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Staff Meeting Report

The Ataraxic Effect of Two Phenothiazine Drugs On An Outpatient Population*†

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The most significant development in the field of clinical psychiatry in the past decade has been the introduction of the chemical compounds commonly called the tranquilizers. Many psychiatrists regard the impact of these compounds as being equal to, or more significant than, the impact of the organic therapies, insulin shock, metrazol, and electroshock in the late 1930's. In the six years since the introduction of the Rauwolfia alkaloids and the phenothiazine drug, chlorpromazine, 15 different compounds have been introduced in the American market, with many more currently being given preliminary trials. There are potentially available, in the family of phenothiazines alone, more than one thousand compounds, the majority still completely untested. Because of the apparent effectiveness of these compounds in the treatment of psychiatric problems, pharmaceutical companies are actively engaged in developing more effective drugs, with greater specificity of action and fewer disturbing side effects.

The critical clinical evaluation of these compounds presents all the difficulties common to the evaluation of any new drug, along with the added difficulty of assessing changes in the patient that are demonstrated in large part through his subjective evaluation of his current emotional state and daily performance. Because of this factor,

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the difficulties of adequately controlling for and evaluating variables such as "placebo effect" are increased to a considerable degree over the usual problems in this area. In a recent paper Koteen[1] has discussed the problem of "placebo effect" in evaluating the clinical effects of meprobamate. He emphasized the effect of uncontrolled variables such as coincidental and environmental circumstances upon the reaction of the patient, pointing out that not uncommonly both patient and physician are inclined to ascribe changes in the patient's emotional state to the effect of the therapeutic agent, rather than to nonpharmacological influences; e.g., an increase or decrease of emotional stress from interfamily relationships, transient and unrelated physical difficulties, or the reassurance and support the patient is receiving from the physician. The need for controlled studies in the evaluation of any drug, especially when the patient's emotional response may be an important component, has been demonstrated by other authors.[2,3,4,5] This is pertinent also to conditions that are primarily organic in etiology.

A further problem in evaluating the effect of any drug upon the behavior of an individual is the lack of adequately standardized scales for rating changes in behavior, especially in the subtler aspects of mood and affect. Because we were unable to find a suitable scale for the evaluation of psychiatric outpatients, we were forced to develop our own scale for this study. The Q-technique for evaluating an individual, developed by Stephenson,[6] was used for this purpose. The Q-pool contained 123 items chosen as measures of various aspects of an individual's behavior and daily performance. These items can be divided roughly into four groups as follows:

1. Items descriptive of general personality patterns
   - D-28 Neat
   - D-65 Is self-indulgent
   - D-67 Has inferiority feelings
   - D-71 Has personal charm
   - D-78 Shows common sense and good judgment
   - D-94 Dependent: seeks help, direction, emotional support
2. Items descriptive of current adaptive problems
   - D-19 Cooperative
   - D-27 Irritable
   - D-33 Shy
   - D-35 Self-confident
   - D-76 Exhibits overt hostility
   - D-85 Is efficient; gets things done

3. Items descriptive of emotional symptoms
   - D-5 Has suicidal thoughts
   - D-12 Agitated
   - D-72 Delusional thinking present
   - D-84 Has feelings of depersonalization
   - D-112 Has ideas of reference (Extreme is delusion of reference.)
   - D-117 Exhibits inappropriate affect (Include shallow or flat affect as a form of inappropriateness.)
4. Items descriptive of physical symptoms, including specific items to detect common side effects of the phenothiazine drugs
   - D-48 Drowsiness
   - D-53 Nausea/vomiting
   - D-54 Dizziness or faintness
   - D-55 Parkinsonoid syndrome
   - D-57 Skin reactions (itching, rash, hives, etc.)

A general description of Q-technique may be helpful in understanding the methodology employed. Basically this involves evaluating not only whether a trait is present or not, which would be a two-step Q-sort, but in evaluating how much of, or how frequently, a trait is present. This attempt at quantitative as well as qualitative evaluation of a given trait is accomplished by sorting the items into several categories, ranging from a five-step to an eleven-step sort in most Q-pools. Placement of an item at one end of the scale indicates that the trait is minimally present, or that the item does not describe the individual. Placement of an item at the opposite end indicates that the trait is maximally present, or that the item describes the individual very exactly.

For this particular study we chose a six-step sort, because this allowed recording of the information from two items in one column on an IBM-card. The IBM-cards were used in calculating the product moment correlations to be discussed later. Each item, representing a particular trait, was sorted into one of the six categories, with Category I representing minimal presence of the trait in the individual, and Category VI representing its maximal presence. To avoid certain errors that often occur in the use of the Q-sort, for example, the error of central tendency (a bunching in the mid-range), a mild forcing of the sort was used, the limitations being that no fewer than 10 items, nor more than 40 items, be placed in any one of the six steps. Thus, the complete Q-sort gives us a quantitative measurement of 123 descriptions of the patient that can be compared with subse-

quent descriptions of the patient using the same set of items. Different placement of any one item on a second or subsequent sort presumably means a shift in the behavior of the patient covered by that item, and may indicate improvement in or intensification of symptoms, depending on the direction of the shift toward or away from the ideal placement for that item.

The second instrument used for evaluating the patients was the Minnesota Multiphasic Personality Inventory, or the MMPI. The MMPI, which is accepted as a well-standardized measurement of personality, was used both in the selection and matching of patients for our experiment and as another, entirely subjective method of evaluating change in a given patient during the experiment.

Because of the difficulties, referred to in our opening remarks, in evaluating the effect of any drug, especially those having to do primarily with changes in psychological behavior, the study was developed as a double-blind study. Two new phenothiazine compounds known only by their laboratory names, TP-21 Sandoz and KS-75 Sandoz, and two matching placebo tablets were used in the study. Each drug and its placebo were indistinguishable in color, size, and taste. The placebo used was an inert placebo rather than one containing a known active agent such as nicotinic acid.

Sixty patients from the psychiatric outpatient clinics of the University of Minnesota Hospitals and the Minneapolis General Hospital were selected for the study, out of a total of 83 patients initially surveyed. Before being accepted for the experiment, these patients were asked if they would like to cooperate in the study of a new tranquilizing drug. The necessity for weekly visits for a minimum period of four weeks, sorting the MMPI cards three times, and a weekly blood and urine examination were described as essential to the project. If the patient agreed to these conditions, he was given an MMPI test as an initial evaluation. The patients were matched in tetrads (groups of four) on the basis of their MMPI profiles, rather than the stated clinical diagnosis, or any set of symptoms. Once the patient was matched in one of the fifteen tetrads, he was assigned to one of the four drug groups by a table of random numbers. The matching of MMPI profiles and assignment of patients to drug or placebo groups, as well as the preparation of the weekly allotments of medication, was handled by one of the experimenters who had no clinical contact with the patients and was not involved in the clinical evaluations and ratings.

Each patient was given an envelope containing his medication at each weekly visit. Neither the patient nor the clinician seeing the

patient, had any knowledge of which drug was involved, or whether the medication was active drug or placebo. This aspect of the double-blind study was, we believe, completely controlled throughout the experiment.

Since only 60 subjects were chosen for the experiment, of the 83 patients initially evaluated, we must explain the loss of 23 patients. Ten patients failed to return to the clinic for a second visit, after having completed the initial MMPI. Eight others were discovered to be too disturbed emotionally to continue in the study; six of these required immediate hospitalization. One patient was discovered to have multiple sclerosis and was not started on a drug. Four patients had severe physical symptoms after being on the drug less than 48 hours. Of these, three were on active drugs and one was on placebo medication; all four discontinued the drug on their own initiative after 24 to 48 hours of medication. Of the 60 patients retained in the experiment, all were on the medication for a minimum period of one week up to a maximum period of four weeks. Forty-five patients completed the entire four weeks on medication.

The original intention was to replace any patient who dropped out before the four-week period was completed, to assure a uniform period of drug administration for each group. On reconsideration, however, it was decided that replacing patients who stopped after at least one week of medication, either because of symptoms that a patient ascribed to the medication, or because the patient felt the medication was not helping, would result in loading our findings in favor of the drugs being studied. The remaining 15 patients, therefore, were kept in the study even though they had not completed the full four weeks. Of these, five completed one week of the study, seven completed two weeks, and three completed three weeks. An evaluation of the symptomatology and reasons for discontinuing medication will be given later.

Following the initial evaluation – including the MMPI, a detailed psychiatric history, and an initial Q-sort by the interviewing clinician – each patient was given one week's supply of medication. This consisted of twenty-one 25 milligram tablets, one tablet to be taken three times a day. An initial urinalysis and complete blood count were also made. When each of the patients returned weekly, a relatively brief interview, directed primarily at securing information about the previous week's patterns of behavior, reactions to the medication, and general psychological state of the patient, was conducted. An attempt was made to keep specific psychotherapeutic activity at the

irreducible minimum, although it was recognized that the procedure of seeing a patient even briefly at weekly intervals would have some psychotherapeutic effect. The urinalysis and complete blood count were repeated at each weekly visit. In addition, the patients were asked to repeat the MMPI after the first week of treatment and again at its completion after the fourth week. The clinician did another Q-sort on each patient immediately after seeing him. Thus, we had at least two MMPI evaluations for each patient in the sample except for three who discontinued their medication after the first week and failed to repeat the MMPI. Thirty-five patients completed three MMPI's. The remaining 22 patients repeated an MMPI either at the end of the first week, or at the completion of the course of treatment. At least two Q-sorts – an initial and a final one – were available for each of the 60 patients.

As has been indicated above, one investigator was charged with the sole responsibility of assigning patients to the four experimental groups and matching the four patients in a given tetrad on the basis of the original MMPI profiles. He was also responsible for preparing the weekly medication, and was the only person throughout the entire course of the study who knew which patient was receiving which medication. Because of the difficulty in controlling possible complications in an outpatient group, it was decided at the beginning of the study to limit our medication to 75 mg. per day, although it was recognized that this dosage might not be sufficient to obtain a clinical effect. In addition, in order to provide for emergencies arising from a reaction to the drugs or from any acute psychological or physical disturbance, it was noted on the chart of each patient that he was on a special drug study, and that information on which drug he was receiving was available to the hospital staff if necessary in a sealed envelope in the psychiatric outpatient office. Since it was not necessary at any time during the study to use this emergency information, this potential break in the control of the double-blind study was avoided.

Five junior medical students were involved in the study during the summer months, and to a lesser degree during the fall quarter of this (1957-58) school year. The medical students carried the major share of the clinical responsibility for evaluating 40 of the patients in the study. The remaining evaluations were done by staff members in the Department of Psychiatry, who also made some simultaneous evaluations along with the medical students, to be used as a check

of their Q-sort ratings. A freshman medical student did all the urinalyses and blood counts.

Evaluation of the effects of the medication upon each patient was both subjective, as determined from what the patient said about himself on the MMPI, and objective, determined by what the clinician said about the patient by means of the Q-sort. The following types of evaluation were made on each patient:

1. A rating of change from the original MMPI profile to the final MMPI profile designated an "improvement score," judged by the total number of T score shifts in a "healthy" direction. A downward shift was considered "healthy" for all scales except K, Pd., and Ma. For these three, a downward shift was considered "healthy" if the patient started out above $T = 50$, and an upward shift was considered "healthy" if he started out below $T = 50$. A shift in the healthy direction on a scale was scored $+1$, in the opposite direction -1, without regard to the *magnitude* of the T score shift. These T score shifts were summed algebraically for each patient, and the resulting number – with a potential range of from $+11$ to -11 – was the "improvement score."

2. Profile "improvement" as judged by experts. The before and after curves on the 57 patients completing two MMPI's were sorted by clinical judges into three categories: improved $= +1$, unchanged $= 0$, worse $= -1$. The ratings of the four judges were then summed for each patient, the range being from $+4$ to -4. This score was then used as the estimate of improvement on this particular rating.

3. Profile "improvement" estimated by scales as continuous variables. All scales on the MMPI except Mf were considered to show improvement if they shifted in a downward direction. The exact amount of T score changes was recorded for each scale and summed algebraically to give a third estimate of improvement. The range of change here was from $+126$ to -118.

4. Comparison of the patient's initial Q-sort profile with the "ideal Q-sort" profile. Product moment correlations were calculated for the initial Q-sort on each against the "ideal Q-short" (see item 5).

5. Product moment correlations of the final Q-sort on each patient against the "ideal Q-sort" were also computed. The difference between these two correlations was then established for each patient. A shift toward the ideal Q-sort was considered a plus value or improvement. A shift away from the ideal sort was considered a negative value or lack of improvement. These difference scores were then used in items 6 and 7.

Since the particular Q-pool that we were using had no standard reference points, a Q-sort was done on an "ideal improved patient" by each of the five staff men engaged in the project. The product moment correlations of each of these Q-sorts with all of the others was then calculated. The range was from .91 to .82, indicating a high degree of agreement among the raters as to what constituted an ideal profile. The lowest correlation was significant at better than the .001 level. As might be expected from these high correlation figures, most of the disagreements about placement were a matter of one step away from the other members of the group. These differences were then compromised in conference, and a final "ideal" placement for each item was decided upon. A shift in the Q-profile of a patient toward this ideal placement was considered improvement, a shift away was considered an intensification of illness or symptoms.

6. An analysis of variance of the difference scores between the product moment correlations of the original Q-sort vs. the ideal and the final Q-sort vs. the ideal was computed for drugs and tetrads. When this was found to show significant differences over the four groups of drugs, we computed:

7. Pair-wise tests for significant differences between each pair of drugs, using the same matching of individuals that existed in the original tetrads.

8. An "improvement score" was computed for the Q-sort information by comparing the absolute shift in item placement from the initial Q-sort to the final Q-sort toward or away from the ideal placement for that item. These ratings were algebraically summed over the total number of items and this score recorded for each patient as an "improvement score." The range of scores was from +123 to −88.

9. An analysis of variance of the improvement scores described above in item 8 was done for drugs and tetrads. When this was found to be significant the following procedure was carried out:

10. Tests for significant differences between each pair of drugs were performed using the original tetrad matching for the pairs of patients, and using the improvement scores that had been obtained in item 8 above.

Results

Table 1 shows the results obtained for each drug group as estimated by the various procedures used, stated simply as either improved or unchanged. Those patients who showed lack of improvement, or appeared to be worse, were combined in the unchanged

TABLE 1

RESULTS OF EVALUATION PROCEDURES

Procedures	TP-21		KS-75		TP-21 P		KS-75 P		X^2	Signif.
	Impr.	Un-chgd.	Impr.	Un-chgd.	Impr.	Un-chgd.	Impr.	Un-chgd.		
Q-sort correlation difference	14	1	6	9	7	8	3	12	17.32	$p<.001$
Q-sort improvement scores	12	3	7	8	7	8	4	11	8.74	$.02<p<.05$
MMPI summed T score shift	10	4	6	8	9	6	2	12	10.6	$.01<p<.02$
MMPI improvement scores	9	5	6	8	10	5	4	10	5.65	N.S.
MMPI clinical sort	7	7	4	10	9	6	3	11	5.85	N.S.

group. The median was used as the dividing line between the improved category and the unchanged or worse category. Statistically significant differences were obtained between the four drug groups on three of the evaluation procedures employed – the Q-sort product moment correlation differences, the Q-sort improvement scores, and the improvement score as measured by the absolute sum in T score shifts on the MMPI. The evaluation of the clinical judges on the MMPI and the improvement scores obtained by qualitative T score shift evaluation did not show significant differences among the four groups.

Table 2 shows the analysis of variance of the product moment correlation differences between the initial Q-sort vs. the ideal Q-sort, and the final Q-sort vs. the ideal Q-sort. The effect of the drugs was

TABLE 2

ANALYSIS OF VARIANCE
PEARSON R CORRELATIONS
Q-SORT

Source of Variance	Sum of Squares	* df	Mean Squares	F †	Signif.
Columns	8041	3	2680	5.73	$p<.01$
Rows	7446	14	531	1.13	NS
Residual	19677	42	468		

* degrees of freedom
† variants ratio

significant at better than the 1 per cent level. The effect of the tetrad matching was not significant in this analysis.

Table 3 shows the results of the pair-wise comparisons of the drugs, using the preceding measures of change. On this evaluation, drug TP-21 gives significantly better results than the other three compounds, none of which are significantly different from each other.

TABLE 3

DRUG VS. DRUG COMPARISON
Q-SORT CORRELATIONS

Drug Groups	$\bar{d}$ *	$\sigma_{\bar{d}}$ †	t‡	Signif.
TP-21 vs. TP-21 Pl.	223.1	82.67	2.698	p=.02
TP-21 vs. KS-75	163.6	64.97	2.52	.05>.02
TP-21 vs. KS-75 Pl.	306.27	79.23	3.86	p<.01
KS-75 vs. KS-75 Pl.	131.07	81.42	1.61	N.S.
KS-75 vs. TP-21 Pl.	59.47	73.31	.81	N.S.
TP-21 Pl. vs. KS-75 Pl.	83.47	71.22	1.17	N.S.

* mean of difference scores
† standard deviation of the mean
‡ Student's t

Table 4 shows the second analysis of variance, using as the measure the improvement scores obtained by comparing the shift between original Q-sort and final Q-sort toward the ideal placement, a quantitative measurement of change. On this evaluation, the effect of the drugs is significant at the 1 per cent level, while the effect of the tetrad matching is significant at better than the 5 per cent level.

TABLE 4

ANALYSIS OF VARIANCE
IMPROVEMENT SCORES
Q-SORT

Source of Variance	Sum of Squares	df	Mean Squares	F	Signif.
Columns	28123	3	9374	8.12	p=.01
Rows	32439	14	2317	2.01	.05<.01
Residual	48514	42	1155		

Table 5 shows the pair-wise comparisons using this measure of change. Here again the drug TP-21 had a significantly different effect, in the direction of improvement, over its placebo and drug KS-75 at the 1 per cent level, and over KS-75 placebo at the 1/10

per cent level. On this evaluation drug KS-75 is significantly different in the direction of improvement from its placebo at the 2 per cent level.

TABLE 5

DRUG VS. DRUG COMPARISON
IMPROVEMENT SCORES

Drug Groups	$\bar{d}$	$\sigma\bar{d}$	t	Signif.
TP-21 vs. TP-21 Pl.	38.67	12.61	3.066	$p<.01$
TP-21 vs. KS-75	30.13	10.07	2.99	$p<.01$
TP-21 vs. KS-75 Pl.	59.8	11.96	5.00	$p<.001$
KS-75 vs. KS-75 Pl.	33.87	11.96	2.83	$p=.02$
KS-75 vs. TP-21 Pl.	12.73	13.52	0.9416	Not sig.
TP-21 Pl. vs. KS-75 Pl.	21.13	13.26	1.9416	Not sig.

It is interesting that while TP-21 placebo was not as effective as its drug, TP-21, it appears to be as effective as drug KS-75, and more effective than KS-75 placebo. An explanation for this may be found in the element of suggestion that is part of the "placebo effect." TP-21 and its placebo were light green, while KS-75 and its placebo were red. In the considerable discussion among the patients in this study about how the drugs made them feel, etc., there were references to the beneficial effect of the drug TP-21 (expressed by the patients as, "The green pills are helping me a lot"), and to the lack of significant beneficial effects from the red pills. This may explain the difference in response to the two placebo medications. If this interpretation, namely that TP-21 placebo patients showed improvement as a result of the suggestion effect, is correct, the fact that patients treated with TP-21 showed significant improvement over those treated with TP-21 placebo suggests that the specific phenothiazine chemical in TP-21 is responsible to some degree over and above the "placebo effect."

The variation in the results obtained by the use of two different methods of evaluation, namely the subjective evaluation obtained by the MMPI, and the objective evaluation obtained by means of the Q-sort, can be explained by the assumption that the Q-sort measures the immediate, obvious changes in the symptomatology of the patient, whereas the MMPI is presumed to measure his basic personality pattern. We believe it is more reasonable to expect obvious change in symptomatology during four weeks of treatment than to expect any

pronounced change in the overall personality patterns of an individual in the same period. The observation that the one MMPI evaluation that showed significant differences between the four groups was one that used a quantitative estimate of change in the profile (in other words, one that had to do with a change in amount of disturbance rather than a shift in the basic profile) seems to confirm the explanation given above.

A brief comment about the complications encountered in the course of the study will help to explain the loss of some patients from the study group. The four patients previously described, who discontinued medication after 24 to 48 hours, complained of the following symptoms: nausea and vomiting, sick feeling in the stomach, dizziness, and drowsiness. As previously indicated, these symptoms occurred in one patient who was on placebo medication, one patient on drug TP-21, and two patients on drug KS-75. Among the patients who were on the medication after one week but failed to finish the whole four weeks, four were on drug TP-21. Two of these patients complained that the medication was not helping them and asked to be put back on their previous medication. The third failed to return for her final appointment and could not be contacted, while the fourth complained that her previous emotional symptoms were returning, and in addition complained of backache, weakness, and blurred vision. Five of the patients were on drug KS-75; three of these patients stopped because of return of their previous symptoms, and two because of nausea, vomiting, diarrhea, and dizziness. The remaining six patients who discontinued were in the two placebo groups. Two of these complained of nausea, vomiting, and dizziness, while the other four became so much worse emotionally that they were returned to their previous medication.

The serial urinalyses failed to show any significant changes in any group during the study. The white blood counts of one patient on drug TP-21 and one patient on drug KS-75 fell to 4,000 per cu.mm. after the second week on the drug, but had returned to 7,000 to 8,000 per cu.mm. by the end of the study.

As indicated earlier, no attempt was made to evaluate the patients on the basis of their psychiatric diagnosis. The groupings used were based on the matching of MMPI profiles, rather than on psychiatric diagnoses or symptom clusters. Table 6 shows the distribution of patients in several broad diagnostic categories over the four drug groups, and indicates the response of the patients to the drugs.

TABLE 6

RESULTS BY CLINICAL DIAGNOSIS

Diagnostic Group	TP-21		KS-75		TP-21 Pl		KS-75 Pl		Total
	Impr.	Un-Chgd.	Impr.	Un-Chgd.	Impr.	Un-Chgd.	Impr.	Un-Chgd.	
Psychoneuroses	5	1	3	4	3	3	1	3	23
Sociopathic Reactions	1		1	1	0	0	2	2	7
Involutional & Manic-Depressive Psychoses	4	1	1	0	4	1	0	4	15
Schizophrenic Reactions	2	1	2	3	0	4	1	2	15
Total	12	3	7	8	7	8	4	11	60

Conclusions

The results of this study show that the phenothiazine compound, Sandoz TP-21, produced an improvement in 12 out of 15 patients treated in the outpatient clinics of the University of Minnesota Hospitals and the Minneapolis General Hospital. This was a significantly better response than that obtained with the drug Sandoz KS-75, and the two placebos for these drugs. In the dosage range used, namely 75 mg. per day, there were minimal side effects and no indication of toxicity.

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Staff Meeting Report

The Effect of Total Cardiopulmonary Bypass on Cerebrovascular Permeability*†

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The general concept of this method of investigation used in the present studies was reported by McIntosh *et al.*[1] one year ago at this meeting. In essence it is the transfer of the dye fluorescein across a normally impervious barrier between the cerebrovascular system and brain tissue after this barrier has been made pervious by the injection of noxious substances into the carotid artery. The present studies are a contnuation of this method, the only variation being a change in the noxious material used to bring about the altered permeability. These studies have been made because it was realized there might be a significant alteration of the normal cerebrovascular permeability occurring with the total cardiopulmonary bypass technique used in cardiac surgery. The need for further knowledge on this subject is apparent from the increasing number of operative procedures involving cardiopulmonary bypass that have been carried out at this and other institutions in recent years.

The background for this type of investigation actually goes back many years. Goldmann[2] in 1913 showed that trypan blue injected intravenously would stain all organs except the brain. The brain did stain, however, if trypan blue was injected into the cerebrospinal fluid, demonstrating that the cerebral vessels possessed a selective permeability to this dye. At that time the brain was thought to be nourished solely by the cerebrospinal fluid, which was believed formed by the choroid plexus, so that the site of blockage of the dye was considered to be the vessels of the plexus. Later Walter,[3,4] Friedman and Elkeles,[5,6,7] and Spatz[8] demonstrated that the nourishment of the brain was implemented directly by its own vessels, which meant

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that the cerebral vessels themselves, as well as those in the choroid plexus, were selectively permeable. Gradually the concept of a barrier existing between the blood and the brain as distinguished from that between the blood and cerebrospinal fluid was evolved. The site of this barrier is generally considered to be the endothelial lining of the cerebral vessels (Broman).[9] There is still, however, considerable controversy in this regard. The authors believe that the endothelium is not the only site of control of permeability, although damage to this structure will increase the normal permeability as evidenced by the uptake by the brain and cerebrospinal fluid of a large molecule dye, fluorescein, as well as of many other substances including D_2O, P_{32}, and RISA.

In studying the effect of total cardiopulmonary bypass, obviously there are a number of possible causes of altered permeability. Last year's report,[1] listed, for example, the various noxious influences used in this laboratory in studying cerebrovascular permeability, including such chemotoxic agents as bile salts, bee venom, cobra venom, saponine, various cerebral angiographic contrast media, and sodium taurocholate. The effects of ischemia and anoxia and perfusion with fluids—at high osmotic pressures, at extremes of acidity and alkalinity, and at various temperature elevations—were studied. In all these investigations the altered permeability was assessed visually by observation of the amount of sodium fluorescein taken up by the cerebral tissues. Other and perhaps more quantitative methods, such as transfer of radioactive isotopes and other dye stuffs, have also been used, but in our experience the transfer of the sodium fluorescein is as accurate as other materials and is much more easily effected.

Method

A total of 67 mongrel dogs believed to be in good condition at the time of experiment were used. Each animal after an overnight fast was given morphine sulfate 15 mg. and atropine sulfate 0.6 mg. One hour later sodium pentothal 2.5 per cent was given intravenously to produce an anesthetic state. Intubation was performed and the animals were allowed to breathe normally. Whenever the chest was opened mechanical respiration with compressed air was instituted. Thoracotomy, when carried out, was performed through the bed of the right fifth rib, and after the required attention to hemostasis, the animals were given heparin 2 mg. per kg. of body weight. In establishing the cardiopulmonary bypass cannulae were inserted into the superior and inferior venae cavae through the right atrial wall, and

were fixed by external occlusive ligatures. In all animals in which perfusions were carried out the Sigmamotor pump was used. Donor blood used for priming of various oxygenators was freshly drawn into 500 cc. siliconized bottles each containing 20 mg. of heparin. Blood pressures were recorded on a mercury manometer connected to a cannula placed in the opposite femoral artery. Thirty minutes before the end of each experiment, the animal received an intravenous injection of 25 mg. of 20 per cent sodium fluorescein per kg. of body weight. At the end of each experiment the animal was sacrificed with intravenous administration of Nembutal,® and its brain was carefully removed for study under a mercury arc lamp with a Woods filter.

The animal's brain was cut coronally into 4 to 6 sections. Asessment of alteration from the normal cerebrovascular permeability was made by examining the surfaces of these sections under the ultraviolet light. The number of fluorescent areas on the cut surfaces were counted and graded on the following basis:

No. Fluorescent Areas	*Grade*
0 -	Negative
1 - 3	Trace
4 - 5	1+
6 - 10	2+
11 - 15	3+
16 or more	4+

Any brains that showed areas of fluorescence larger than 2-3 mm. were automatically placed in Group 4+.

After this assessment of altered permeability was made, the tissues were fixed in formalin for preparation of histological sections.

Group I. Anesthesia Controls: A series of five dogs each weighing from 6.8 to 12 kg. was used. The animals were anesthetized in the usual manner, after which they were given the usual dosage of sodium fluorescein intravenously, and were sacrificed thirty minutes later. None of these dogs showed any evidence of increased cerebrovascular permeability.

Group II. Sham Operation Controls: A series of seven dogs each weighing from 6.8 to 11 kg. was used. The dogs were anesthetized in the usual manner and various sham procedures were performed, including a thoracotomy on each dog; in addition, cannulae were placed in the venae cavae of two animals, and in the carotid artery of another; in two others the right carotid artery was ligated. After a period of 30 minutes, all seven dogs were sacrificed. In none was

there any evident alteration from the normal cerebrovascular permeability.

Group III. Hypotensive Controls: A series of five dogs each weighing from 7 to 11 kg. was used. After the dogs were anesthetized, one cannula was placed in the femoral artery and one in the femoral vein—the former in order to measure pressure and the latter to permit administration of dilute Arfonad® solution sufficient to maintain the arterial pressure below 40 mm. Hg for one hour. The animals were then sacrificed. Four dogs showed no evidence of altered cerebrovascular permeability, while one animal had multiple punctate areas of fluorescence (Grade 4+).

Group IV. Air Embolism Controls: A series of three dogs each weighing from 6.5 to 10 kg. was used. The dogs were anesthetized, one of the carotid arteries was exposed in each, and a measured quantity of air (0.2 cc., 0.4 cc., 0.6 cc. respectively) was injected. The animals were sacrificed 30 minutes later. The brain of the animal which had received 0.2 cc. of air showed no abnormal fluorescence; the other two (given 0.4 cc. and 0.6 cc.) exhibited 4+ alteration. The studies were not extended further for two reasons: these results were consistent with those obtained previously in similar experiments on rabbits and dogs, and also the survey experiments had demonstrated that meticulous care was necessary in setting up the bypass technique, for a few bubbles of air in the extracorporeal tubing would cause 4+ fluorescence of the brain.

Group V. Bypass (Pump) Controls: A series of five dogs each weighing from 8.6 to 13 kg. was used. Four dogs were perfused with extracorporeal pump bypass without oxygenator and without filters for a period of two hours at a flow rate of 50-100 cc/kg/min. the fifth dog was perfused similarly but with the addition of an antifoam free plastic reservoir chamber in the bypass. In four of these animals blood was shunted from the femoral artery to the axillary artery, while in the fifth animal it was shunted from the femoral directly into the carotid artery (proximal end). The brains of four dogs revealed no evidence of altered permeability, while the fifth was graded as a trace on the basis of a single fluorescent area; this last animal had been perfused using the antifoam free plastic reservoir chamber.

Group VI. Bypass with Excess of Antifoam: A series of four dogs each weighing from 5.7 to 13 kg. was used. Each animal was perfused with the extracorporeal pump bypass system in which a reservoir containing an excessively heavy coating of Dow Corning Antifoam A had been interposed between the suction cannula and the pump. In

these animals the shunt was from the femoral to carotid artery (proximal end) in three, while in the fourth it was into the axillary artery. These animals were perfused for a period of two hours with a flow rate of 65-100 cc/kg/min. At the time of sacrifice the brains of all four animals showed 4+ fluorescence, indicating a markedly altered cerebrovascular permeability.

Group VII. Controlled Cross Circulation: A series of ten dogs each weighing 6.8 to 12 kg. was perfused over a period of one hour at flow rates of 30-100 cc/kg/min using cross circulation. Donors consisted of a group of ten dogs each weighing 18.7 to 35 kg. which were anesthetized in the usual manner and given 2 mg. of heparin per kg. of body weight; cannulae were inserted through the femoral artery and femoral vein as previously described. When these animals were sacrificed, five brains were negative, three showed a trace, and two revealed 1+ grading of altered permeability.

Group VIII. Disposable Sheet Oxygenator: A series of twelve dogs each weighing from 10 to 20 kg. was perfused for 15 minutes to two hours at flow rates of 35-70 cc/kg/min using the disposable type sheet oxygenator, Sigmamotor pump, and gravity venous drainage with a plastic reservoir. Each oxygenator was primed with 1250 cc. of freshly drawn heparinized blood. In six animals the cannula was placed into the femoral artery, and in the other six it was placed into the right carotid artery. At the time of sacrificing, the brains of all twelve animals showed 4+ breakdown of the normal permeability.

Group IX. Disposable Sheet Oxygenator with Autogenous Lung Filter: A series of five dogs each weighing from 9.6 to 16 kg. was used. The arterial cannula was inserted into the right atrium through the azygos vein. The animals were perfused with the sheet oxygenator for a period of one hour at a flow rate of 50 cc/kg/min. This experiment used the lung as a physiological filter. At the time of sacrifice none of the brains showed any evidence of altered permebility.

Group X. Helix Reservoir Oxygenator: A series of nine dogs, each weighing from 7.8 to 15.7 kg. was used. Each dog was perfused for a period of one to two hours at a flow rate of 50-70 cc/kg/min with a helix reservoir type oxygenator (DeWall). This oxygenator had a light film of Dow Corning Antifoam A in the debubbling chamber, as generally recommended. At the time of sacrifice, two of the animals revealed a trace, five showed 1+, and two showed 3+ breakdown of the normal permeability.

Group XI. Antifoam Controls: A series of two dogs with weights

of 8.4 and 10.3 kg. was used. In the first animal, purified antifoam 0.5 cc. was injected into the carotid artery on one side, and at the time of sacrifice 30 minutes later, there was 4+ breakdown of the vascular permeability. Purified antifoam, 4 cc. was then injected in the second animal intravenously, so that the lung would act as a purifier; the brain of this animal revealed no evidence of abnormal permeability, but the lung showed a large area of infarction.

TABLE 1
SUMMARY OF RESULTS

Study Group		Number of Dogs	Degree of Breakdown of Blood Brain Barrier				
			Neg. Trace	1	2	3	4
Group 1	Anesthesia Controls	5	5	0	0	0	0
Group II	Sham Operation Controls	7	7	0	0	0	0
Group III	Hypotensive Controls	5	4	0	0	0	1
Group IV	Air Embolism Controls	3	1	0	0	0	2
Group V	Bypass Pump Controls	5	4	1	0	0	0
Group VI	Bypass with Excess of Antifoam	4	0	0	0	0	4
Group VII	Controlled Cross Circulation	10	5	3	2	0	0
Group VIII	Disposable Sheet Oxygenator	12	0	0	0	0	12
Group IX	Disposable Sheet Oxygenator with Autogenous Lung Filter	5	5	0	0	0	0
Group X	Helix Reservoir Oxygenator (DeWall)	9	0	2	5	0	2	0
Group XI	Antifoam Controls (Intracarotid)	1	0	0	0	0	0	1
	(Intravenous)	1	1	0	0	0	0	0

Discussion:

A method of determining disturbances in the normal cerebrovascular permeability has been utilized in the study of effects of total body perfusion on the central nervous system. These same basic techniques have previously been used in studying cerebral edema with special reference to brain tumor localization, complications of cerebral angiography, and identification of epileptogenic foci. The present studies reveal that a number of factors are influential in producing alterations in the cerebrovascular permeability: Air embolus (Group IV) utilizing only minute amounts of air has been shown to produce definite defects in the permeability. Antifoam A, by virtue of its presence in the method utilized in Group VI and by its absence in Group V, as well as the absence of appreciable breakdown when using the autogenous lung as a filter (Group IX), is unquestionably a factor. When Antifoam A is reduced to a minimum and fixed to the defoaming chamber by autoclaving, it is possible to reduce considerably the frequency of disturbances in the vascular

permeability. The influence of hypotension on the cerebrovascular permeability does not appear to be uniformly adverse, as shown in Group III. But the fact that hypotension by itself has some influence in breaking down the normal cerebrovascular permeability suggests that when it occurs together with other noxious influences sometimes associated with total cardiopulmonary bypass, the probabilities of altering the normal permeability are greatly increased. The efficacy of the lung as a filter is demonstrated by the results obtained in Groups IX and XI. Evidence obtained in these studies indicates that defects seem to exist in the perfusion techniques utilizing extracorporeal oxygenation. All of the techniques used for bypass produced some evidence of altered permeability. Procedures utilizing crosss circulation resulted in the least amount of altered permeability. But since this method of total cardiopulmonary bypass has obvious disadvantages for clinical use, it seems advisable that refinements be sought for the artificial perfusion apparatus.

Conclusions:

1) Results are given of the effect on cerebrovascular permeability of certain methods used for total cardiopulmonary bypass.

2) All methods for total cardiopulmonary bypass described in this report increased cerebrovascular permeability to some degree.

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Editorial

In Appreciation

There are many needs of a hospital in terms of services and equipment, both technical and what can be called just ordinary, which hospital funds are never sufficient to supply. Hospitals vary so in their needs, and the public varies so in its interests that it is hard to set a pattern for requests.

Most of all, the hospital needs an understanding of what it is attempting to do, and it needs the assistance of many people outside the paid staff who contribute the personal time and sometimes financial aid. Just as important as this financial help is the thoughtful service given by many people to the patients and the personnel who care for them in the hospital.

The University of Minnesota Hospitals is fortunate in having many interested groups and individuals who contribute much to the success of the hospitals. It is fitting that we thank the Variety Club, and the Variety Club Auxiliary, for their support to the Variety Club Heart Hospital, the University Hospitals Auxiliary, and other sections of the University Faculty Women's Club, which have continued their generous efforts in behalf of our patients, the Crippled Child Relief and the Minnesota Society for Crippled Children and Disabled Adults, the State Division of Social Welfare and the County Welfare Boards for their assistance, the various nursing homes for their cooperation, the Traffic Club, which year after year provides entertainment, gifts, and cheer to our patients at Christmas, the Sunshine Society, the Camp Fire Girls and the Girl Scouts, the Needlework Guild, the Junior League, the Minneapolis Council of Churches, the Minneapolis and Hennepin County Chapter of the American Red Cross, the Volunteer Service Bureau, and many other organizations and individuals who have contributed to our patients' welfare, including, of course, chaplains who minister to the spiritual needs of our patients.

We of the Hospitals wish to express our sincere appreciation to our corps of volunteers working at the information desks and in patient areas. We wish to thank the many people throughout the state who have contributed to our service and research funds during the past year. To all members of the professional and service staffs of the Hospitals, the administration wishes to express its gratitude for their loyal devotion to duty and considerate care of the patients.

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Faculty Publications

LICHSTEIN, H. C.: Bound Biotin in Oxalacetic Carboxylase Preparation. Arch. Biochem. Biophys. 71:276, 1957.

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NEUMEISTER, CHARLES A.: Carcinoma of the Rectum and Sigmoid Colon. Minn. Med. 40:313, 1957.

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ROSS, J. D., and GIFFORD, G. E.: Manometric Calibration of Warburg Flasks. J. Lab. & Clin. Med. 49:802, 1957.

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ROTH, F. J., JR., FRIEDMAN, JACK, and SYVERTON, J. T.: Effects of Roentgen Radiation and Cortisone on Susceptibility of Mice to *Candida Albicans*. J. Immunology 78:122, 1957.

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SYVERTON, J. T.: Host-Parasite Relationships in Living Cells, pp. 47-62. Charles C Thomas, Publisher, Springfield, Illinois, 1957.

SYVERTON, J. T., MCLEAN, D. M., MARTINS DA SILVA, M., DOANY, H. B., COONEY, M., KLEINMAN, H., and BAUER, H.: Outbreak of Aseptic Meningitis Caused by Coxsackie B5 Virus. J.A.M.A. 164: 2015, 1957.

SYVERTON, J. T., and MCLAREN, L. C.: Human Cells in Continuous Culture. I. Derivation of Cell Strains from Esophagus, Palate, Liver, and Lung. Cancer Res. 17:923, 1957.

WATSON, D. W.: Type-Specific Toxins in Group A Streptococcal Lesion Extracts. Fed. Proc. 16:437, 1957.

Coming Events

March 17-19 . . . . . Continuation Course in Internal Medicine for Internists

March 18 . . . . . GEORGE E. FAHR LECTURE: *Pulmonary Hypertension;* DR. PAUL WOOD, Institute of Cardiology, London, England; Mayo Memorial Auditorium; 8:00 A.M.

March 20 . . . . . Continuation Course in Surgery for Surgeons

March 21 . . . . . E. STARR JUDD LECTURE: *A Concept of the Pathogenesis of Gastric and Duodenal Ulcers;* DR. LESTER R. DRAGSTEDT, Professor of Surgery, University of Illinois College of Medicine, Chicago, Illinois; Mayo Memorial Auditorium; 4:00 P.M.

March 31 - April 2 . . Continuation Course in Gynecology for General Physicians

April 7-9 . . . . . Continuation Course in Radiology for General Physicians

April 10-12 . . . . . Continuation Course in Arthritis and Physical Medicine for General Physicians

April 12 . . . . . Continuation Course in Trauma for General Physicians

April 14-16 . . . . . Continuation Course in Gastroenterology for General Physicians

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
Thursday,	11:30 A.M. to 12:30 P.M.	TUMOR Todd Amphitheater University Hospitals
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.