficit to touch on both right and left leg, although the lesion was unilateral. There was a return to normal on both sides following excision of the focus. The next, M2, had no deficit as an epileptic monkey but following excision was hemiparetic and did show a deficit to touch conditioning on the right side only. This was the animal with an infarcted pre-central motor cortex and was the only one made worse by excision. Thus it appears that the discharging lesion, even though unilateral, damages the sensory apparatus bilaterally, whereas a deficit produced by ablation, when present, is confined to the representation in the ablated area. Furthermore, the motor cortex involvement is

TABLE 3

TRIALS TO CONDITION BEFORE AND AFTER ABLATION OF EPILEPTIC FOCUS

		Simple Conditioning				Differential Conditioning			
		Tone	Touch		Light	Tone	Touch		Light
Left Temporal (M1)	Epileptic	81	7		13	400nc	28		41
	Post Excision	11	7		9	62	28		34
Bilateral Temporal (M4)	Epileptic	200nc	3		8	400nc	21		31
	Post Excision	15	6		10	230	16		49
Left Occipital (M10)	Epileptic	9	7		200nc	27	31		400nc
	Post Excision	8	6		15	16	20		42
			Rt.	Left			Rt.	Left	
Left Post-central (M13)	Epileptic	10	-200nc	112	13	29	400nc	400nc	33
	Post Excision	12	18	7	15	25	31	22	19
Left Post-central (M2)	Epileptic	4	10	6	7	24	34		15
	Post Excision	9	78	6	9	17	400nc	24	24

nc=not conditioned

probably a critical factor here because M13 actually had a much larger post-central excision than M2 had.

Table 4 is the same comparison in monkeys with lesions of the so-called association cortex. Those with the left frontal placement showed no impairment either before or after the excision. The two monkeys with lesions in the region of the amygdala revealed the widespread impairment noted before. After the excision both animals were hemiparetic and hemianopic, but in M7 seizures ceased, and in M6 they persisted. The difference between the two animals in required

TABLE 4

TRIALS TO CONDITION BEFORE AND AFTER ABLATION OF EPILEPTIC FOCUS

		Simple Conditioning			Differential Conditioning		
		Tone	Touch	Light	Tone	Touch	Light
Left Frontal (M5)	Epileptic	3	4	11	21	12	29
	Post Excision	10	4	12	20	17	35
Left Amygdaloid Complex (M6)	Epileptic	70	25	143	400nc	400nc	400nc
	Post Excision	107	5	200nc	400nc	400nc	400nc
Left Amygdaloid Complex (M7)	Epileptic	57	7	110	420nc	24	400nc
	Post Excision	8	5	84	48	18	227
Blank Craniotomy (M11)	1st Operation	5	5	9	31	22	39
	2nd Operation	14	9	18	20	16	21

nc=not conditioned

trials to condition is clear: M6 had not improved; M7 had improved considerably. Finally, response of the animal with the blank craniotomy is shown, indicating that the operative procedures alone do not significantly alter conditioning results. These results were somewhat surprising, since the evidence of impairment conflicted with the results of a previous study that the author made with Dr. Torres in which no impairment was found in the conditioned alpha reaction in man immediately following a major seizure. Figure 9 demonstrates an experiment from that series. The heavy vertical line represents the onset of a brief complex tone (whistle) to which alpha blocking had been previously conditioned. This was forty minutes after a major seizure with unconsciousness and bilateral tonic and clonic phases. Though the cortical pattern had returned to normal, the patient appeared dazed and his motor reaction time was prolonged to 1.2 seconds (measured to the blink artifact in the frontal leads). Nevertheless, the conditioned alpha response was prompt and accurate. Clearly, in this case the seizure had no prolonged effect on temporary connections. Of course, no testing could be done during the actual discharge.

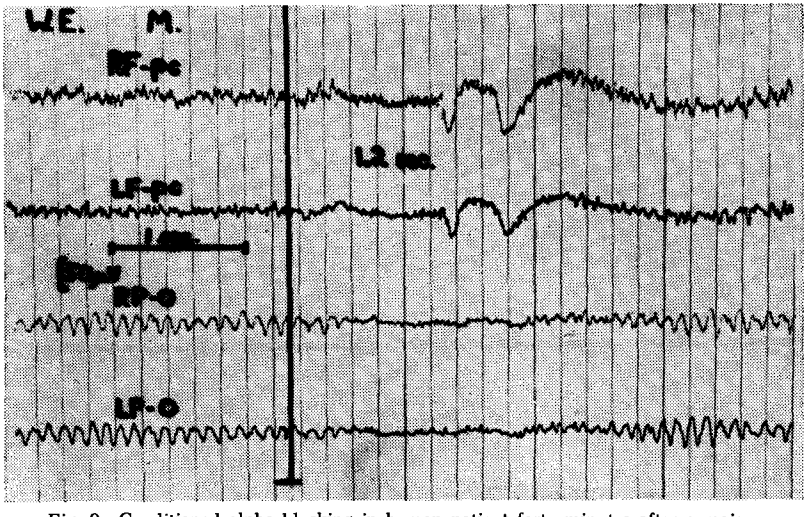

Fig. 9. Conditioned alpha blocking in human patient forty minutes after a major seizure. Heavy vertical line indicates brief complex tone (whistle) to which alpha blocking had been previously conditioned. The "blink artifact" seen in the frontal leads is the requested motor response to the same tone. The motor reaction is prolonged to 1.2 seconds, while the conditioned alpha blocking is prompt and has a normal latency. At this moment, although cortical rhythms had returned to normal, patient seemed confused and speech was slowed.

The small and well-circumscribed focus in animal M2 provided the necessary clarifying evidence and also demonstrated a unique advantage of the investigative method used. As noted before, the expected impairment to touch stimuli in this animal did not appear. Temporary connections were formed very promptly. A of Figure 10 demonstrates the conditioned blocking reaction to touch (right leg). As the paired stimuli were being presented, it was noted that the left parietal spike focus became intermittently and sporadically active, sometimes with spread to opposite hemisphere (B), sometimes without (E). A well-established conditioned connection, such as that

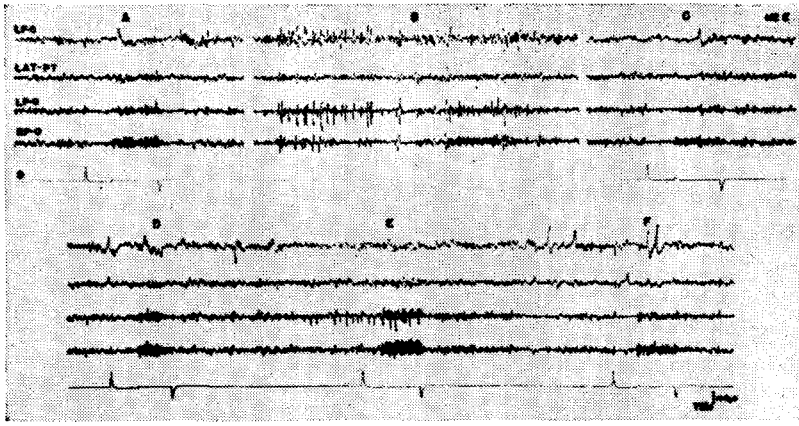

Fig. 10. Effect of active discharge in the left post-central leg area on temporary connection to touch (right leg): *A:* Established conditioned blocking to touch stimulus during period when focus is quiescent. *B:* Next stimulus pair is delivered during burst of spikes spreading from left parietal focus. The conditioned connection is completely wiped out, while the unconditioned (photic driving) remains intact. *C:* Next stimulus pair comes when the epileptiform discharge has subsided. Note full restoration of conditioned blocking response. The three trials are consecutive with an intertrial interval of one minute. *D, E,* and *F* are consecutive trials with a twenty-second intertrial interval. A minor spike discharge, showing no spread in the same or to the opposite hemisphere, appeared at *E.* This was sufficient to wipe out the conditioned connection (blocking) but not the unconditioned (photic driving). Twenty seconds after cessation of the discharge, the conditioned blocking is fully restored (*F*). Each stimulus pair indicates touch to right leg reinforced by flicker.

seen in A, when the focus is quiescent, was suddenly and completely wiped out when the paired stimuli were presented in the midst of a spike discharge (B). Only the conditioned connection was affected, the unconditioned remaining intact. The brief burst of spiking then subsided, and the very next trial (less than one minute later) revealed an intact conditioned connection. D, E, and F form another continu-

ous sequence showing an established conditioned blocking, the wiping out of the conditioned connection by a rather minor spike discharge, and prompt and full restoration of the conditioned connection when the spike activity ceases. The integrity of the temporary connection thus depends upon whether or not the hypersynchronous discharge is firing into the circuit at the very instant the connection is being made. It is not surprising, therefore, that Morrell[20,21] and Henry and Pribram[14] found retention of a conditioned reflex or a learned discrimination "within minutes" after a generalized seizure.

We now have a concrete demonstration of the extremely intimate relationship between the paroxysmal discharge and the making of a temporary connection. Even in a clinically epileptic animal, if the focus was only sporadically firing, the making of a conditioned linkage was easily accomplished in the intervals between such firing and was defective only during the actual discharge. Furthermore, the effect may be exquisitely discrete and localized, damaging only that particular linkage which requires the cortical region involved in the electrographic seizure. Figure 11 demonstrates clearly that a conditioned connection in one area may remain intact even during active discharge in another area. This shows the response of an animal with a very

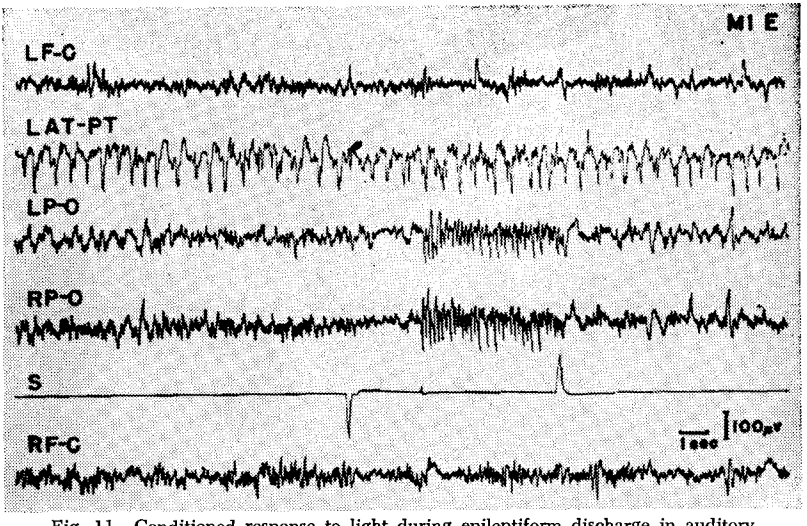

Fig. 11. Conditioned response to light during epileptiform discharge in auditory area. Signals indicate light stimulus (CS) reinforced by flicker (UCS). The conditioned blocking response to light is still present (slightly diminished) during a discharge strictly localized to temporal regions. The conditioned response to an acoustic stimulus was completely abolished during this same period.

active left temporal lobe focus. A conditioned blocking response to light was still present (slightly impaired) during active firing as long as the discharge remained confined to the temporal region. (Note that the parietal and occipital leads were free of spike activity.) The conditioned response to a tone, however, was completely abolished during this same period.

It may be important to note that contrast between the supreme sensitivity of the conditioned connection and the relative insensitivity of the unconditioned connection (photic driving) to the effects of paroxysmal epileptogenic discharge.

Summary and Conclusions

Of the eight animals subjected to excision of the discharging lesion, five displayed marked improvement in ability to form a conditioned alpha response via the previously impaired sensory modality. Of the three showing no improvement, one was the animal with the frontal excision which disclosed no change; one had previously been impaired, but following the post-central excision had a mild deficit to conditioning to touch stimulus on right leg; and one had had an excision of the amygdala placement in which not all of the abnormally discharging tissue had been removed.

The fact that unilateral ablation in animals does not in itself result in a learning deficit is in agreement with a large body of previous experimental work. In addition, it seems evident that simple destruction of cortical tissue or replacement by the cicatrix cannot account for the effect, since in the removal of the focus considerably more cortical tissue was ablated than was actually involved in the meningocerebral cicatrix. It must be assumed that it is the specifically discharging quality of the lesion that produces this result. The constantly firing cells exert a more far-reaching influence, functionally paralyzing either the remaining viable cortical tissue or the subcortical integrative systems or both. These investigations provide an experimental demonstration of the nociferous influence of the damaged cortex. Ablation of such a focus allows normal function of remaining tissue in the same or opposite hemiphere sufficient to cope with the task of establishing conditioned connections.

These results have suggested applications to human disease, especially to post-traumatic and postinfectious epilepsy where the source of the seizure discharge is the tissue surrounding a gliotic and connective tissue scar. Surgical removal of the abnormal tissue may improve the patient not only in terms of seizure control but also in

the ability to establish adaptive responses to changing environmental signals. The lack of this ability may explain many of the behavior disorders and much of the mental impairment seen in many patients in periods between convulsive seizures. The observation that more widespread disturbances occurred in animals with amygdala-hippocampal lesions is also consistent with the fact that patients with psychomotor or temporal lobe epilepsy, in which the anatomical and electrographic lesion involves these entoretinal nuclei, are the most likely to exhibit behavioral, intellectual, and psychological disturbances.

REFERENCES

1. Arieff, A. J., and Yacorzynski, G. K.: Deterioration of patients with organic epilepsy. J. Nerv. Ment. Dis. 96:47-55, 1942.
2. Blum, J. S., Chow, K. L., and Pribram, K. H.: A behavioral analysis of the organization of the parieto-temporo-preoccipital cortex. J. Comp. Neurol. 93:53-100, 1950.
3. Collins, A. L.: Psychometric records of institutionalized epileptics. J. Psychol. 11:359-370, 1941.
4. Collins, A. L., Atwell, C. R., and Moore, M.: Stanford-Binet response patterns in epileptics. Am. J. Ortho. 8:51-63, 1938.
5. Chow, K. L., and Obrist, W. D.: EEG and behavioral changes on application of $AL(OH)_3$ cream on preoccipital cortex of monkeys. Arch. Neurol. Psychiat. 72: 80-87, 1954.
6. Deutsch, C. P.: Differences among epileptics and between epileptics and non-epileptics in terms of some memory and learning variables. Arch. Neurol. Psychiat. 70:474-482, 1953.
7. Eccles, J. C.: The Neurophysiological Basis of Mind. London, Oxford Press, 1953.
8. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence. Springfield, Illinois, Charles C Thomas, Third Edition, 1952.
9. Fox, J. T.: The response of epileptic children to mental and educational tests. Brit. J. M. Psychol. 4:235-248, 1924.
10. Gibbs, F. A., Davis, H., and Lennox, W. G.: The electroencephalogram in epilepsy and in conditions of impaired consciousness. Arch. Neurol. Psychiat. 34:1113-1148, 1935.
11. Gibbs, F. A., Gibbs, E. L., and Lennox, W. G.: Electroencephalographic classification of epileptic patients and control subjects. Arch. Neurol. Psychiat. 50:111-128, 1943.
12. Harrower-Erickson, M. R.: Psychological Studies of Patients with Epileptic Seizures, in Penfield and Erickson: Epilepsy and Cerebral Localization. Springfield, Illinois, Charles C Thomas, 1941, pp. 546-574.
13. Hebb, D. O.: The Organization of Behavior. New York, John Wiley and Sons, 1949.
14. Henry, C. E., and Pribram, K. H.: Effect of aluminum hydroxide cream implantation in cortex of monkey on EEG and behavior performance. EEG Clin. Neurophysiol. 6:693-694, 1954.
15. Jasper, H. H., and Kershman, J.: Electroencephalographic classification of the epilepsies. Arch. Neurol. Psychiat. 45:903-943, 1941.
16. Jasper, H. H., and Nichols, I. C.: Electrical signs of cortical function in epilepsy and allied disorders. Am. J. Psychiat. 94:835-851, 1938.
17. Keith, H. W., Ewert, J. C., Green, M. W., and Gape, R. P.: Mental status of children with convulsive disorders. Neurology 5:419-425, 1955.
18. Kopeloff, L. M., Barrera, S. E., and Kopeloff, N.: Recurrent convulsive seizures in animals produced by immunologic and chemical means. Am. J. Psychiat. 98:881, 1942.
19. Mayman, M., and Rapaport, D.: Diagnostic Testing in Convulsive Disorders, in Hoch, P., and Knight, R., Eds.: Epilepsy: Psychiatric Aspects of Convulsive Disorders. New York, Grune and Stratton, Inc., 1947, pp. 123-135.

20. Morrell, F.: Conditioned alpha response in patients with seizures of focal cortical and of centrencephalic origin. EEG Clin. Neurophysiol. 6:694-695, 1954b.
21. Morrell, F.: Studies in the pathophysiology of focal epilepsy. Epilepsia 3:120, 1954a.
22. Morrell, F., and Ross, M.: Central inhibition in cortical conditioned reflexes. Arch. Neurol. Psychiat. 70:611-616, 1953.
23. Morrell, F.: Interseizure disturbances in focal epilepsy. Neurology 6:327-334, 1956.
24. Morrell, F., and Jasper, H. H.: Electrographic studies of the formation of temporary connections in the brain. EEG Clin. Neurophysiol. 8:201-215, 1956.
25. Morrell, F., Roberts, L., and Jasper, H. H.: Effect of focal epileptogenic lesions and their ablation upon conditioned electrical responses of the brain of the monkey. EEG Clin. Neurophysiol. 8:217-236, 1956.
26. Pribram, K. H.: Some aspects of experimental psychosurgery: The effect of scarring frontal cortex on complex behavior. S. Forum (1950) 315-318, 1951.
27. Somerfeld-Ziskind, E., and Ziskind, E.: Effect of phenobarbital on the mentality of epileptic patients. Arch. Neurol. Psychiat. 43:70-79, 1940.
28. Walter, W. G.: The Living Brain. London and New York, Norton, 1953.

Staff Meeting Report

Isotope Circulation Studies in Congenital Heart Disease*

Richard H. Greenspan, M.D.†
Richard G. Lester, M.D.‡
James F. Marvin, Ph.D.§

Introduction

The difficulties in demonstrating the site and hemodynamic behavior of right to left intracardiac and extracardiac shunts are apparent to those who deal with the diagnosis and treatment of congenital heart disease. Oxygen content of blood samples withdrawn from various chambers and vessels by means of the cardiac catheter is extremely helpful in pin-pointing the location of left to right shunts; but in the initial diagnosis of right to left shunts, the catheter is only directly useful when it happens to pass through the defect. Angiocardiography, with injection being made into the arm, or selectively at the time of catheterization, yields somewhat more accurate results. However, this procedure has two main drawbacks: the first is that a small shunt may be missed because an insufficient amount of dye passes through it, or that dilution of the dye will be so rapid that the small jet is missed; the second is the technical difficulty of the procedure. In addition, although hazards have been reduced by utilizing newer contrast media, there is still some inherent danger in injecting large amounts of iodinated contrast material.

Dye dilution, which has proved very successful when performed by those with experience and competence, is at best a rather cumbersome procedure. For the most accurate results, arterial puncture is necessary. Although this can be accomplished with relative ease in the adult, the placing of an indwelling arterial catheter in the infant or young child is a fairly difficult procedure that may well upset the physiologic state of the patient. Although oxymetric measurements in the ear obviate the need for arterial puncture, they have been

*This report was given at the Staff Meeting of the University of Minnesota Hospitals on November 22, 1957.
†Instructor, Department of Radiology
‡Assistant Professor, Department of Radiology
§Associate Professor, Division of Radiation Therapy

reported as considerably less accurate than values obtained by arterial sampling, particularly in infants and young children.[1]

Because of these difficulties, the authors decided to investigate the possibilities of a new procedure for the detection of shunts. This procedure consists of injecting trace amounts of a radioisotope into various chambers or the great vessels at the time of catheterization, and of recording appearance time and concentration slopes by means of externally placed, collimated counters.

The possible advantages of this procedure appeared to be as follows: The need for arterial puncture would be obviated, since the counter would be placed over an extremity (preferably over a large vessel), and direct, continuous recordings would be made. Information could be obtained from a collimated counter located over the heart and from counters placed over the lungs, which would indicate the presence of pulmonary recirculation and possibly of ischemia. With conventional dye dilution methods, any data regarding the actual blood flow through the heart and lungs are obtained by inference, whereas with this system they would be determined through direct recording. An additional advantage foreseen was the possibility of using multiple counters in different locations. This would be particularly useful in patients with a suspected reversing patent ductus arteriosus, in whom fully saturated blood would be reaching the head and upper extremities, while partially desaturated blood would be present in the lower extremities. Counters placed over the arm and leg should detect a significant difference in time of appearance of the radioactive material, with appearance at the leg earlier than at the arm. Another advantage of this procedure was its obvious simplicity: The placing of counters and the injection would take only a few minutes; exact timing of the injection would be unnecessary, since the counter placed over the precordium would detect the appearance of the radioactive material at the heart, and timing would be from heart to peripheral artery, rather than from arm, or catheter end, as with dye dilution.

Method

Initially, and until recently, radioactive iodinated albumin, supplied in sterile form, was utilized as the tracer material in these studies. Between 10 and 100 microcuries were used per injection, depending upon the age and size of the patient, and upon the number of injections to be made. The majority of studies were made at the time of catheterization by means of a three-way stopcock con-

nected to the cardiac catheter. The iodinated albumin, which was usually diluted so that it occupied one-quarter cc., was injected into the catheter and was rapidly washed into the heart with 5 cc. of saline solution. Because of the desirability of reducing radiation to the patient to an absolute minimum, and with the idea of combining isotope circulation studies and angiocardiography in the near future, the tracer material has recently been changed to radioiodinated Renografin.®* Since Renografin is a urographic contrast material, it is very rapidly excreted, so that at the end of two hours, 80 to 90 per cent of the injected dose is found in the urine. Because it is considerably denser it can be layered in a syringe in front of 5 cc. of saline solution, and the entire injection can be made as one bolus.

Following the injection, collimated scintillation counters suspended from a ceiling track, were rolled into position over the heart and femoral artery. At the start of the study, the recording apparatus consisted of a Berkeley Computing Rate Meter and an Esterline Angus

*Kindly prepared for and supplied to us by E. R. Squibb & Sons, through the Squibb Institute for Medical Research, New Brunswick, N. J.

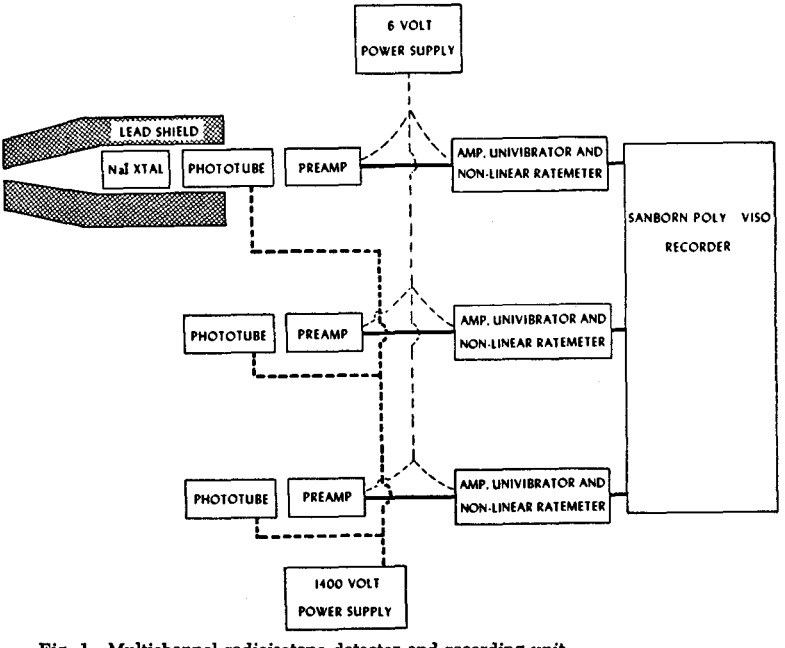

Fig. 1. Multichannel radioisotope detector and recording unit.

recorder. With this apparatus, it was not possible to record several simultaneous curves, so that separate indicators had to be used for time of injection and appearance time at the heart. (The latter was recorded by a single impulse obtained when one hundred counts had accumulated from the counter placed over the precordium.) Several modifications of electronic apparatus have subsequently been made, and at present a transistor-equipped integrating rate meter developed by one of us (J.F.M.) is being used (Fig. 1).

Impulses from the collimated scintillation counter are fed into a battery-powered transistor-equipped pre-amplifier, amplifier, and rate meter, and then are recorded on a four-channel Sanborn Poly-Viso Recorder, along with electrocardiogram, and one-second time intervals. The apparatus as presently utilized is semilogarithmic and can be adapted to quantitative recording after proper standardization; to date, only qualitative studies have been performed.

Results

Preliminary work was carried out on normal dogs and on animals with experimentally produced shunts. Following this, studies were made on patients with a variety of congenital defects, as well as on normal subjects.

When the injection is made into a cardiac chamber or the great

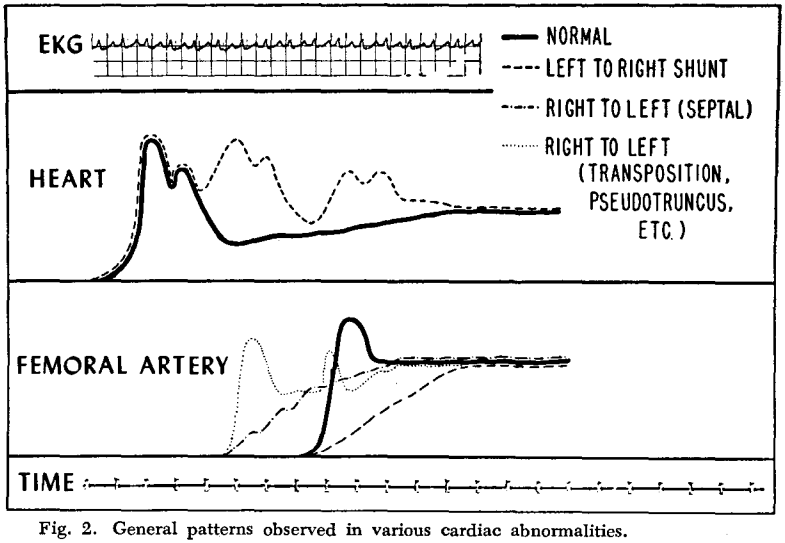

Fig. 2. General patterns observed in various cardiac abnormalities.

veins at the time of catheterization, the counter over the heart records the radioactive material as a large bolus. If injection is made into a peripheral vein or the pulmonary artery, the bolus effect is not as marked. The normal curve exhibits a sharp rise in the radioactivity recorded at the femoral artery seven seconds or longer after the bolus has reached the heart. This is followed by a slight decrease, and then equilibrium is rapidly reached. Time of appearance of radioactivity depends partly on cardiac rate. Persistence of the large bolus at the heart is brief, and precordial counts decrease by the time femoral artery counts have begun increasing (Fig. 2). When the precordial counter is well collimated, a double contour is obtained. The initial rise occurring as the bolus is in the right side of the heart, the decrease in activity presumably representing exodus of the radioactive material to the pulmonary circulation, and the second increase indicating return to the left side of the heart (Fig. 3). It is expected that this explanation will be confirmed by the addition of a third collimated counter over the lung.

The down-slopes of the femoral artery curves have no significance in the present state of development of the procedure, since the counter

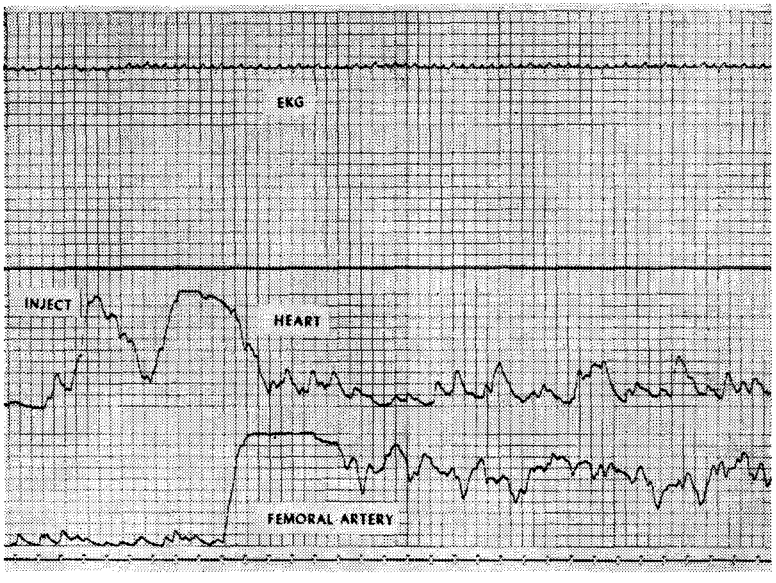

Fig. 3. Normal pattern. Injection made into right ventricle. Note sharp rise at femoral artery. Seven-second appearance time.

placed over the upper leg is recording radioactivity not only from the femoral artery but also from veins and capillaries. It is expected that the placing of a tourniquet just below the leg counter, with sufficient pressure to delay venous return, may help to explain the down-slope of this curve.

Right to left shunts are characterized by a short interval between appearance of the radioactive material at the heart and its appearance at the femoral artery, as the isotope containing desaturated blood is shunted into the systemic circulation (see Fig. 2). Two general

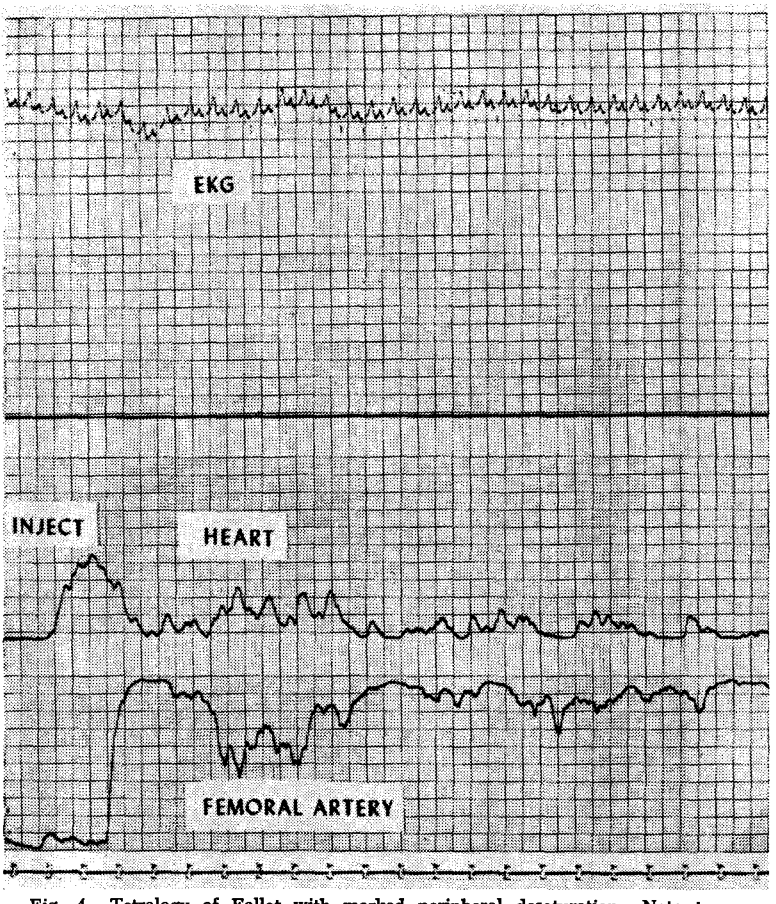

Fig. 4. Tetralogy of Fallot with marked peripheral desaturation. Note two-second appearance time.

groups have been observed: grossly cyanotic patients, in whom a considerable portion of the systemic cardiac output consists of desaturated blood, exhibit the early appearance of a large bolus of radioactivity at the femoral artery and a short stay of the material at the heart. This pattern occurs in patients with transposition of the great vessels, cyanotic Tetralogy of Fallot, and pseudotruncus (Fig. 4).

Patients with smaller right to left shunts, most frequently septal, show early appearance as in the grossly cyanotic group, but the amount of radioactivity appearing early is small and variable, and a shallow slope of appearance is often seen over the femoral artery. (See Fig. 2.) These defects are frequently, although not necessarily, associated with left to right shunts.

Location of the right to left shunt is determined by making multiple injections into various chambers. The most distal chamber or vessel that, when injected, will produce early appearance of radioactivity at the femoral artery is the site of the right to left shunt. A cyanotic boy on whom previous cardiac catheterization and angiocardiography had failed to make a definite diagnosis was studied by

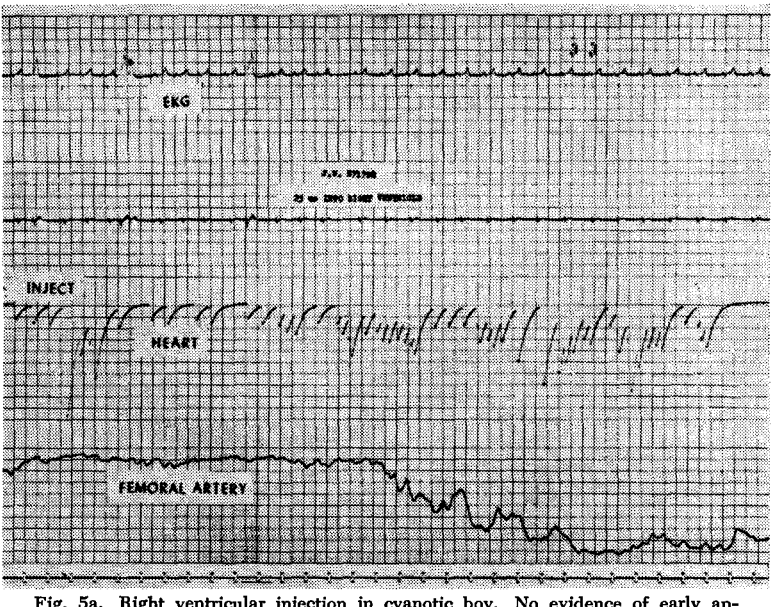

Fig. 5a. Right ventricular injection in cyanotic boy. No evidence of early appearance at femoral artery. Electronically inverted study. (Increased radioactivity recorded by downward slope.) Heart counter insensitive.

this method. Injection was made into the right ventricle, and 12 seconds later (somewhat longer than the usual time of appearance), radioactivity appeared at the femoral artery (Fig. 5a).

The catheter was withdrawn to the right atrium, and upon re-injection a three-second interval between the appearance of radioactivity at the heart and at the femoral artery was recorded (Fig. 5b), clear evidence of a right to left shunt at the atrial level.

Typical patterns of the precordial records for the various anatomic malformations producing right to left shunts have not, as yet, been noted. It is possible that a few of the more common anomalies in this large group may exhibit constant precordial curves, but as yet, this has not been the case in the limited experience of the authors. It is expected that the addition of a collimated counter over the lung

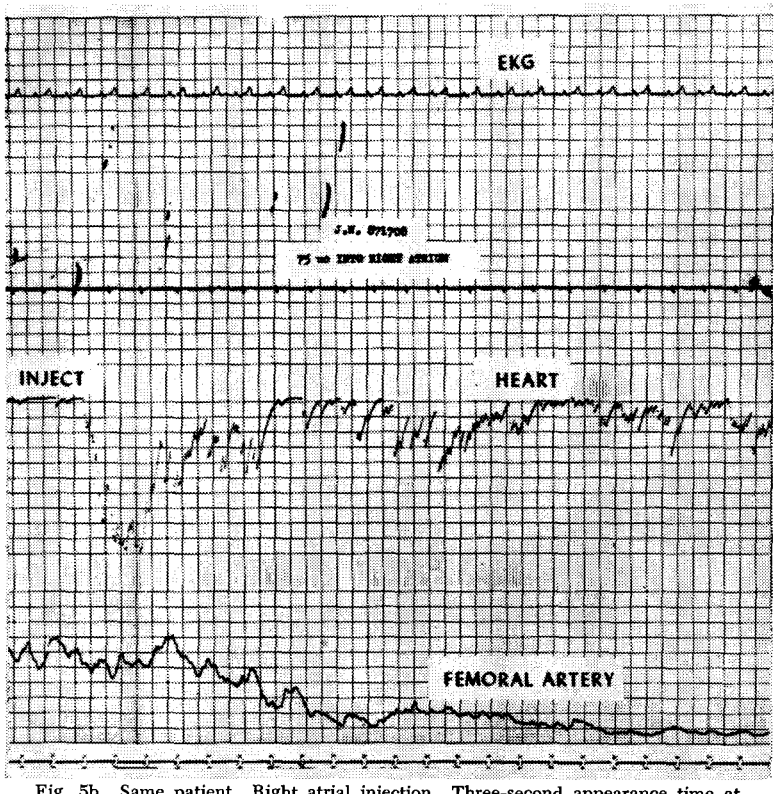

Fig. 5b. Same patient. Right atrial injection. Three-second appearance time at femoral artery. Right to left shunt at atrial level.

field may provide evidence of abnormalities in the pulmonary circulation.

Patients with left to right shunts present a different pattern. The appearance time of the radioactivity at the femoral artery is the same in these patients as in normal subjects, but the slope of the rise is considerably more gradual, and several seconds may elapse before equilibrium occurs (Fig. 2; Figs. 6 and 7, next page).

In these patients the cardiac counter has recorded continued high activity indicative of pulmonary recirculation, a phenomenon that should be even more clearly demonstrable when a third counter is placed over the lung field. Location of the left to right shunt cannot be determined by this method, since recirculation will occur no matter where the injection is made. Patients in cardiac decompensation and those with particularly large hearts also exhibit a gradual rise in femoral artery counts which cannot be differentiated from left to right shunts.

Discussion

This procedure is still being developed. Two major problems have yet to be solved: sensitivity adjustments are difficult and quite critical, and natural variation in isotope counting produces irregular, rough tracings. The sensitivity problem is electronically correctable, and in the near future all records are expected to be approximately standardized, so that variations in isotope concentrations will always produce a certain degree of deflection in the recording device. Natural variation in counting rate is a problem inherent in all isotope work. In order to obtain smoother tracings, it is necessary to have higher counting rates, which can be obtained either by using more sensitive counters or by injecting higher doses of isotope. The counters, at present, consist of one-inch sodium iodide crystals collimated and protected by approximately 20 pounds of lead. If, to make the counters more sensitive, larger crystals were used, much more lead would be needed for adequate collimation and shielding from background radiation, and therefore the bulk of the counters would be formidable. The answer, then, should lie in increasing the dosage. This can be accomplished by utilizing the rapidly excreted Renografin. Thus a much larger dose of isotope can be injected per study—while still decreasing the radiation to the patient—as compared to that delivered by iodinated albumin, since the latter has a biological half-life of approximately three days, and the half-life of Renografin in the patient with normal kidneys is well under one hour.

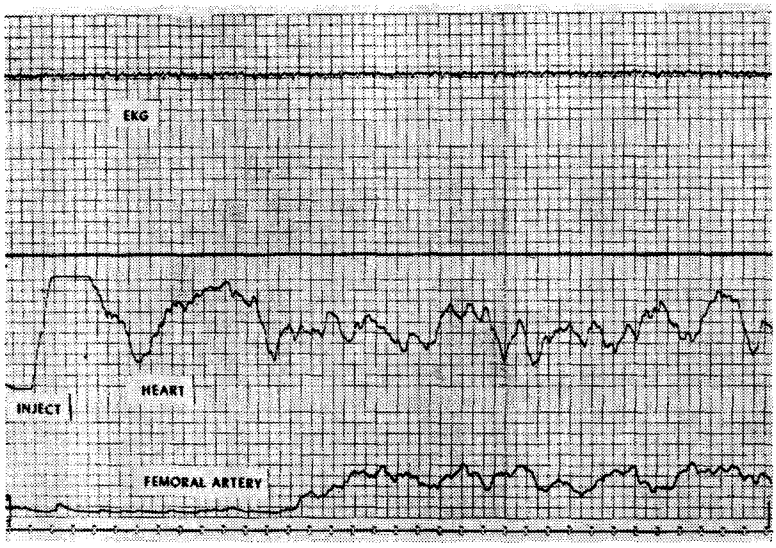

Fig. 6. Large left to right shunt. Note gradual slope of appearance at femoral artery. Continued high counts over heart.

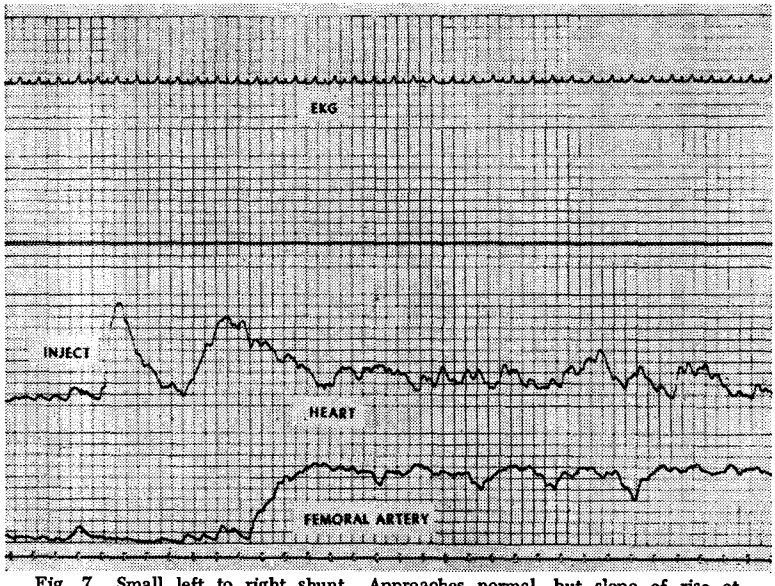

Fig. 7. Small left to right shunt. Approaches normal, but slope of rise at femoral artery more gradual. Less than 2 volumes per cent increase in oxygen saturation at atrial level by Van Slyke method.

Although most of these injections have been made at the time of catheterization, a few direct intravenous injections have been given. In these cases the bolus obtained at the heart has not been as sharp as when injection is made through the catheter. However, this should not affect the detection of a right to left shunt, since the studies presented indicate that the heart to femoral artery time interval should be diminished.

Previous work has been done with counters placed over the heart. Goldring and his associates,[2] employing radiocardiography with a single counter placed over the heart, studied patterns of appearance in normal subjects and in patients with congenital heart disease. Surgical and anatomic studies, however, indicate the difficulties encountered in determining the position of the various chambers in severe cardiac anomalies. Others have measured the cardiac output using radioactive materials. The Western Reserve group[3,4,5] has devised a method necessitating arterial puncture. Mack and his associates[6] placed a scintillation counter over the heart, as did Zacks,[7] who recorded the appearance and disappearance of radioactive iodine from within the heart. None of these methods, however, has used a precordial counter together with one or more peripheral counters, a combination which would appear to be necessary for obtaining precise information regarding shunts.

Summary

A new method for the detection of intra- and extracardiac shunts has been described. Although still in the developmental stage, this method, which obviates the need for arterial puncture, offers a simple and precise procedure for detecting and locating right to left shunts, as well as for detecting left to right shunts. It promises to yield additional direct information concerning the pulmonary and intracardiac circulation of the sort that previously has been obtained only by inference.

The authors wish to acknowledge the cooperation of the departments of pediatric and adult cardiology, without which this study could not have been carried out. We are particularly indebted to Dr. Paul Winchell, whose many suggestions have been invaluable. We should also like to thank Dr. Kurt Amplatz, who has been performing many of the recent studies.

References

1. Wood, E. H., Swan, H. J. C., and Helmholz, H. F., Jr.: Recording and basic patterns of dilution curves: normal and abnormal. Proc. Staff Meet. Mayo Clinic 32:463, 1957.
2. Goldring, D., Rogers, H. M., Jr., Ter-Pogossian, M., Seaman, W., and Behrer, M. R.: Radiocardiography in congenital heart disease. Jour. Pediatrics 44:392, 1954.

3. MacIntyre, W. J., Pritchard, W. H., Eckstein, R. W., and Friedell, H. L.: The determination of cardiac output by a continuous recording system utilizing iodinated (I^{131}) human serum albumin; I. Animal studies. Circulation 4:552, 1951.
4. Pritchard, W. H., MacIntyre, W. J., Schmidt, W. C., Brofman, B. L., and Moore, D. J.: The determination of cardiac output by a continuous recording system utilizing iodinated (I^{131}) human serum albumin; II. Clinical studies. Circulation 6:572, 1952.
5. MacIntyre, W. J., Storaasli, J. P., Krieger, H., Pritchard, W. H., and Friedell, H. L.: I^{131} labeled serum albumin: Its use in the study of cardiac output and peripheral vascular flow. Radiology 59:849, 1952.
6. Mack, R. E., Wells, H. J., and Pollack, R.: An in vivo method for the determination of cardiac output. Radiology 68:245, 1957.
7. Zacks, A.: Experimental and clinical studies in radiocardiography. Am. J. Roent., Rad. Therapy and Nuclear Med. 77:493, 1957.

Editorial

Man in Space

With the prospect of man's leaving the earth's atmosphere and ascending into space, radical changes in the physiological problems of aviation medicine have taken palce. We know that at altitudes up to 10,000 feet man operates reasonably efficiently without artificial aids. Between 10,000 and 40,000 feet, oxygen equipment that will provide a mixture of oxygen and air, automatically adjusted according to the altitude and providing 100 per cent oxygen above 30,000, is required. At an altitude of about 34,000 feet, 100 per cent oxygen maintains an alveolar oxygen tension equal to that which is provided by air at sea level. Above this altitude alveolar oxygen tension falls below normal even with 100 per cent oxygen as the inhaled gas. The absolute ceiling for humans breathing 100 per cent oxygen at ambient pressure is 40,000 feet.

Above 40,000 feet, oxygen at ambient pressure is inadequate, and higher pressure in the aircraft must be provided. In pressurized aircraft outside air is pumped into the cabin and near sea-level conditions are maintained. Practically all commercial aircraft now use this method of providing minimal changes in cabin pressure while they fly at altitudes above 10,000 feet.

Above 80,000 feet, pressurization becomes inadequate, and sealed cabins, providing their own atmosphere and completely independent of the outside environment, must be utilized. In this situation, minimum conditions in the cabin necessary for life would be: an oxygen tension of approximately 150 mm. of mercury, absorption of exhaled carbon dioxide to maintain a CO_2 tension approaching zero, cabin temperature compatible with normal body temperature. Obviously, if flights are to extend over long periods of time, food and water must be made available and disposal of body wastes provided for. That these minimum conditions can be met is attested by the Russian dog that was kept alive for several days in Sputnik II.

The additional problem of weightlessness provides grounds for considerable speculation. Precisely how humans will react to this strange condition over long periods of time, and what influence this will have on their behavior and ability to function normally, remains to be seen. The fact that interpretation of sensations from our environment is largely a learning process – as evidenced, for example,

by the relearning necessary to interpret the environment when inverting prisms are worn for glasses – makes it seem likely that humans can also learn to interpret their environment correctly even when weightless. When I was a small boy in grade school I often daydreamed that I was weightless and that I could fly through the open windows and sail around in the air. If the sensation of weightlessness is anything like the sensation that I imagined at that time it will be very pleasant. Anybody for a trip to Mars?

Medical School Activities

Faculty News

DR. C. WALTON LILLEHEI, Professor, Department of Surgery, participated in the William Harvey Tercentenary Commemoration sponsored by the National Heart Institute and the National Library of Medicine and held in Bethesda, Md., on September 17. His subject was "Cardiovascular Surgery."

MR. RAY M. AMBERG, Director of the University Hospitals, was named President-Elect of the American Hospital Association at its national meeting during October in Atlantic City.

DR. ARNOLD LAZAROW, Professor and Head of the Department of Anatomy, has been appointed special consultant to the United States Public Health Service to serve on the Metabolism and Nutrition Study Section of the National Institutes of Health.

DR. J. S. BLUMENTHAL, Clinical Associate Professor, Department of Medicine, has been appointed a member of the National Committee on Allergy of the American College of Chest Physicians.

DR. LAURENCE O. PILGERAM has been appointed Assistant Professor of Physiology and Principal Investigator of the Atherosclerosis Research Laboratory established by the St. Barnabas Hospital Research Foundation. This laboratory is to be operated in close affiliation with the Department of Physiology of the Medical School. Dr. Pilgeram will participate in the teaching program of the Department of Physiology both on the campus and at the Laboratory.

Several members of the Medical School faculty have been appointed by the National Institute of Health as scientific counselors to advise the various institutes concerning the intramural research programs conducted with in the institutes. DR. CECIL J. WATSON was appointed chairman of the board for the Institute of Arthritis and Metabolic Diseases; DR. WALLACE D. ARMSTRONG, a member of the board for the Institute of Dental Research; and DR. DENNIS W. WATSON, a member of the board for the Division of Biologics Standards.

DR. RICHARD C. LILLEHEI, Medical Fellow, Department of Surgery, was awarded a Certificate of Achievement by the Medical Department of the United States Army. The award was in recognition of Dr. Lillehei's contribution, while on active duty from 1954

to 1956, to the advancement of the service's research and development program through his work on hemorrhagic shock.

DR. E. GELLHORN, Professor of Neurophysiology, was awarded a medal "for outstanding achievement in medical research" by the Carbon Dioxide Research Association. He is presently writing a monograph, "Autonomic Imbalance and the Hypothalamus," which will be published by the University Press.

Student News

MR. STEPHEN A. KIEFFER, Senior, was awarded third prize in the 1957 essay contest of the American College of Chest Physicians for his essay, "Atrial Septal Defect: An Evaluation of Surgical Closure." The contest was open to undergraduate medical students throughout the world.

MR. JAMES JANACEK, JR., and MR. ROBERT L. SADOFF, Juniors, were awarded honorable mention for their manuscripts submitted in the 1957 Schering Award Contest on the topic, "Recent Advances in the Biochemical Aspects and Treatment of Mental Disease."

MR. PHILIP L. ECKMAN, Junior, presented a paper entitled, "Increasing Incidence of Liver Necrosis: Possible Relationship to Administration of Vasopressor Amines" at the 30th Scientific Session of the American Heart Association in Chicago, Illinois. DR. JOEL G. BRUNSON, Assistant Professor of Pathology, and MR. JOHN B. CAMPBELL, Junior, were co-authors of the paper.

Postgraduate Education

Ophthalmology for Specialists

The University of Minnesota announces a continuation course in Ophthalmology for Specialists, which will be held at the Center for Continuation Study on the University Campus during the week of January 6 to 10, 1958. Guest speakers will be DOCTORS HAROLD WHALEY BROWN, Clinical Professor of Ophthalmology, New York University College of Medicine, New York City; HERMANN M. BURIAN, Professor of Ophthalmology, State University of Iowa College of Medicine, Iowa City; and HAROLD G. SCHEIE, Professor of Ophthalmology, University of Pennsylvania School of Medicine, Philadelphia. The course will be presented under the direction of DR. ERLING W. HANSEN, Clinical Professor and Head, Department of Ophthalmology. The rest of the faculty will be drawn from the University of Minnesota Medical School and the Mayo Foundation.

The Newer Drugs in General Practice

The University of Minnesota announces a new continuation course in The Newer Drugs in General Practice to be held on the University campus from January 9 to 11, 1958. Pharmacological aspects and clinical application of drugs acting on the central nervous system, cardiovascular drugs, chemotherapy in bacterial and fungus infections and in blood dyscrasias and neoplasms will be discussed. Acute poisonings and toxicology will be taken up also. The guest faculty will include DOCTORS NORMAN F. CONANT, Professor of Mycology and Associate Professor of Bacteriology, Duke University School of Medicine, Durham, North Carolina; ALFRED FARAH, Professor, Department of Pharmacology, State University of New York College of Medicine, Syracuse; and ARNOLD J. LEHMAN, Director, Division of Pharmacology, Bureau of Biological and Physical Sciences, Department of Health, Education, and Welfare, Food and Drug Administration, Washington, D. C. The remainder of the faculty will include members of the faculty of the University of Minnesota Medical School and the Mayo Foundation. The course will be directed by DR. RAYMOND N. BIETER, Professor and Head, Department of Pharmacology.

Coming Events

December 5-7 . . . . Continuation Course in Fractures for General Physicians

December 6 . . . . . JOURNAL-LANCET LECTURE: *Mechanism of Parathyroid Function*; Dr. William F. Newman, Associate Professor of Pharmacology and Biochemistry, University of Rochester School of Medicine and Dentistry, Rochester, New York; Mayo Memorial Auditorium; 11:30 a.m.

January 6-11 . . . . . Continuation Course in Ophthalmology for Specialists

January 9 . . . . . PHI DELTA EPSILON LECTURE: *Formation, Character, and Drainage of Aqueous Humor*; Dr. Hermann M. Burian, Professor of Ophthalmology, State University of Iowa College of Medicine, Iowa City; Mayo Memorial Auditorium; 11:00 a.m.

January 9-11 . . . . . Continuation Course in The Newer Drugs in General Practice

January 30–
February 1 . . . . . Continuation Course in Emergency Surgery for General Physicians

February 6-8 . . . . . Continuation Course in Cardiovascular Diseases for General Physicians

February 10-15 . . . . Continuation Course in Neurology for General Physicians and Specialists

WEEKLY CONFERENCES OF GENERAL INTEREST

Physicians Welcome

Monday,	9:00 to 10:50 A.M.	OBSTETRICS AND GYNECOLOGY Old Nursery, Station 57 University Hospitals
	12:30 to 1:30 P.M.	PHYSIOLOGY- PHYSIOLOGICAL CHEMISTRY 214 Millard Hall
	4:00 to 6:00 P.M.	ANESTHESIOLOGY Classroom 100 Mayo Memorial
Tuesday,	12:30 to 1:20 P.M.	PATHOLOGY 104 Jackson Hall
Friday,	7:45 to 9:00 A.M.	PEDIATRICS McQuarrie Pediatric Library, 1450 Mayo Memorial
	8:00 to 10:00 A.M.	NEUROLOGY Station 50, University Hospitals
	9:00 to 10:00 A.M.	MEDICINE Todd Amphitheater, University Hospitals
	1:30 to 2:30 P.M.	DERMATOLOGY Eustis Amphitheater University Hospitals
Saturday,	7:45 to 9:00 A.M.	ORTHOPEDICS Powell Hall Amphitheater
	9:15 to 11:30 A.M.	SURGERY Todd Amphitheater, University Hospitals

For detailed information concerning all conferences, seminars, and ward rounds at University Hospitals, Ancker Hospital, Minneapolis General Hospitals, and the Minneapolis Veterans Administration Hospital, write to the Editor of the BULLETIN, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14, Minnesota.