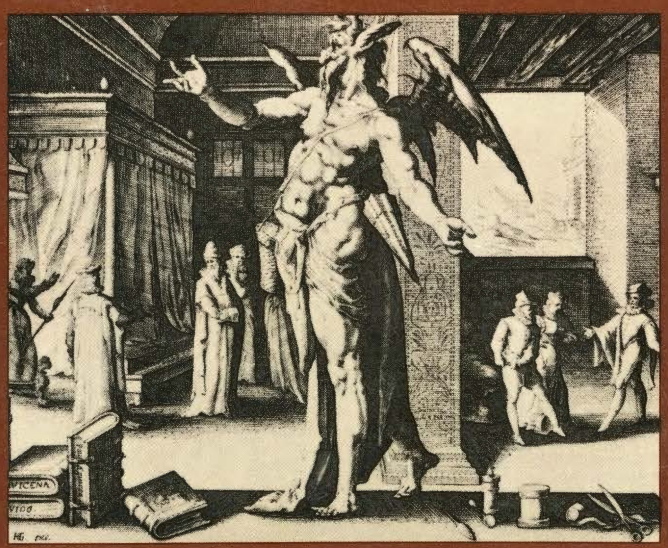
MCV/Q

MEDICAL COLLEGE OF VIRGINIA QUARTERLY

VOLUME THREE • NUMBER THREE • 1967

The physician is a god

The physician is a man



The physician is a devil

The physician is an angel


"Well, he finally decided
to clean the attic.
Almost had the job done, too..."
"...Yeah, until he tried to lift me.
It sure put his back out of whack.
His doctor's got a real job to do
—trying to ease both
the pain and the strain."

when stress results in muscle strain and pain

When the normally sedentary person suddenly turns active—cleaning the attic, for instance—the outcome is sometimes a strain or sprain in the back, neck or shoulders.

Fortunately, however, most patients with muscle spasm and pain are highly responsive to therapy with Robaxisal. This rationally based formula provides the well-known relaxant benefits of methocarbamol for strained, tense skeletal muscle plus the dependable analgesic and anti-inflammatory effects of aspirin. Investigators have found methocarbamol a well-tolerated agent with "specificity of action."[1] And methocarbamol potentiates the salicylate levels of aspirin so that, in combination, *higher salicylate levels* are produced than with equivalent doses of aspirin alone.[2] When the Robaxisal combination* was administered to a group of 22 patients with painful musculoskeletal disorders, 20 (91 per cent) showed an excellent or good response.[2]

With Robaxisal you can conveniently fulfill the most important objectives in treatment of muscle spasm: relaxation of skeletal muscle, relief of pain, restoration of mobility and normal muscle tone. And when mild anxiety is a factor in the spasm-pain syndrome, consider Robaxisal®-PH.

*In this investigation, 400 mg. methocarbamol was combined with 300 mg. aspirin.
References: 1. Weiss, M., and Weiss, S.: J. Am. Osteopath. A. *62*:142, 1962. 2. Truitt, E.B., Jr.; Morgan, A.M., and Nachman, H.M.: South. M.J. *54*:318, 1961.

Robaxisal® brings relief for both

Robaxisal®
Each pink and white laminated tablet contains:
Robaxin (methocarbamol, Robins) ..... 400 mg.
U.S. Pat. No. 2770649
Aspirin (5 gr.) ..... 325 mg.

Robaxisal®-PH
Each green and white laminated tablet contains:
Robaxin (methocarbamol, Robins) ..... 400 mg.
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Aspirin ..... 81 mg.
Phenobarbital (1/8 gr.) ..... 8.1 mg.
(Warning: May be habit forming)
Hyoscyamine sulfate ..... 0.016 mg.

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Robaxisal and **Robaxisal-PH** are indicated when both analgesic and skeletal muscle relaxant effects are required, as in strains and sprains, painful disorders of the back, "whiplash" injury, myositis, pain and spasm associated with arthritis, torticollis, and headache associated with muscular tension.

Contraindications: Hypersensitivity to any one of the components.

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MCV/Q

MEDICAL COLLEGE OF VIRGINIA QUARTERLY

A Scientific Publication of the School of Medicine

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COVER: 16th Century satirical engravings executed at Haarlem, the Netherlands, 1587 under the direction of Hendrik Goltzius (1558-1617).

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Origins of Congenital Defects: Epidemiologic Approach

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This presentation consists of several short stories from personal experience to illustrate the complementary nature of epidemiologic and laboratory research in the study of congenital malformations.

Visual Acuity

The Child Health Survey in Hiroshima and Nagasaki from 1958 until 1960 was concerned with a comprehensive examination of about 3500 children born of parents who were cousins and an equal number whose parents were not cousins (Schull and Neel, 1965). An evaluation of the effects of inbreeding was the primary objective, but there was also a chance to study the influence on health of a wide variety of environmental variables. All children had been examined earlier as controls in an evaluation of the genetic effects of radiation (Neel and Schull, 1956). The later consanguinity study concerned children whose parents had received very little or no radiation exposure. Thus, the effects of inbreeding were not confounded by those of radiation. The children were 5 to 11 years of age at the time of this follow-up examination.

The loss of distant visual acuity —that is, vision of 20/70 or worse in at least one eye—was classified as due to congenital organic defect when some abnormality could be found by external examination of the eye or by use of the ophthalmoscope. When no such defect was found, the visual acuity loss was attributed to refractive error, principally myopia. The prevalence of congenital organic lesions of the eye increased very significantly with inbreeding, from 1.69 per 1000 for children of unrelated parents to 10.01 per 1000 for children whose parents were first cousins. Since the rates of these lesions are normally very low, the risk to the child of a consanguineous mating, even though six times normal, is not very great.

Virtually no refractive errors were found among children under 6 years of age. Those occurring thereafter were considered to be due to myopia. The role of inheritance was implicated in the genesis of this defect by the increase in frequency as the degree of inbreeding increased, by the tendency for cases to aggregate in families, and by the greater rates in Japan as compared with the United States (racial difference ?). The influence of the environment early in life was suggested by finding that the risk of myopia was increased among children whose birth weight was less than 2500 grams, as previously found in several studies from Great Britain and the United States, and by the independent tendency in Hiroshima for rates of myopia to be higher among children born during the first half of the year, particularly those born in the spring months (Miller, 1963). There was no relationship of childhood myopia to maternal age or to birth order, to socioeconomic status as indicated by average food

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costs or number of floor mats in the home, to evidence of major disease as revealed by the history or the physical examination, to growth as determined by four measurements, to neurologic or intellectual capacity as indicated by a battery of screening tests, or to dental health or development as indicated by caries rates and average number of primary and secondary teeth erupted. The age-specific prevalence rates of myopia were consistently higher in Nagasaki than in Hiroshima.

The accumulated evidence to date suggests that the defect in childhood myopia is present at birth or soon thereafter and that environmental stresses later in life have little influence on its occurrence. The results of our survey indicate that it would be profitable in the future to investigate the origin of myopia through family studies, well-controlled racial comparisons involving Japanese migrants to the United States, and surveys relating myopia in embryologic and at-birth events. In such studies the epidemiologic approach affords an opportunity to weigh genetic and environmental influences in the genesis of a maldevelopment of the refractive system more easily than can be done in the animal laboratory.

Cytogenetic Defects

The relationship of mongolism to maternal age is an epidemiologic observation first made in 1909 (Shuttleworth), more than 50 years ago. Obstetricians have sensed for decades that miscarriages also increase with maternal age, but documentation was poor until two years ago when a group of statisticians—not obstetricians—showed that miscarriages in the first 12 weeks of pregnancy were three times more common among women 35 years of age and older than among women 20 to 24 years of age (Shapiro, Jones, and Densen, 1962). As in mongolism, the maternal age effect on miscarriages is due to some extent to meiotic nondisjunction, which increases in frequency with maternal age. Recently cytogenetic defects have been found in about 25% of selected abortuses (Carr, 1967).

Three studies have shown that childhood leukemia also increases in frequency with the mother's age at the birth of the child (MacMahon and Newill, 1962; Stewart, Webb, and Hewitt, 1958; Miller, 1963). One may wonder whether this relationship also reflects an influence of non-disjunction in some cases of childhood leukemia. In this regard it would be of interest to compare the chromosomal patterns of leukemic children in remission with respect to maternal age or maternal history of miscarriage.

Study of individual families has suggested that occasionally there may be an unusual recurrence of non-disjunction (Hecht et al., 1964). Thus, in the same sibship one may find that two children have trisomy 21, that one child has trisomy 21, that another has Klinefelter's syndrome, and that another pregnancy resulted in a miscarriage. From individual family histories one cannot tell whether or not these occurrences are due to chance. More conclusive evidence awaits epidemiologic studies which evaluate the frequency of disorders associated with non-disjunction among relatives in families ascertained through a child with a non-disjunctive chromosomal error.

These examples indicate that, in the study of cytogenetic defects, there is a substantial interaction among observations made in the laboratory, at the bedside, and by epidemiologic studies.

Coexistence of Congenital Malformations with Cancers of Childhood

The recognition of the link between mongolism and leukemia has contributed to the understanding of the etiology of leukemia. To afford a similar opportunity in the study of Wilms' tumor, the medical charts of 440 children with this neoplasm were reviewed in a search for an excessive occurrence of specific congenital malformations (Miller, Fraumeni, and Manning, 1964). Six of the children were found to have congenital absence of the iris of the eye, giving a rate of 1:73 as compared with the expected at-birth incidence of 1:50,000. Four of these children had cataracts and a fifth had glaucoma, defects known to be secondary to aniridia. Three of the aniridic children had small head circumferences and mental retardation. Thus, there appears to be a syndrome of Wilms' tumor, aniridia, cataracts or glaucoma, mental retardation, and small head circumference.

Among the 440 Wilms' tumor cases in the series, there were three children with congenital hemihypertrophy contralateral to the Wilms' tumor. In one case the hemihypertrophy was limited to the face and tongue. Congenital hemihypertrophy occurs so rarely that no estimate of its frequency in the population is available.

Of 437 children in our series without hemihypertrophy, 4 had extensive pigmented nevi and 8 had significant hemanglomata (4 of them internal), defects known to be associated with hemihypertrophy. Nineteen of the children with Wilms' tumor had congenital abnormalities of the urinary tract other than hypospadias. There were 4 children with horseshoe kidney, 5 with duplications of the upper urinary tract, 2 with aplasia or hypoplasia of the kidney, and 8 with other urinary tract defects. Among the 223 boys, 5 had hypospadias as compared with 0.6 cases expected, and 11 had undescended testes as compared with 3.3 cases expected.

Recognition of the extensive concurrence of certain congenital defects with Wilms' tumor provides

the opportunity to examine the etiology of the tumor in the light of what is known of the malformations. Shaw, Falls, and Neel (1960) concluded from their statewide study in Michigan that aniridia in man is due to the action of a dominant autosomal gene which is almost completely penetrant and which has few, if any, phenocopies. Of their 82 male aniridics, at least two had hypospadias, and three had cryptorchidism, anomalies found in our study to be excessive among children with Wilms' tumor. On the basis of data from the Michigan study, four of our six cases with aniridia were expected to have an aniridic parent, but none did. If the iris defect was genetically determined, it was due to mutation in our series significantly more often than usual. The possibility exists that aniridia and the associated Wilms' tumor were due to concurrent mutations of different genes, or that the gene leading to aniridia enhanced the expression of an already existent Wilms'-tumor gene complex in the manner postulated by Neel (1958). On the other hand, in the rat, maternal vitamin A deficiency has induced aniridia, horseshoe kidney, hypospadias and cryptorchidism, a finding which suggests that in man these defects may be due to a single gene with pleiotropic effects or to an environmental agent (Miller, 1966).

Despite the very low frequency of congenital hemihypertrophy in the general population, 16 cases have now been reported with Wilms' tumor, 4 with adrenal neoplasms, and 3 with liver neoplasms. In congenital hemihypertrophy there is an excess of pigmented and vascular nevi. These benign neoplasms were also seemingly in excess among our Wilms' tumor cases in the absence of hemihypertrophy. This array of associated diseases suggests a congenital growth excess, a hyperplastic-neoplastic diathesis, which is quite variable in expression.

Although aniridia and hemihypertrophy have not been reported in the same patient and although they apparently have different etiologies and underlying mechanisms, they are alike in having a teratogenic-oncogenic influence on the genitourinary tract, for both have been associated with cryptorchidism, hypospadias, and Wilms' tumor. Further research concerning the origins of any one of the diseases in the constellation associated with Wilms' tumor should provide insight into the genesis of the others and may lead to new clues for laboratory research concerning congenital malformations or neoplasia.

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Diagnostic Ultrasonography*

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It was the development of radar and sonar during the last World War which made the ultrasonic techniques I am going to talk about possible. Following the War, Dr. K. T. Dussik had the idea that, if one directed ultrasonic waves into the body, one might obtain echoes reflected from tissue surfaces in the same way that the Navy received echo information reflected from the submarine's hull. When he did this, he did get reflected echoes from within the body, and this opened the door for other investigators to demonstrate how this echo information could be made useful in diagnostic medicine. The next step was to display these echoes in a form which the physician could recognize and utilize diagnostically. The first part of this presentation will tell you about the various methods we can use to display this echo information, and the second part will give you examples of its diagnostic application in many different medical specialties. Ultrasound is applicable for visualization of soft tissue structures in all parts of the body.

The essential components of an ultrasonic diagnostic unit are a pulser, a transducer, a receiver, an amplifier, and a display system (oscilloscope). (Holmes and Howry, 1963; Holmes, Wright, and Howry, 1964) Originally, the pulser initiated a 1000 volt pulse, but later, with development of more sensitive equipment, this has been reduced to 300 volts. The ultrasonic waves are produced by pulsing a piezo electric crystal contained in the transducer specially constructed so the ultrasonic waves directed into the body come only from the face of the transducer. Ultrasound, like light, can be focussed; thus, by use of appropriate lenses, it is possible to narrow the ultrasonic beam and direct it to desired depths. When the ultrasonic waves strike a tissue interface of different density, they are reflected back to this same crystal, which acts as a receiver converting the ultrasonic energy into electrical energy which passes through the amplifier-receiver system and is displayed on an oscilloscope screen. The simplest display is that used in materials testing (time base). When the transducer is placed on a bar of aluminum, there is displayed an echo "pip" for the near side of the bar, a "pip" for the flaw in the aluminum bar, and a "pip" for the far side of the aluminum bar. By measuring the distance between the flaw echo in relation to the echoes representing the two sides of the bar of aluminum, one can locate the flaw rather precisely. This simple display is often called A-mode presentation. With early X-ray the medical profession really needed the technique, so they developed it and the engineers paid little attention to it. The reverse has occurred with ultrasound, since for the new rocket programs it became imperative to have better materials testing techniques.

The echoes can also be displayed on the screen as a bright dot representing each tissue interface. The

* Supported in part by USPHS Grants #HE 02115 and #HD 01669.

equipment sends and receives ultrasonic energy at the rate of 400 times per second. Thus, if the transducer is moved mechanically around the body, these bright dots will coalesce on the screen to trace the tissue outline, for example, the front edge of the liver or the spleen. To insure a proper relation between organ interfaces as the transducer's position is changed, one must incorporate into the system a position indication and deflection system. This insures that the information displayed on the scope screen reproduces exactly the anatomical pattern the transducer is looking at as it moves about the body. This system is called a B-mode presentation (intensity modulation), and the movement of the transducer is called scanning. To display irregular surfaces, a rocking motion of the transducer is coupled with the movement around the body. This is called compound scanning. The ultrasonic power level delivered to the tissues is .04 to .004 watts per square centimeter. In physical medicine for heat therapy they are using ultrasound at power levels of 1 to 3 watts per square centimeter without toxic effects in treating patients with rheumatoid arthritis. Thus, we feel that the power level used for diagnostic purposes is within safe limits. We have exposed pregnant rabbits at diagnostic doses of ultrasound for periods of five days and found no evidence of toxicity in mother or fetus.

The simple display described above is used clinically for echoencephalography. The transducer surface is covered with lubricating jelly and placed on the side of the head, and the picture obtained is similar to the one I described for the aluminum bar. There are echo "pips" representing the midline of the brain, the near side of the skull, and the far side of the skull. The picture has the appearance shown in Figure 1. (Holmes, 1964a) The transducer is then placed on the opposite side of the head and a similar but inverted picture obtained, which is displayed directly under the first picture, as shown in Figure 1. Finally, a receiving transducer is placed on the opposite side of the head from the sending transducer and a "pip" obtained for the midline position between the two transducers, as shown on the bottom line of Figure 1. The permanent record is obtained by photographing the oscilloscope screen with a Polaroid camera.

Interpretation depends on the relative position of the echo "pips". In the healthy individual the "pips" representing the midline of the brain should fall directly above each other, thus indicating an equidistance between the skull echoes and that of the midline of the brain. However, if there is an intracranial lesion which shifts the midline of the brain to one side, then the echo pattern, as presented on the right-hand side of Figure 1, will show the two "pips" representing the center of the brain displaced in opposite directions. In general, if the shift between the two midline "pips" is greater than 2 mm, it is probably clinically significant. (Jeppsson, 1961) Difficulties in interpretation by the inexperienced operator result from the fact that other structures within the brain may produce echoes as, for example, the interface between the ventricle and brain. Whenever this echo is mistaken for the one representing the midline of the brain, there will always be a shift. There are several tricks in helping to identify the midline echo. Usually, the midline echo

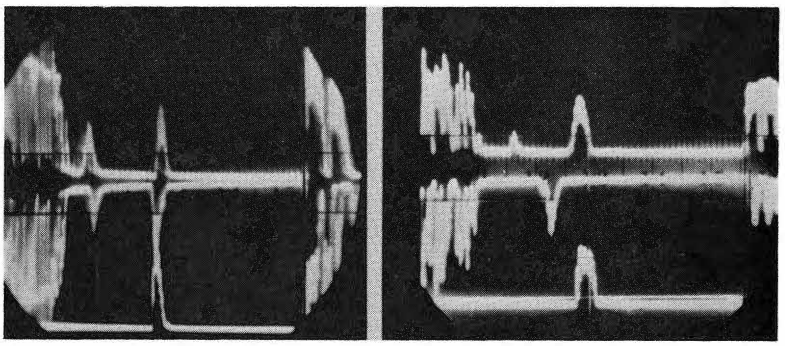

Fig. 1—Shows on the left an echoencephalogram in a healthy normal individual, and on the right an echoencephalogram from a patient with intracranial tumor which produced a shift in the position of the midline echo. Reprinted from *Digest* (Otago Univ. Med. Students Assoc. Dunedin, New Zealand) 6: 27, 1964.

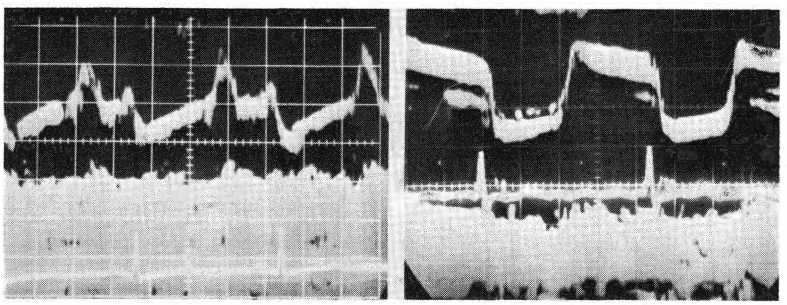

Fig. 2—Picture on the left shows the wave motion pattern of the anterior leaflet of the mitral valve in a healthy individual, and on the right a patient with mitral stenosis. Reprinted from *Digest* (Otago Univ. Med. Students Assoc. Dunedin, New Zealand) 6: 27, 1964.

has an M-shaped appearance. In addition, the midline echo should move back and forth due to vascular pulsations. Finally, in a true shift, the two echoes representing the brain midline must fall on either side of the bottom echo representing instrument midline. As the operator becomes skilled in this technique, he will learn to recognize the midline echo readily, and very few mistakes will be made. (White, 1966)

In approximately 1000 cases examined by Ford and Ambrose in England, the accuracy of this technique in detecting midline shift range from 90% to 95%. (Ford and Ambrose, 1963) Similar series have been reported by other investigators. (Jeppsson, 1961) The echoes reflected from the brain ventricular interface have been used to determine the size of the third and lateral ventricles. (Ford and McRae, 1966)

Echoencephalography can be readily used in the Emergency Room of a large hospital as a screening procedure, since the equipment is simple and quite portable. Furthermore, in a head injury, serial pictures can be obtained, thus predicting a progressive shift. In many hospitals the echoencephalograph is housed in the EEG Department, and when the two techniques are used together, the information obtained is complementary. Thus, if the midline is shifted away from the side of increased electrical activity, it usually confirms the diagnosis of tumor. If shifted toward it, there may be cerebral atrophy.

The same equipment with slight modifications can be used for emergency-type examinations of the eye, as described by N. R. Bronson at the 1967 Miami meeting on ultrasound in medicine. One can obtain reflected echo "pips" from the cornea, the lens, the retina, (personal communication, N. R. Bronson) and from a foreign body in the eye. Thus, different echo patterns will be obtained in retinal detachment, tumor and anatomical displacement of the intraocular structures. Here again, ultrasound has a great advantage as a screening procedure.

The A-mode presentation is also used to measure the biparietal diameter of the baby's head in utero. (Taylor et al., 1964) After palpating the location of the head, the transducer is placed on either side of the baby's head and an echo pattern obtained similar to that noted in Figure 1. A midline echo must be obtained to confirm positioning of the transducer as truly biparietal. Measurements are then made between the echo patterns representing the two sides of the baby's skull. In our series, the measurements of the biparietal diameters of the fetal head were within 3 mm of the measured diameter at delivery in 95% of the babies. (Taylor et al., 1964) Thus, in the Labor Room it is possible to determine easily whether the baby's head is of normal size and will readily pass through the birth canal.

If the echo-producing structure has motion, then the dot will move back and forth on the screen. When the transducer is placed over the mitral valve, one obtains a characteristic motion pattern for the anterior leaflet of that valve. By using an electronic sweep, the dot's movement can be displayed in wave form, as shown on the left-hand side of Figure 2.

The normal wave pattern for the mitral valve shows a high peak in mid-diastole, followed by a steep slope (posterior motion), and then a second smaller peak which occurs at the time of a trial systole (Fig. 2). In the normal, the velocity of maximum posterior motion exceeds 80 mm/sec. The picture on the right side of Figure 2 is that of a stenosed mitral valve. The difference between the two patterns is quite apparent, even to the uninitiated eye. Furthermore, the velocity of posterior motion is always less than 45 mm/sec in those patients with stenosis of sufficient severity to require surgery. (Joyner, 1966)

In experienced hands other information can be deduced from this record. (Joyner, 1966; Edler, 1966) The slope of the line correlates fairly well with the degree of valve movement, and this correlates with the degree of stenosis. Judgment can be made of the thickness of the valve by the thickness of the echo pattern and its degree of motion. If mitral insufficiency is present, the echo pattern will be similar to that of the normal, except the amplitude may be greatly increased. After mitral valve commissurotomy, the motion pattern of the valve has the same appearance as prior to surgery, except for a much steeper slope. If the valve restenoses as the patient is followed postoperatively, then this slope approaches that obtained prior to surgery. Thus, by careful examination of mitral valve motion, it is possible to deduce the presence of mitral stenosis—often the degree of stenosis; estimate the thickness of the valve; and, after surgery,

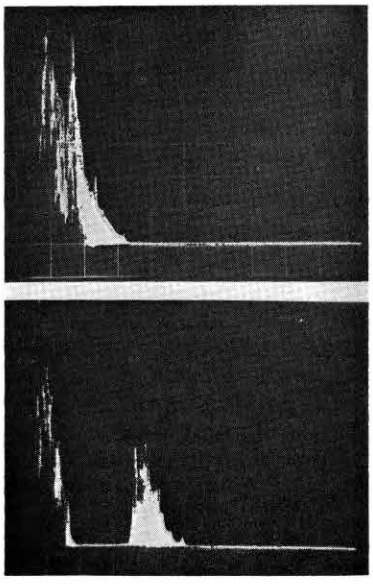

Fig. 3—Shows, above, the echo pattern obtained by A-mode technique of the lung in a healthy laboratory worker, and, below, the pattern obtained in a patient with pleural effusion.

detect the reappearance of stenosis. This has proved to be valuable information for the surgeon, since it can be obtained easily and serially on the same patient. As in all ultrasonic studies, the information obtained should be used to supplement other clinical information.

Another practical application for ultrasound is the detection of pericardial effusion. The anterior and posterior walls of the heart will have a definite motion pattern. Normally, these will be placed immediately adjacent to the echo patterns reflected from structures of the anterior and posterior walls of the chest. However, if there is pericardial effusion, since fluid transmits sound well, there will be a clear black area between the chest wall echoes and the motion patterns of the anterior or posterior wall of the heart. This clear black area will disappear after aspiration of the effusion. Again, in inexperienced hands, difficulties will be encountered in identifying the motion pattern representing ventricular wall and, thus, diagnostic errors will be made.

Recently, ultrasound was shown to be useful in detecting pleural effusion. Since air rapidly attenuates sound, the echo pattern of the normal lung shows a rapid decrease in amplitude of the echo pattern within one to three centimeters of the chest wall (upper picture of Figure 3). When there is pleural effusion, there will be a clear dark area representing good sound transmission between the chest wall echoes and those characteristic of normal lung (lower picture of Fig. 3). When there is consolidation of the lung due to any cause, the ultrasonic echo pattern will extend farther into the lung tissue when compared with Figure 3. Further work is needed to develop this technique for diagnostic application in the lung, but ultrasound does appear to be able to provide supplementary information which will help diagnostically.

As stated previously, compound scanning provides a cross-sectional, anatomical picture of the structures examined. The equipment necessary for obtaining these pictures is shown in Figure 4. In this particular scanner, the transducer moves in a sector scan, mechanically, 30° each side of the perpendicular, while the transducer carriage is simultaneously moved across the abdomen. (Holmes et al., 1965) This represents the double scanning motion previously described. We also have a scanner in which the double motion is provided entirely by the operator's hand. The coupling between transducer and skin surface is obtained by applying mineral oil to the skin. We also have a scanner in which the patient is placed against a plastic membrane while the transducer moves within a water bath which provides the ultrasonic coupling.

How do we know that we are obtaining a true outline of anatomical structures? Figure 5 shows, on the left, a sonogram through the liver region of a cat. (Holmes and Howry, 1963) At the top is the echo outline of the spine and the lumbodorsal muscle groups. The clear black area below and to the left represents the liver which

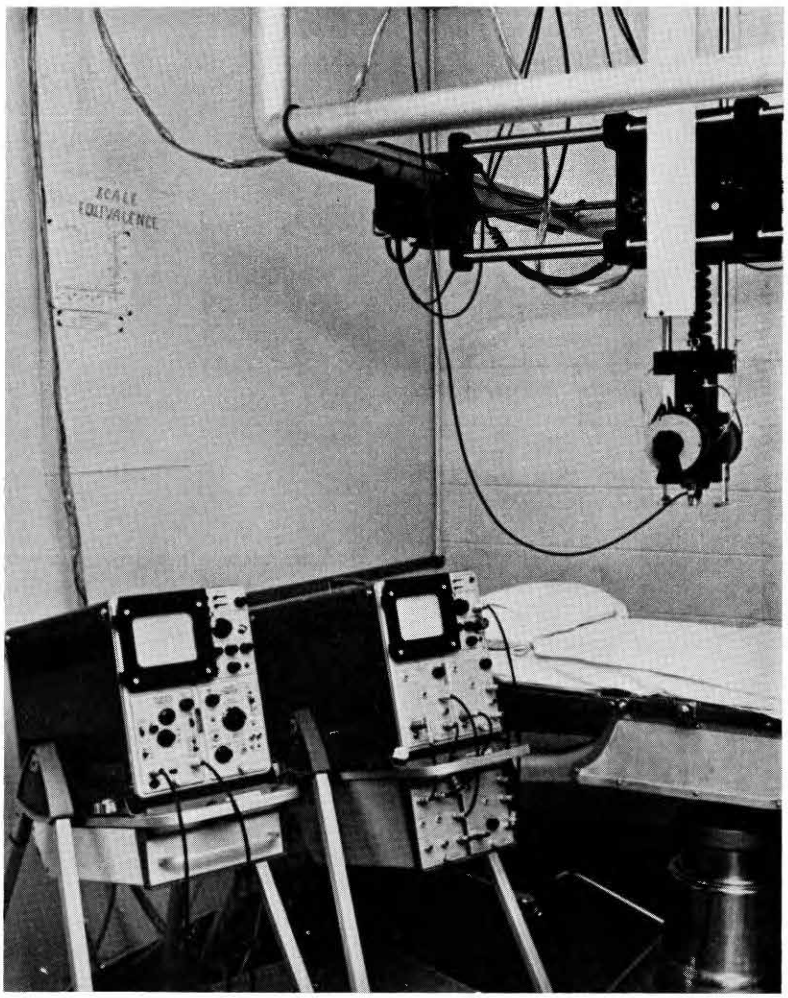

Fig. 4—The first compound contact scanner built at this institution, which has a mechanical sector scan moving 30° each side of the perpendicular, while the transducer carriage is simultaneously moved across the anatomical area being examined, thus achieving a compound scanning motion.

transmits sound well. The echo pattern below and to the right outlines the stomach. The picture on the right is the cross-sectional picture of the same animal at the same level as the sonogram so you can directly compare anatomical structures.

The next ultrasonic cross section is that of a dog at the level of the bladder (Fig. 6). The echo outlines of the spine and lumbodorsal muscle groups are seen above. The clear black area surrounded by an echo pattern represents the full bladder, and there is a smaller echo pattern, just above and to the left, representing a loop of the intestine. The echo in the center of the urine-filled bladder is the catheter. Lower in the picture one sees the flank folds and the echo pattern of the penis.

In a separate study, echo patterns of the cat were obtained as shown in Figure 5. Then an experimental liver abscess was produced by injection of E-coli and turpentine. A definite nest of echo patterns appeared at the site of the abscess. Pathological specimens of a normal liver and a cirrhotic liver were scanned. (Holmes and Howry, 1963) The normal liver appeared as a clear black area, while the cirrhotic liver had multiple echo patterns within the liver area. Now we are ready to examine clinical material.

Figure 7 shows, below, a scan through the liver region of a normal person, and, above, a similar type scan through the liver region of a patient with alcoholic cirrhosis. The normal liver, as in the animal pictures, transmits sound well and appears as clear black area with echoes outlining the anterior and posterior surfaces. In contrast, the picture in the cirrhotic patient shows multiple echo patterns within the liver. These are scattered in a somewhat indiscriminate pattern. The numbers of echoes seen within the cirrhotic liver do appear to have some correlation with the degree of cirrhosis.

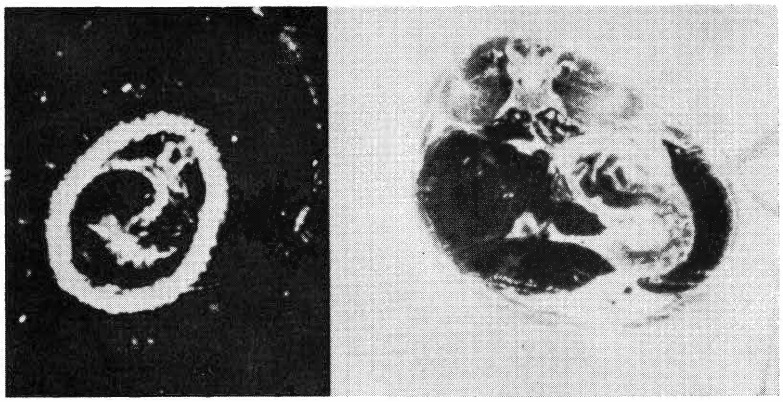

Fig. 5—On the left is a sonogram through the liver region of a cat, while on the right is shown the corresponding anatomical cross section, so that structural comparisons can be made. Reprinted from *Am. J. Digest. Diseases* 8: 12, 1963.

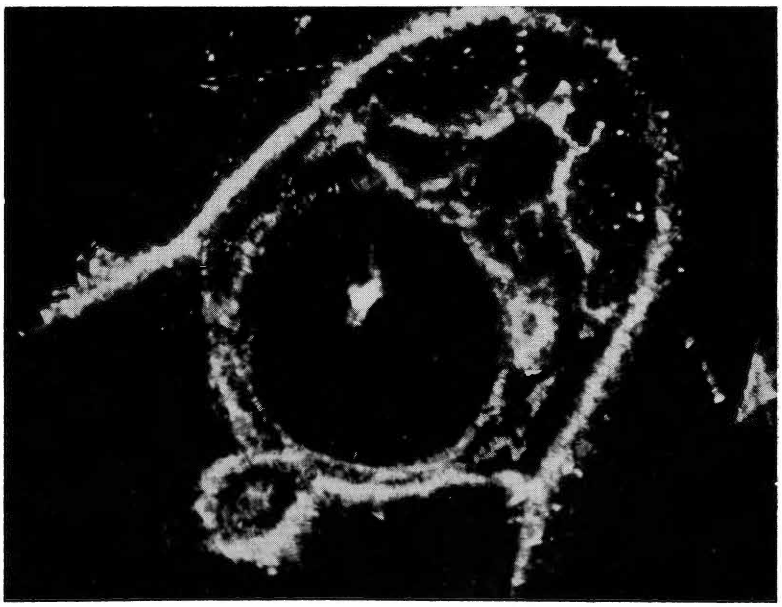

Fig. 6—Sonogram of a dog through the bladder region. A catheter was inserted and the bladder filled with fluid to simulate the urine-filled bladder. Reprinted from *Am. J. Digest. Diseases* 8: 12, 1963.

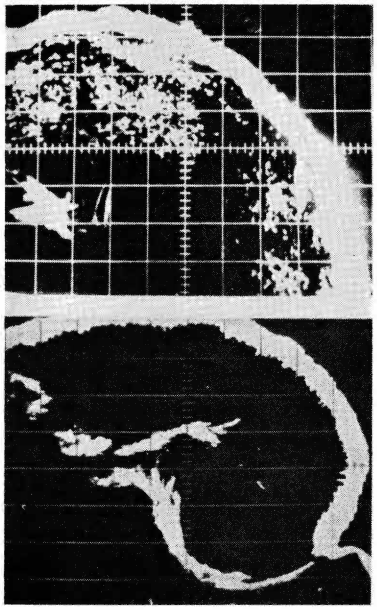

Fig. 7—The lower sonogram is the liver region in a healthy laboratory worker, and the upper sonogram the corresponding liver area in a patient with alcoholic cirrhosis. Reprinted from *Biomedical Science Instrumentation*. Vol. 2. New York: Plenum Press, 1964, p. 11.

Liver abscess either in humans, or experimentally produced in animals, shows a defined nest of echo patterns within the liver. Figure 8 shows the liver sonogram in a patient with metastatic carcinoma of the liver. There are scattered nests of echoes within the usual clear black area representing liver. With carcinoma of the liver or other organs, we can find an abnormal echo pattern in 90% of the cases. This is confirmed by autopsy, biopsy, or surgical examination. However, the echo pattern for tumor is variable. (Holmes, 1966a; Holmes, 1967a) Sometimes it has the scattered pattern of a cirrhosis; at other times it will have the echo nests seen above. In some patients it may appear as a dense echo pattern surrounding a clear black area which is the usual pattern for cysts. This particular tumor will reflect sound exceedingly well from its surface and does not permit it to penetrate to the center of the tumor. Thus, we demonstrate cancer or tumor in areas like the liver, but can we do even more by predicting the type of cancer from the type of echo pattern obtained? If so, we might provide a great deal of diagnostic help for the clinician.

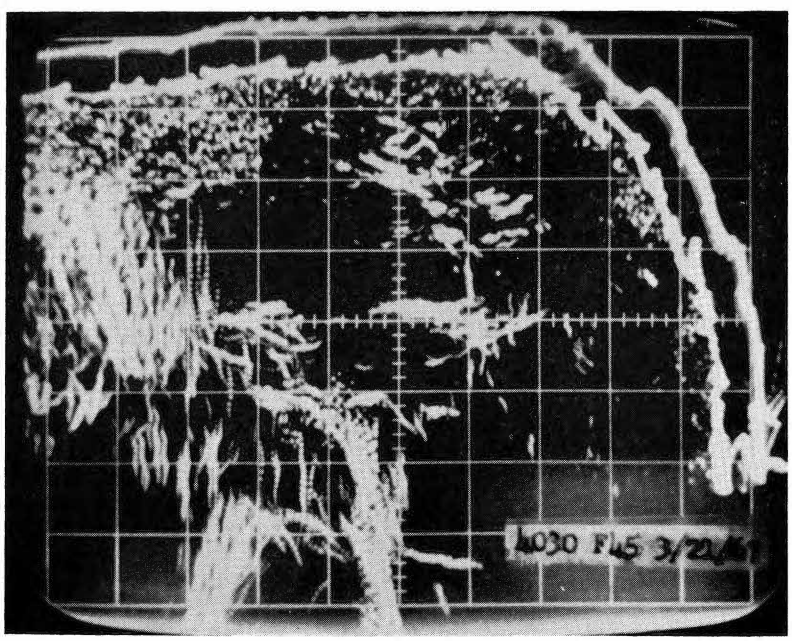

Fig. 8—Shows the scattered echo pattern of the liver sonogram of a woman with metastatic carcinoma of the liver confirmed at autopsy.

Another anatomical area where ultrasound can be helpful is the examination of a fluid-filled organ such as the bladder. (Holmes, 1966b) The upper picture in Figure 9 shows an outline of the urine-filled bladder taken with the water path scanner. The lower picture shows the scan after removal by catheter of 500 cc of urine. The clear black area has entirely disappeared.

Figure 10 indicates the use of this technique to demonstrate residual urine without catheterization. The upper picture shows the bladder of a woman prior to voiding. She voided 250 cc, and the lower picture shows her bladder after voiding. There is still a significant amount of urine in the bladder. This technique has been most valuable in detecting the presence of residual urine in patients we don't want to catheterize, and we have been able to calculate the amount of urine within a 10% error. Ultrasound has helped us in determining whether the prescription of a triple voiding technique is going to be effective in treating a patient. We have used ultrasound in our anuric patients to visualize bladder urine when we don't want to introduce a catheter in a patient because he has an intrinsic renal lesion. We look at the bladder, and if the bladder is full, then we can proceed with a GU evaluation.

We can outline the kidney in most patients, but we can't obtain a very distinct outline of calyceal structures. Thus, with ultrasound we can estimate renal size and also estimate the depth at which one should introduce a biopsy needle. Figure 11 is a sonogram of a kidney, in this instance a transplanted kidney located in the groin area. I chose this picture because it shows very well what we visual-

ize in the kidney at the present time, i.e., a good renal outline (on the right), but only an undifferentiated "echo" nest representing the calyces and pelvis. However, polycystic kidney produces a characteristic echo pattern, i.e., clear black areas with interlacing echo lines, presumably representing each cyst wall. (Holmes, 1967c) In addition, the size of the kidney outline is significantly enlarged. In patients with polycystic kidney, we have often been able to demonstrate the lesion at a much earlier date than we observed X-ray changes based on the intravenous pyelogram. Single cysts of the kidney also have a characteristic appearance in the sonogram. (Holmes, 1967c)

In thin individuals we can obtain a complete picture of the intra-abdominal structures (Fig. 12). Below is the echo outline of the spine, and the major vessels above. At the top right is the liver area, and, to the left, scattered echoes probably representing stomach filled with food; if it were filled with water, its appearance would be similar to the bladder. One can see the pancreatic area. In two cases of proven pancreatic tumor there were dense echo patterns in this area. We can also visualize the spleen and determine splenic size, which may be of diagnostic value. This picture suggests the diagnostic potential of ultrasound, especially for diagnosis in diseases involving the two major blood vessels or the pancreatic area.

In contrast to Figure 12, the next sonogram (Fig. 13) shows the entire anterior portion of the abdomen displayed as a dense echo pattern. At autopsy, the anterior abdomen was filled with metastatic carcinoma. However, another patient with a similarly palpable mass of the abdomen, when scanned with ultrasound, was found to have a clear black area surrounded by the dense echo pattern typical of cyst. In patients with ascitic fluid,

Fig. 9—At top, sonogram of a full bladder containing 500 cc of urine, taken with a water-path scanner. The lower picture shows the scan of the bladder region after removal of the urine by catheter. Reprinted from *Am. J. Digest. Diseases* 8: 12, 1963.

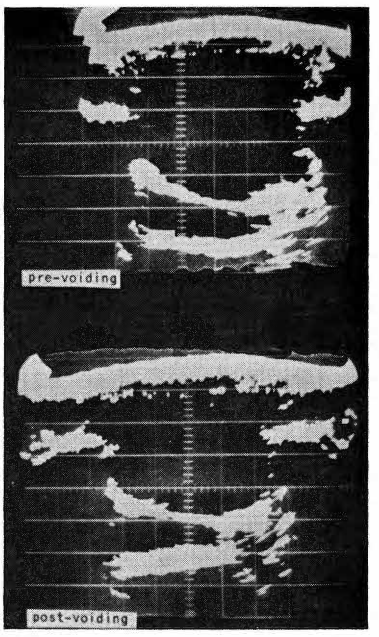

Fig. 10—Shows cross section of the bladder area pre-voiding in the upper picture, while the lower picture shows the same bladder area after the patient voided 250 cc and illustrates the use of ultrasound for diagnosis of bladder retention without catheterization. Reprinted from *J. Urol.* 97: 654, 1967.

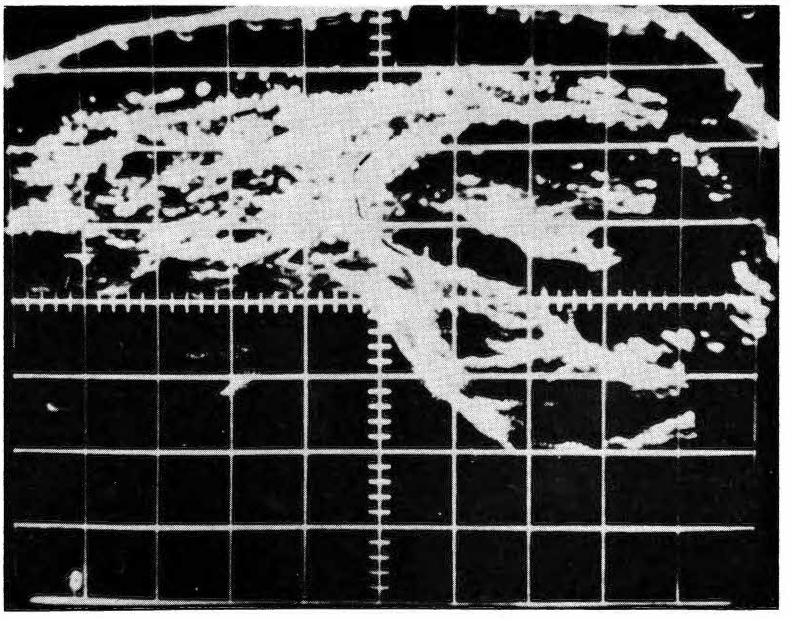

Fig. 11—Sonogram of a transplanted kidney located in the right groin to illustrate the ultrasonic technique in outlining the kidney. The nest of echoes within represent calyceal structures but lack characteristic definition. Reprinted from *Diagnostic Ultrasound: Proceedings 1st International Conference.* C. C. Grossman et al. (eds.). New York: Plenum Press, 1966, p. 249.

clear black areas will appear diffusely throughout the abdomen, with the echo pattern representing intestine and stomach pushed together, sometimes anteriorly, sometimes posteriorly. When peritoneal dialysis encounters difficulty or unsatisfactory results, a scan of the abdomen ultrasonically may reveal what has happened and demonstrate the areas of fluid distribution. Occasionally, a swollen abdomen thought to be ascites will have the outline of a circumscribed cyst with the fluid limited to one specific area. Our resident staff feel that ultrasound has contributed most significantly in the differential diagnosis of abdominal masses. (Holmes, 1967c)

Pregnancy has presented an ideal anatomical situation for the contact scanner. Because of the rounded abdomen, we have the most effective scanning path for the transducer. Furthermore, since the uterus is fluid-filled, it will accentuate visualization of the fetal structures. Figure 14 presents a cross-sectional picture of a pregnant uterus with the fetal chest displayed at the top of the uterus. The fetal spine is seen at the top of the fetal chest, and, to the left are echoes representing the fetal limbs. This was taken in the eighth month of gestation. This type of scan permits us also to determine fetal position. Furthermore, from pictures of this type taken at different stages of pregnancy, one can estimate fetal development. The present measurements we are using for estimating fetal development include the biparietal diameter of the head and the circumference of the thorax. (Thompson et al., 1965)

If there is a multiple pregnancy, then we will see two thoraces and two fetal heads, usually a head near the fundus and a head in the pelvis. In the left-hand picture of Figure 15 are shown the thoraces of two babies, while, in the upper right, is the outline of the fetal head of the lower twin. The lower picture shows the X-ray, depicting by

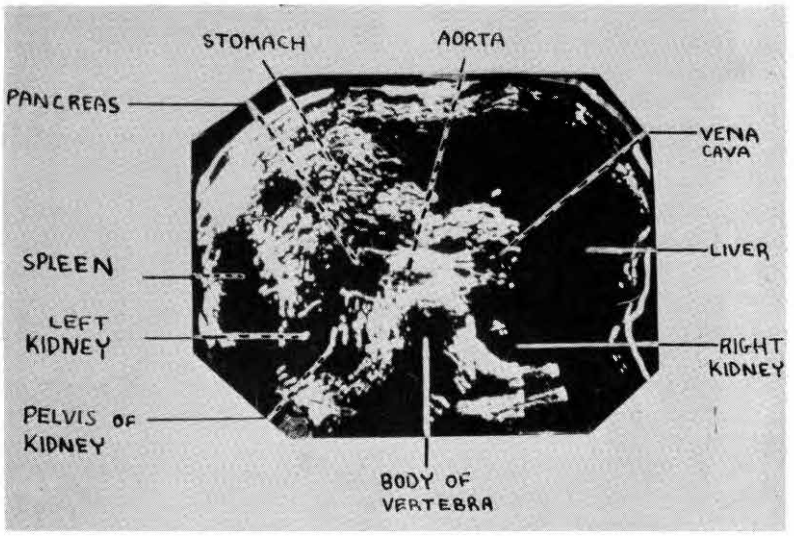

Fig. 12—Sonogram through the abdomen of a 10-year-old boy at the liver area to illustrate the various intra-abdominal structures which can be seen, including the echo outline of the spine and the major blood vessels. Reprinted from *Proceedings Third Annual Rocky Mountain Bioengineering Symposium.* New York: Institute of Electrical and Electronics Engineers, 1966, p. 78.

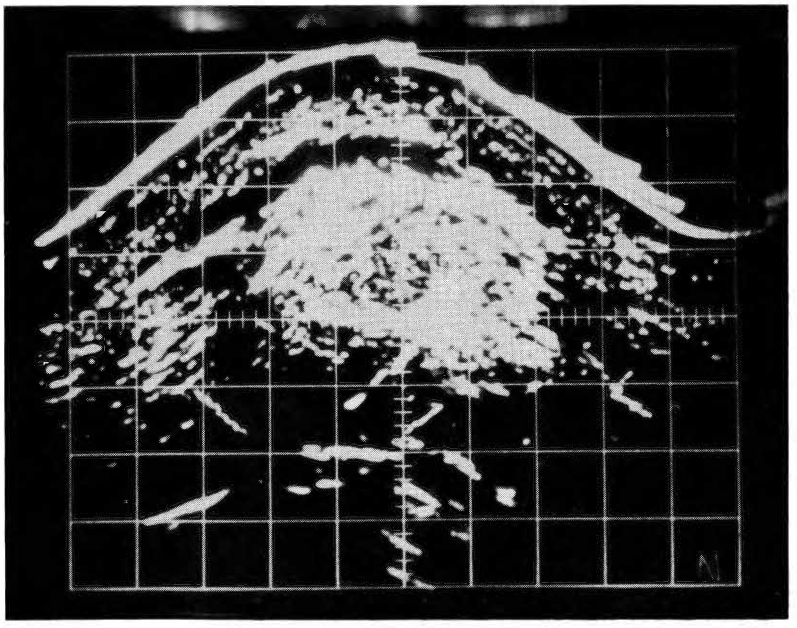

Fig. 13—Sonogram of anterior abdomen in a patient with metastatic carcinoma throughout the anterior abdomen confirmed by autopsy. The dense echo pattern obtained can be contrasted with the echo pattern of the previous Figure. Presented at Miami meeting, American Institute for Ultrasound in Medicine, Miami, 1967.

white lines the levels at which the sonograms were taken. Often we can help the obstetrician further by telling him which baby, the larger or the smaller, is presenting first. If there is an increased amount of fluid in the uterine cavity, this is easy to demonstrate. We find the most frequent requests for ultrasonic examination involve the pregnant woman with a uterus either too big or too small for the calculated time of gestation. In this type of case we can determine whether the fetus is developing normally or whether some other defect such as a hydatid mole is present.

We can also visualize the placenta as an area of diffuse dots (Fig. 16). In 112 patients in which the placental position was confirmed, either by manual removal or Caesarian section, the position was correctly determined by ultrasound in 97%. (Gottesfeld et al., 1966) Placental visualization has had clinical use in suspected cases of placenta previa and whenever the physician desires to do an amniocentesis. In anteriorly placed placentas, one can map the exact location and size of the placenta by serial ultrasonic sections. This may have future diagnostic potential.

In the diagnosis of hydatid mole, ultrasound has achieved almost 100% accuracy. (Gottesfeld et al., 1967) A typical pattern of hydatidiform mole is shown in Figure 17. The very character of the hydatidiform mole means that it will provide a scattered diffuse echo pattern which is entirely different from the organized form of echo patterns previously presented for the developing fetus. In some instances it is necessary to examine the patient one or more times before arriving at a final diagnosis of hydatidiform mole.

When fetal death occurs, the fetal echo pattern begins to change shortly after death. Our residents have given this the nickname "brush border" appearance. The echo pattern becomes broad-

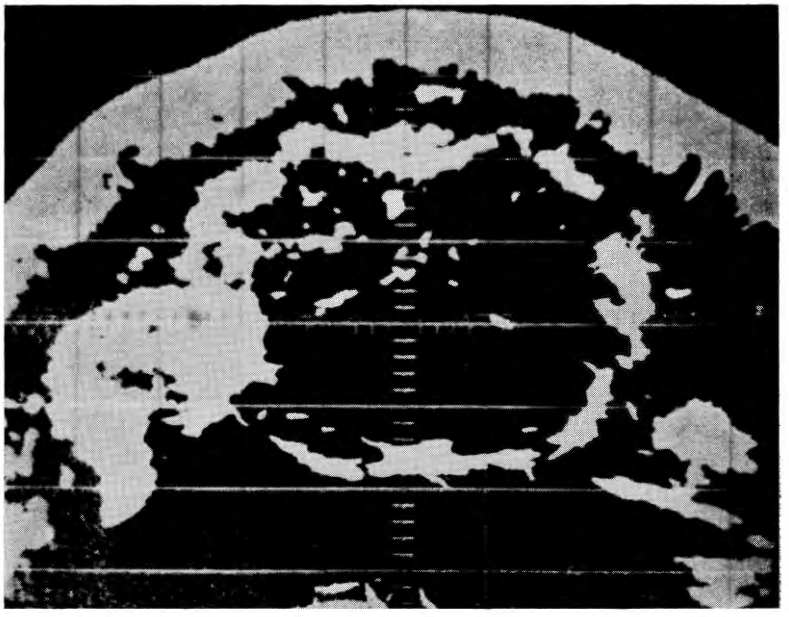

Fig. 14—Sonogram of a pregnant woman at 34 weeks gestation. At the top is the outline of the fetal thorax with the fetal spine delineated; on the left are echo patterns probably from a fetal extremity. Reprinted from *Am. J. Obstet. Gynec.* 92: 44, 1965.

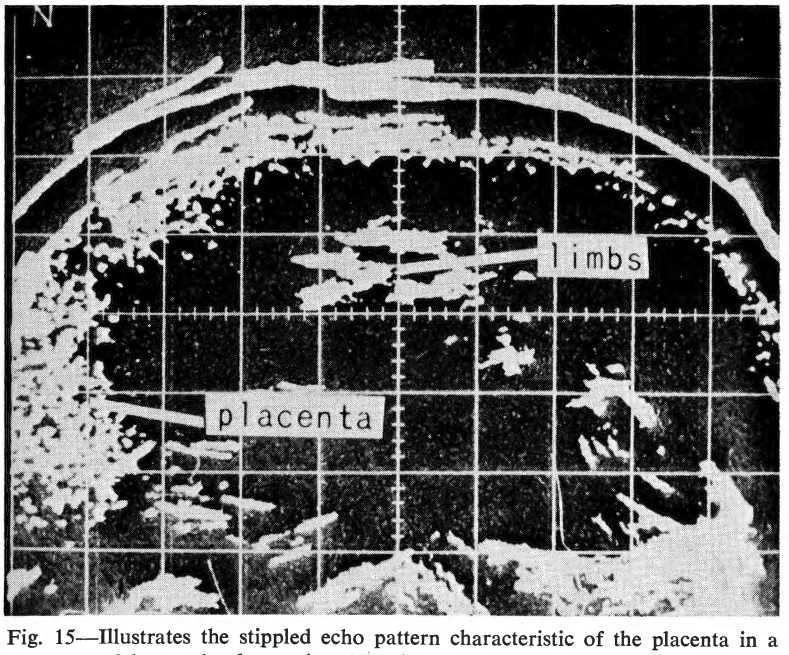

Fig. 15—Illustrates the stippled echo pattern characteristic of the placenta in a woman at 8th month of gestation. The fetal echo patterns in the center of the uterus represent echoes from the fetal extremities.

stroked, rather than fine-stroked. Furthermore, as time from death increases, the organized appearance of the fetal echo pattern begins to disintegrate, and the fetal head outline, for example, becomes less distinct. On an empiric basis we have been able to predict fetal death in a number of instances when it was important to have this information. It is interesting that this same type of echo pattern has been observed in babies of Rh negative and severely diabetic mothers. We have no good explanation for the change in echo pattern configuration with fetal death. We have been doing some experimental work by changing fluid balance in rabbits, and it would appear that the echo pattern difference between a dehydrated and overhydrated animal has some of the same characteristics we note in association with fetal death or in the fetus of a diabetic mother. Further work needs to be done in this area.

Ultrasound has been diagnostically useful in a number of gynecological lesions, particularly in the differentiation between solid and cystic tumor of the pelvis. (Thompson et al., 1967) Figure 18 shows the ultrasonic picture of a pseudomucinous ovarian cyst. There is a clear black area well outlined by echoes. The presence of echoes within the cyst is suggestive of malignancy, and this patient did have metastases to omentum and peritoneum. The appearance of the tumor at surgery is shown in the upper pictures of Figure 18.

Figure 19 illustrates how ultrasound may have diagnostic potential in muscular areas like the leg. (Holmes and Howry, 1958) The picture on the left shows a sonogram with the muscle fascia and the outline of the two leg bones clearly seen as compared with the corresponding anatomical cross section on the right. This was an amputated leg. The muscle area in the normal apparently has a characteristic echo pattern, while in two

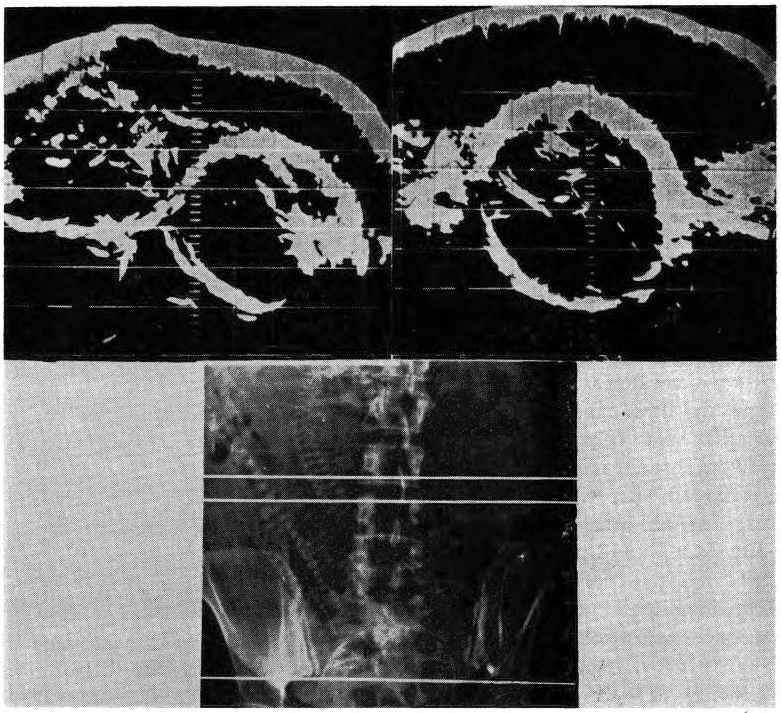

Fig. 16—Sonogram of a multiple pregnancy showing, in the upper left, the outline of the fetal thorax in each of the twins. The head of the lower twin is outlined on the right. The corresponding X-ray showing the cross-sectional levels of the sonograms is shown below. Reprinted from *Am. J. Obstet. Gynec.* 90: 655, 1964 (C. V. Mosby).

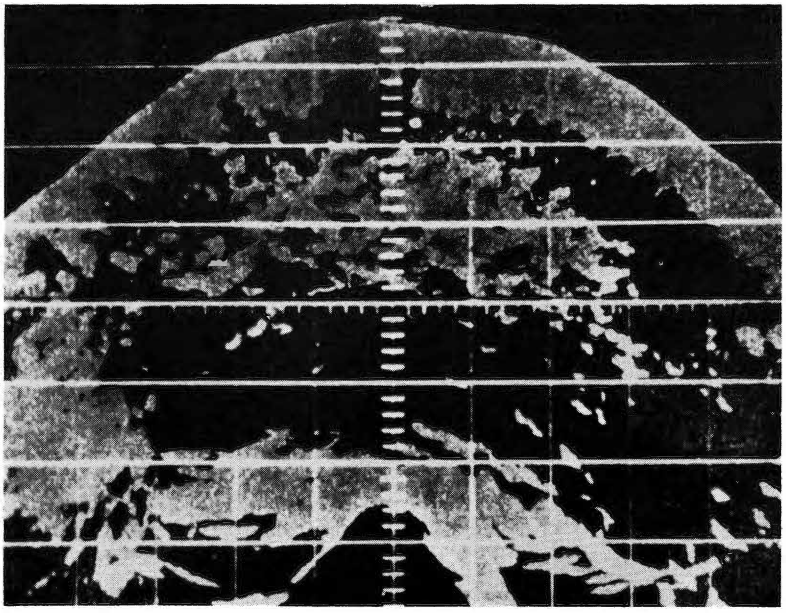

Fig. 17—Sonogram in a patient at 16 weeks of gestation who had a proven hydatidiform mole. This characteristic echo pattern is quite different from that seen in previous pictures of the well-organized outline of fetal parts. Reprinted from *Am. J. Obstet. Gynec.* 90: 655, 1964. (C. V. Mosby)

cases with muscular disease, the pattern was quite different. In the leg with edema, clear black areas appear under the skin. Thus, ultrasound may have diagnostic potential in orthopedics, for example, in athletic injuries where the X-ray is negative.

While the sonograms I have shown look pretty good, they do not tell the entire story. At the present time, we still find about 15% of the examinations are unsatisfactory and we can make no interpretation. This relates to equipment deficiencies, difficulty in calibrating equipment, inadequate examining techniques, and problems in training technicians. When we get a good picture with ultrasound, as you have seen from the examples shown, then it has significant diagnostic value. How do we solve this problem of obtaining a good sonogram with every examination and being able to obtain a good picture in repeat examinations from day to day? We have set up a daily standardization technique for our equipment, but it is still insufficient in calibrating all variables of the equipment. Furthermore, each technician scans in a different manner, which makes comparison difficult unless the same technician makes successive examinations. Improved training can eliminate these differences, and we have devised scanning tanks and other training equipment to help eliminate this variable. At the present time there are five different companies selling equipment and, if one chose a piece of equipment from each, one would have to learn to operate each piece of equipment separately, because each has different characteristics. Eventually, we should achieve standards for equipment so that a technician could operate readily any standard piece of equipment designed for diagnostic ultrasound.

Diagnostically ultrasound can examine certain areas more easily and with less patient hazard and preparation than is required by

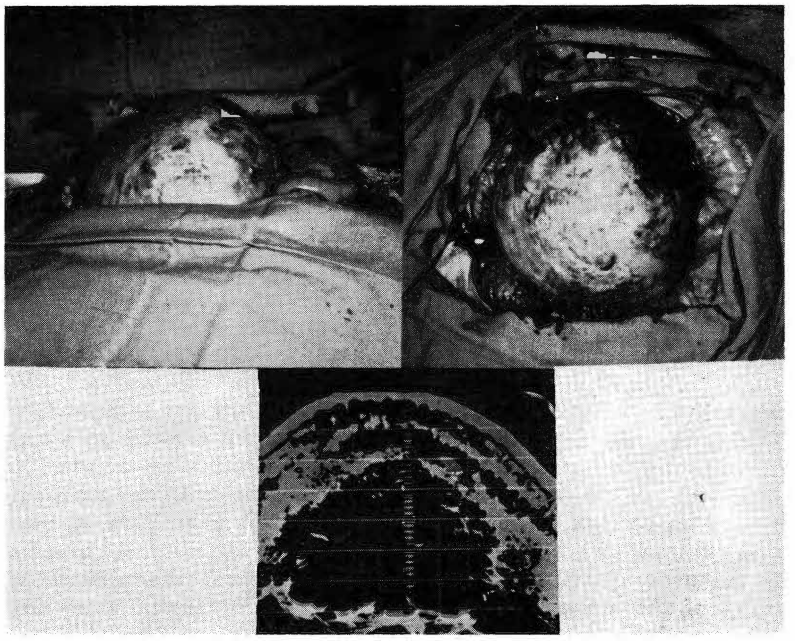

Fig. 18—Sonogram on the bottom shows a clear black area surrounded by dense echo pattern characteristic of a pseudomucinous ovarian cyst. The appearance of the tumor at surgery is shown in the upper two pictures. Reprinted from *Am. J. Obstet. Gynec.* 90: 655, 1964. (C. V. Mosby)

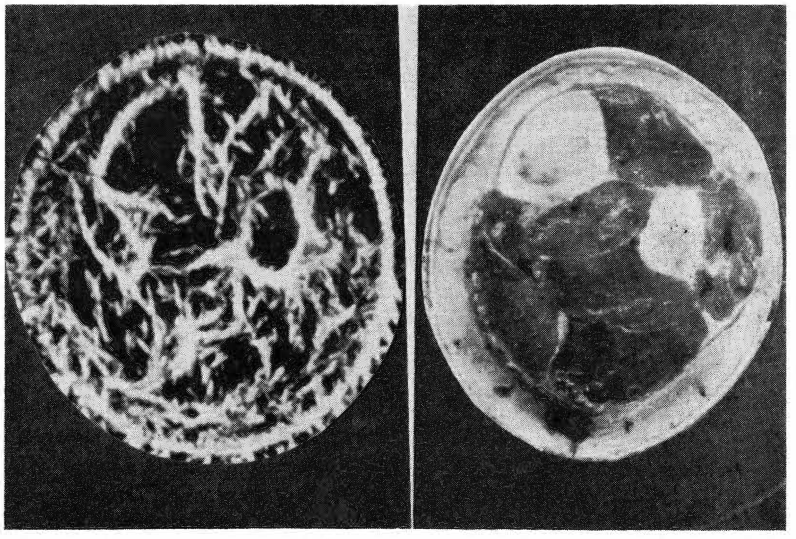

Fig. 19—On the left is a sonogram of an amputated leg to illustrate the characteristic echo pattern of the leg bones and the muscle area. The picture on the right shows the corresponding anatomical cross section for structural comparison. Reprinted from *Trans. Am. Clin. Climat. Assoc.* 70: 225, 1958.

other techniques. For example, ultrasound can visualize certain anatomical structures without the use of contrast media. This may be very helpful for visualizing a gallbladder which does not take up dye or in determining renal size in the uremic patient.

The best contrast media we have for ultrasound is 0.9% NaCl. In our animal studies I can improve visualization by injecting 0.9% saline into the anatomical area of study. Perhaps 0.9% saline, properly injected under sterile conditions, can be used in man. We have shown that, with ascites, ultrasonic visualization of the peritoneal cavity and its contents is improved. In the stomach all one has to do is ingest water to obtain good visualization of the stomach wall.

Pregnancy has proved the most practical and routine diagnostic use for ultrasound at the present time. Using this technique, we can visualize the fetus from about the fifth or sixth week up to term. The fetal head is demonstrated at about twelve to thirteen weeks, and the fetal thorax at about sixteen weeks. Thus, we have the potential of following fetal development and being able to tell the obstetrician whether it is proceeding normally. From measurement of the biparietal diameter of the fetal head and the circumference of the fetal thorax, we have been able to estimate fetal weight within 400 gms in over 95% of babies. However, converting fetal measurement to an estimation of weight in order to predict fetal development seems like an indirect approach fraught with many inaccuracies. With further study we should establish direct measurements of fetal parts at each stage of gestation and be able to predict more precisely fetal development. This would be useful in predicting the best time for section, in eliminating complications of delivery, and in evaluating babies of Rh negative and diabetic mothers.

Equipment is cheaper than X-ray equipment. The less complicated A-mode unit costs between $3000 and $7000; with time motion incorporated, the cost increases to $7000 to $8000. The compound scanner costs about $16,000. I have described what each will do diagnostically.

There are still many problems to be solved. We are in a stage of development of ultrasonic techniques where we still have to learn many of the applications that can be made with it diagnostically. We also must learn how to standardize the equipment (developing proper standards) so that we are sure it is operating the same way from day to day. We must learn to train technicians effectively. We have the problem of what department should operate the equipment in any hospital. We have found that everyone wants to use ultrasound in his own specialty, and that brings up the problem of whether the equipment should be located in a service division, like the X-ray department.

There is a very simple technique (Doppler) that has just come out using ultrasound. This utilizes a transducer placed directly over a blood vessel or fetal heart, and the equipment produces a sound which varies in pitch according to the rate of flow in the vessel. It also picks up more easily than fetal EKG the fetal heart beat so that, ever since we bought our first instrument, our obstetricians have been using it almost constantly to determine viable fetuses. The tone is also different if the transducer is placed over the placental vessels, so that one can tell with about 90% accuracy where the placental vessels are located in the uterus. This represents a simple technique for locating the placenta. The technique also has potential application for detecting obstruction of peripheral vessels, and we have been using it in situations like an A-V anastamosis in chronic dialysis patients to tell how much flow is going through the venous side of the A-V anastamosis. This is the most recent development in the ultrasonic diagnostic field.

I would be happy to answer questions. Although I am prejudiced, I think that within four or five years ultrasound will be utilized in most hospitals for routine diagnostic purposes. It has diagnostic applications which are not possible with other techniques. Although the word "scan" is used in ultrasound, let me point out that it is supplying different diagnostic information than isotopic scans. If you use the two techniques together, the isotope measures the changes in cellular activity and uptake, while ultrasound demonstrates changes in tissue density. Thus, the two techniques used together provide more information than either one alone.

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Continuing Education for What? *

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The answer to the question posed by the title of this presentation would seem to be obvious: the purpose of continuing education is clearly to improve the quality of patient care. While this generalization would probably produce full agreement, it is incomplete without the next question: what care needs improvement? At this point the appearance of harmony may begin to disintegrate as discordant notes of special pleading begin to emerge. Out of the ensuing noise, one common theme can be identified: practitioners need more information. There may be no consensus about what information they need, but there is little dissent from the view that the world of medicine is changing so rapidly as a result of contemporary research that what is current today will be dated in a few months and obsolete in a few years. And the cries of despair are mounting as the gap allegedly widens between the explosive growth of new knowledge and its application at the bedside.

In the face of such a growing threat to their professional competence, it is no wonder that practitioners clamor for some better means of dealing with the flood of information that threatens to engulf them and that educational programmers grasp at any straw which gives some promise of worth. The current straws are familiar to all: programmed instruction, 8 mm. single-concept films, television—both one and two way, either live or taped—among others. Each has been identified as a potent mechanism for meeting this educational need in a fashion that makes it easy for the already overworked practitioner to dip into the treasures that teachers have found for him. And when, on those rare occasions that we press him, he demonstrates that he can recall verbatim (or at least in reasonable facsimile) the information he has sampled, then we are very pleased, particularly if he also reports that he has enjoyed both the dose and the vehicle.

I am sure you recognize the tone of irony; but lest there be any doubt, let me state bluntly the conclusion to which I have been led by the inescapable evidence of our failures: we have been educating for the wrong thing.

It is not my intent to deny the critical importance of biomedical research or the splendor of an incredible expansion in the body of information available to those who seek a detailed understanding of human health and disease. It is simply to point out that the exquisite elaborations of contemporary investigation are generally of major significance in the care of relatively few patients. In our eager dissemination of new information, we seem most often to be working at the upper extremity of an S-shaped curve where an immense instructional investment is likely to result in a very small increment in the quality of patient care. The ques-

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tion then is not one of absolute worth of new knowledge, but of relative priorities in continuing education. Shall attention be given chiefly to those things that will benefit only a few, or to those things likely to be of great import in the care of many. Realistically, in the matter of new knowledge that is potentially beneficial to the many, it must be evident that a physician will scarcely be able to avoid it if he reads a daily newspaper, *Time*, or one of the summary news sheets that appear so regularly in our mail.

Categorical Content Model

What then is the problem? Any careful review of continuing medical education in the United States today will lead inexorably to the conclusion that most programs are based upon a categorical content model. They are built around subjects: cardiology, oncology, physiology, biochemistry, endocrinology. Name a department or subdivision of a medical school and you have named a continuing education program. Name a diagnostic or therapeutic tool and you have identified another. The assumption that appears to underlie this educational model, an assumption derived from the long tradition of the schools (note that the reference here is to experience, not success), is that practitioners who learn more about these topics will transform this knowledge into action. Yet the fact seems to be that such translation does not necessarily occur. From John Youman's study (1935) to John Williamson's study (1965), there have been repeated and disheartening examples of the failure of education built upon the content model to alter substantially the behavior of practitioners. By what devious path, one might reasonably ask, are we then led to the conclusion that more information about the importance of doing Pap smears for early detection of cervical cancer will lead physicians to carry out this test when it has been the discouraging experience of the American Cancer Society and the National Cancer Institute that in spite of an intensive informational program for a decade this simple maneuver is omitted from the physical examination more often than it is performed.

Yet we persist in talking of bringing more information to the practitioner, of bringing it to him at his hospital or his office or his home, of making the communication more appealing and more convenient. We talk of better printed informational sources, of primary publications and abstracts and bibliographies. We try to convince each other of the importance of telephone lines to carry information through illustrated presentations, or ingenious dial-a-lecture methods. We talk of wide-band communication systems for television and computers, bidirectional to allow active participation. We seem enchanted by the idea of a network that allows the videotape lectures and demonstrations made in one center to be shipped to another for their delectation. It is true that these are all magnificent and exciting technologic advances, but some of those outside medicine who look more coolly at the educational potential of such devices are not quite as enthusiastic as we seem to be. At a recent conference jointly sponsored by the Department of Defense and the Office of Education on the topic "Engineering Systems for Education and Training" one of the most perceptive spokesmen noted:

> . . . the education technology industry . . . knows a great deal about the science and technology of information processing and transmission, but it knows very little about the human receiver of that information. The human receiver, the man who must learn and recall the information transmitted by this sophisticated new equipment remains largely untouched. . . .

And at another point in the proceedings the same acute observer was heard to say about the value of speed reading courses for executives who must cope with an increasing flow of information across their desks:

> The problem will never be solved by speed reading courses. What we really need are courses to teach people to write things that are worth reading slowly.

Process Model

For all these reasons, it would seem that the time has come to try a different educational model—one built upon solid evidence about the way adults learn rather than upon the long-honored methods of teaching them. There is ample evidence to support the view that adult learning is not most efficiently achieved through systematic subject instruction; it is accomplished by involving learners in identifying problems and seeking ways to solve them. It does not come in categorical bundles but in a growing need to know. It may initially seem wanting in content that pleases experts, but it ultimately incorporates knowledge in a context that has meaning. It is, in short, a process model of education.

Let me hasten to assure you that I do not mean to assert that knowledge and performance are unrelated; they are clearly overlapping qualities. It is also clear that they are not identical dimensions. The best performance is built upon sound information; but the provision, or even the acquisition, of sound information is no assurance that it will occur. Let me illustrate this by describing the first stage of a long-term demonstration and study of continuing education which has been launched at the University of Illinois Center for the Study of Medical Education, with the support of the USPHS Bureau of State Services.*

* Dr. John Williamson and Dr. Marshall Alexander were the primary investigators and a complete report of the work will be published shortly.

It began with a question developed by the study group representing a community hospital and the medical school: to what extent do physicians respond to unexpectedly abnormal results on 3 routine admission laboratory tests—hemoglobin, urinalysis, and fasting blood sugar? The charts of patients discharged during a one-month period were systematically studied to answer this question, and the answer was not particularly reassuring: only 35 per cent of the unexpected abnormalities produced any perceptible physician action. A startled education committee agreed that an educational problem existed, and a decision was reached that the instructional method to correct it would be a simple presentation and discussion of the data with expert consultants. More than 80 per cent of the staff members took part in the meeting; and at its end there was a general acknowledgment that something must, and would, be done promptly to correct what the staff judged to be unacceptable professional performance. One might have concluded from this response that the educational effort had been successful, but confirmation required data. These were gathered by replication of the chart study one month later—and with identical results.

I will not describe the rest of the effort which transformed this initial educational failure into ultimate success for the outcome is irrelevant here, but the simple and long-documented fact illustrated by this vignette is that men learn what they want to learn. The first step in this long process is not to tell them what they need to know, it is to help them to want what they require. It means involving participants in identifying their own educational needs, in selecting the learning experiences most likely to help them to meet the needs, and in assessing whether they have learned what was intended, not merely determining whether they took part in the learning experience, or even whether they liked it. And if the final evidence clearly demonstrates that the desired learning did not occur, then another look must be taken at both the objective and the instructional method to determine which requires change.

Physicians are basically pragmatic and seek things that are useful to them. Academicians, on the other hand, appear to equate the pursuit of basic principles (as we like to describe what we do in our daily work) with ultimate truth and are inclined to demean the practitioner who keeps asking for practical answers. There is no implication in this observation that educational programs should become answer-giving sessions, but it is important for educators to acknowledge and exploit the pragmatic orientation. It is just as legitimate to be interested in therapy as in diagnosis, in the indications for a specific medication as in the mechanisms which produce its effect. Either may be the means of attacking a problem—or an exercise in pedantry.

Objectives

In a very practical sense, the most important element of continuing education may be that of leading practitioners to a study of what they do, to an identification of their own educational deficits, to the establishment of realistic priorities for their own educational programs. There must be many ways of accomplishing this end, but one with which we have gained some experience begins by delineating the health needs of the population served by an individual practitioner or a hospital staff. Using available hospital data as it is recorded in the professional activities study, John Williamson developed a computer program that orders these health needs by weighting 3 variables. The first is disease incidence, for, other things being equal, diseases that are more frequent probably deserve more educational attention than those less regularly seen (in contrast to what occurs in many hospital programs where the grand rounds built upon a patient problem no one has ever seen before or is likely to see again is widely applauded). The second variable weighted in the computation is individual disability produced by these diseases. This is estimated through such components as mortality and morbidity rates or the number of complications produced. Again, other things being equal, it seems logical to give more educational attention to those things which produce great disability than to less disabling disorders. Third, a variable labeled "social disruption" is estimated, using such elements as the number of dependents, the age of the patient, and the cost of illness as indexes of the degree to which individual illness may affect the family and related social units. While the weighting may be arbitrary, it is not immutable; and the method provides a start in systematic definition of the individual and social problems physicians encounter in the patient population with which they deal.

A modification of this general methodology was utilized by Storey and Castle (1966) as part of the Utah Pilot Study in the late lamented National Plan of the American Medical Association. Here individual physicians were asked to record the clinical problems they encountered over a forty-eight-hour period, as well as a personal perception of their educational needs. Bergman and his associates at the University of Washington (1967) did an observational analysis of the work of pediatricians from which it was possible to identify many of the performance skills required by this medical specialist. Similar studies of office practice have been carried out by Greenhill in Canada (1965) and Baker and associates in Missouri (unpublished data). Each represents a method of initiating the process

of establishing educational objectives by identifying the problems with which the potential learner must deal, rather than building programs upon problems a faculty would like to teach him how to solve.

Once health needs of a target population have been determined, an inventory of the resources (information, professional skills, diagnostic and therapeutic tools) available to meet them can be developed. If it becomes clear that little or nothing can significantly influence the outcome of a frequently encountered clinical problem, then wisdom would suggest that educational attention be directed to other things about which something can be done, while encouraging research on the problems that remain to be solved. This is another way of illustrating a rarely verbalized observation that research interests of teachers are unlikely to be the most useful program determinants in the continuing education of practitioners, since the ever changing interface between the known and the unknown is rarely the point at which the most profitable educational investment can be made.

Finally, practitioners need to be involved in an analysis of the extent to which they use themselves and the available resources to meet needs that have been identified. The documentation of discrepancies between optimal and actual performance is not an end in itself —it is merely the beginning of an educational process with the greatest likelihood of success: that which is built upon demonstrated and acknowledged need.

Even this hasty conceptual sketch of a process model for continuing education must make one thing very clear: the role of both teacher and learner will be far different from that to which we have become accustomed. As one observer has put it, the practitioner-learner must progress steadily from listener to questioner to participant to contributor. If the practitioner is to accomplish this shift, the academician teacher must also change, but in the opposite direction, until at last he becomes a thoughtful listener to those who are trying desperately to tell him some of the things they need if they are to be more successful in their work, instead of remaining a gifted dispenser of things they might use to become more like him.

Conclusion

Continuing education should mean continuing self-education, not continuing instruction. If this desirable goal is to be accomplished, there must be movement away from the content model, which encourages dependence upon teachers, to a process model, which demands a significant measure of self-reliance—a shift away from preoccupation with courses and methods, toward an augmented concern for educational diagnosis and individualized therapy. It does not mean an immediate abandonment of present program forms, but it is likely to be accompanied by a slow erosion of the faith which presently supports them.

However, even those who accept the conclusion might reasonably ask whether it is practical. My own response is an unequivocal yes, for we have a rich variety of mechanisms both old and new that are readily available if we will only reach out and grasp them. Let me note only 2 that have captured the contemporary stage. The Regional Medical Programs (P. L. 89-239) is one which requires cooperative ventures among medical schools, the health professions, voluntary health organizations, public agencies, and the public at large. While it has an unfortunate categorical orientation, the categories are sufficiently broad to permit bold new ways of attacking the problems of continuing education through the study of patient care. Happily, those who are guiding the program seem disinclined to encourage merely an increased pace in the development of more refined tools to carry out the same old educational strategies. They seem instead to be calling for innovation coupled with evaluation and to be ready with the funds that make it possible to do these sometimes costly things.

A second resource is the Interuniversity Communications Council, better known as EDUCOM. The basic mission of this agency is to explore the means by which contemporary educational and communications technology can be exploited by universities acting in concert, rather than singly. A Task Force on Continuing Education has recently been established by the Council and it is prepared to respond to the needs of the health education community as well as to the other professions represented in the university. The early descriptions of EDUCOM may appear to have emphasized television, radio, and computer networks for purposes of information storage, retrieval, and transmission; but there is no basic reason why they cannot also be used for other things that can serve educational diagnostic as well as instructional purposes (for example, computer simulations of clinical problems).

The ultimate question, however, is whether content-oriented educators can mount successful process-oriented continuing education programs. I am not optimistic that this can be done without some retreading of the older ones among us and some training of new leaders in the science of education. Fortunately, there are steadily widening opportunities for those who have committed themselves to an educational career in medicine to gain these special skills. For example, the Center for the Study of Medical Education now offers one- to two-year fellowships in educational research and development or, jointly with the College of Education, a graduate program leading to a Master of Education

(in medicine) degree; with the support of the Bureau of State Services a more abbreviated six-week introduction to educational science is being developed specifically for individuals directing programs of continuing education; and with support of the National Institutes of Health's Division of Regional Medical Programs, a series of one-week programs is being planned to orient educational practitioners in medicine to some of the content of educational science in such specific fields as instructional systems and evaluation.

But those who direct programs of continuing medical education are not unlike the practitioners who are the objects of this effort. Until they recognize a need to know, it is unlikely that they will learn. If there is no perceived need to change, then neither new information nor vigorous instruction will alter their basic behavior. Instead, they will continue with increasing skill to do things which, in my view, have not proved to be very useful. They will go on developing attractive, even dazzling new programs, methods, and hardware for the communication of information; but they are unlikely to be any more successful in the future than they have been in the past in changing the behavior of recipients.

The gauntlet is down, the lists have been entered, and the battle for better continuing education can be joined. But as the pace quickens, it may be well for all to remember the prophetic words of Pogo: "We have met the enemy, and they are us."

Acknowledgments

The author wishes to acknowledge his debt to associates, past and present, whose influence upon the ideas presented in this paper has been great, even though it may be difficult to tease out the specific contributions of each. Among these, deserving special note are Dr. John Williamson; Miss Christine McGuire; Dr. Marshall Alexander; and, most recently, Mr. Michael Goran, a senior medical student at the University of Illinois.

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Adrenergic Stimulation and Sodium Transport*

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Epinephrine is known to influence electrical and, therefore, ion transport phenomena in cell membranes in various tissues, including cardiac pacemaker (Hutter and Trautwein, 1956) and contractile cells (Webb and Hollander, 1956), smooth muscle (Bulbring, 1960) and skeletal muscle (Dockry et al., 1966). Also, administered catecholamines and sympathetic nerve stimulation alter renal excretion of electrolytes (Kruhoffer et al., 1960), although it has been postulated that these changes are related primarily to hemodynamic alterations rather than to a direct effect of adrenergic stimulation on renal tubular ion transport mechanisms. However, Koefoed-Johnsen et al. (1953) reported that epinephrine produced changes in sodium transport and electrical properties of isolated frog skin.

Ahlquist (1948), comparing the potency of various catecholamines, postulated the presence of two types of adrenergic receptors (alpha and beta) in effector cells such as smooth muscle, cardiac muscle, and salivary glands. Since that time, adrenergic blocking agents which specifically block alpha or beta stimulation have been developed (Ahlquist, 1965). The studies to be presented here were undertaken to clarify further the nature of the alterations in sodium transport in isolated frog skin (a model system for study of ion transport), particularly in relation to the Ahlquist concept of alpha- and beta-adrenergic receptors. Previous studies in living animals suggest that the frog skin is responsive to both alpha and beta stimulation (Watlington, 1965).

The skin model used here (Fig. 1) is based on the work of many investigators, and its application is particularly well exemplified by the studies of Curran and co-workers (Curran et al., 1963; Cereijido et al., 1964). Sodium transport inward is thought to be by a two-step process across the epidermis, both steps being rate limiting. As shown in figure 1, there is passive diffusion across the epidermal permeability barrier into the active transport site followed by active transport inward into the internal medium. Outflux, which is small relative to influx (thus accounting for net flux or net transport of sodium), may be primarily a passive process. The mucous glands offer a possible pathway for sodium movement although they are not felt to be important in the unstimulated isolated skin.

Methods

In most of the sodium flux experiments single pieces of abdominal skin of frogs (*Rana pipiens*, 40 to 60 gm) were used. Sodium influx and sodium outflux were determined on different pieces of skin. Influx was measured by placing Na^{22} on the epidermal side and sampling the inside or corium side. In outflux experiments Na^{22} was placed on the corium side, and samples were removed from the epidermal side. The estimation of rate coefficients (see "Results") was performed on paired skins using Na^{24}. The skin pairs were obtained by dividing the belly skin of larger frogs (70 to 90 gm) into halves. Determination of rate coefficients also requires knowledge of the skin extra-cellular space as measured from the outside solution; C^{14} inulin was used for this purpose. Na^{22} and Na^{24} activity was measured in a crystal scintillation counter. C^{14} activity was measured by liquid scintillation counting.

The skins were mounted between two conical Lucite chambers, placed one on each side of the skin. The chambers were filled with Ringer's solution of the following composition: NaCl, 110 mM; KCl, 10 mM; $NaHCO_3$, 4 mM; Na_2HPO_4, 1.3 mM; pH 8.1. The solutions were aerated and mixed by bubbling with moisturized air. Each chamber was provided with Ringer agar bridges connected to

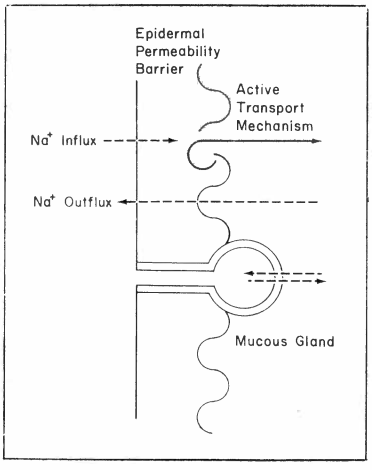

Fig. 1—Pathways for sodium transport across frog skin.

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calomel half cells so that during the flux experiments the skins could be continuously short-circuited by the method of Ussing and Zerahn (1951). This experimental approach simplifies the study of active ion transport by eliminating the two major passive forces across the skin which influence rates of ion movement, namely those resulting from chemical and electrical potentials. Use of identical Ringer's solution on each side eliminates a chemical potential gradient of ions. Short-circuiting the skin eliminates the spontaneous skin potential difference (P.D.) or the electrical potential gradient. The short-circuit current which flows across the skin under the above conditions is measured and its equivalent in ionic flow, the short-circuit current equivalent (SCCE), is then calculated. The SCCE is considered to be the sum of all ions flowing across the membrane and the result of active transport by the membrane, since the major passive forces have been eliminated. Figure 2 depicts the relationship between sodium flux and SCCE. In the non-stimulated skin, there is active transport of sodium only. In this case, sodium influx minus sodium outflux (which is net flux) is equal or equivalent to the SCCE. If active transport of another ion or ions occurs, net sodium flux is not equal or not equivalent to the SCCE. In other words, non-sodium current appears.

Table 1 lists the drugs and the concentrations used for adrenergic stimulation. All compounds were placed in the solution in contact with the inside of the skin. Catecholamines were administered at the end of a one hour control flux period. Epinephrine was used for combined alpha and beta receptor stimulation, as it has both types of effects. Alpha stimulation was achieved with epinephrine, administered one-half hour following blockade of its beta effect with pronethalol. Beta stimulation was produced with isoproterenol which

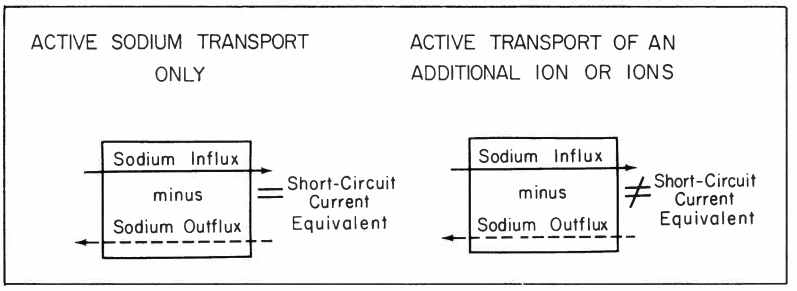

Fig. 2—Relationship between sodium flux and SCCE in the isolated frog skin in the absence of electrical and chemical gradients across the skin.

TABLE 1.
Drugs used for adrenergic stimulation. See text for time of administration.

Receptor Type	Drugs
Alpha and Beta	Epinephrine (3.9×10^{-6}M)
Alpha	Epinephrine (3.9×10^{-6}M) Beta blockade-Pronethalol (1.7×10^{-4}M)
Beta	Isoproterenol (0.78×10^{-6}M)

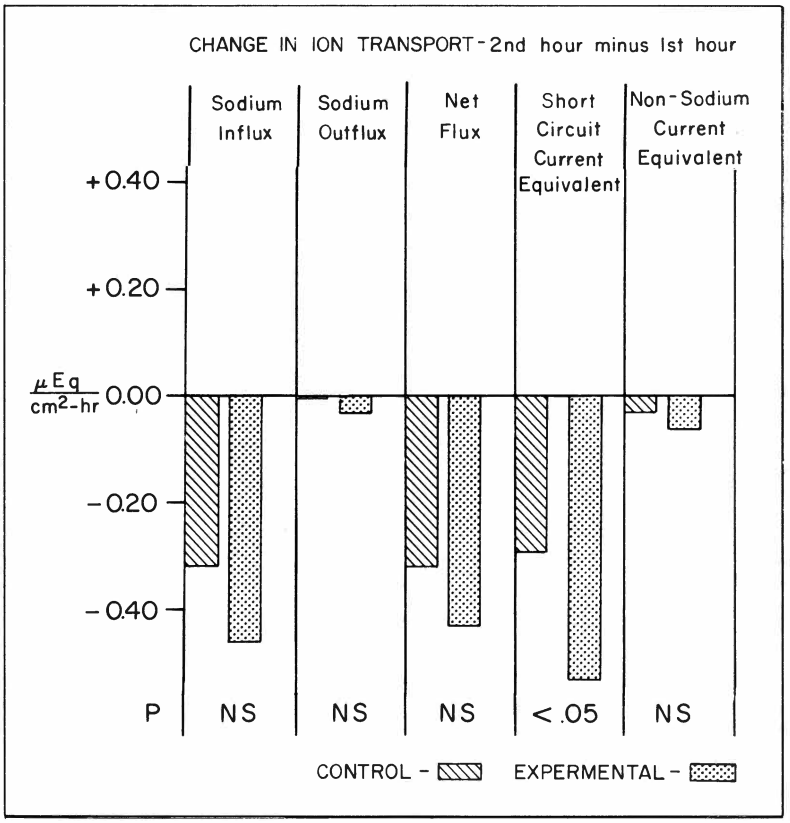

Fig. 3—Effect of alpha-adrenergic stimulation (pronethalol plus epinephrine) on sodium flux and short-circuit current. *P* refers to *t* test comparing change in experimental group to change in control. *P* values greater than .05 are considered not significant.

exerts little if any alpha-adrenergic effect (Ahlquist, 1965). Isoproterenol is 3 to 10 times as potent as epinephrine in beta stimulation effect (Mayer and Moran, 1960); therefore isoproterenol was used in one-fifth the concentration of epinephrine. Eight influx and eight outflux experiments were performed concomitantly in each of these categories, as well as in a control series in which two sequential one hour flux periods were performed without administration of catecholamines.

Results

Figure 3 compares the average changes in sodium flux and short-circuit current produced by alpha stimulation to the average changes in the control series. Epinephrine was placed in the inside chamber at the beginning of the second hour flux periods (30 min after beta blockade with pronethalol). The resulting changes in fluxes and current are compared to the changes that occurred spontaneously during this time period in the control group of experiments. After alpha stimulation, average sodium influx, outflux, net flux, and SCCE all decreased more than in the control experiments. The greater decrease in SCCE was significant and was nearly accounted for by the greater decrease in net sodium flux. Thus, little if any non-sodium current equivalent appeared, indicating that the SCCE change was due to sodium transport change only.

The decrease in net sodium transport produced by alpha-adrenergic stimulation could be caused by an alteration in either of the two steps for sodium transport. Therefore, the rate coefficients for the permeability step, k_{12}, and the active transport step, k_{23}, were estimated with eight paired skins obtained as discussed in "Methods." The control skins of each pair were exposed to pronethalol (1.7×10^{-4}M). Pronethalol alone produced no alteration in sodium transport at the drug concentration used. Alpha stimulation was produced with pronethalol plus epinephrine (1.6×10^{-6}M). The permeability rate coefficient, k_{12}, is significantly reduced ($P < .05$) by alpha stimulation when compared to control (Fig. 4). There is no significant difference in the rate coefficients for active transport, k_{23}, in the two groups. These findings indicate that alpha stimulation depresses sodium transport by decreasing permeability in the epidermal pathways for sodium transport.

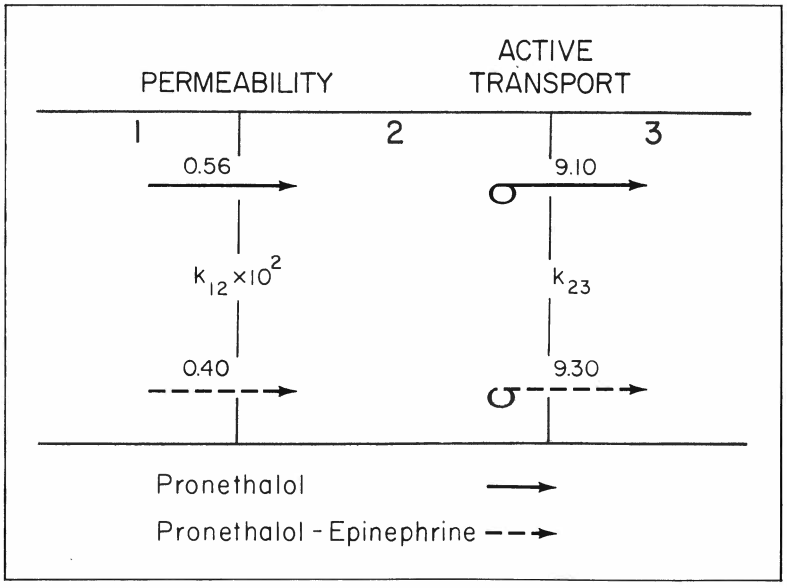

Fig. 4—Effect of alpha-adrenergic stimulation (pronethalol plus epinephrine) on the rate coefficients (hr^{-1}) for the epidermal sodium transport system. *1* and *3* represent the outer and inner bathing solutions respectively, and *2* represents the epidermal sodium transporting compartment.

The results with beta-adrenergic stimulation with isoproterenol were quite different (Fig. 5). Sodium influx and outflux increased greatly. It is of particular interest that the differences between the spontaneous change in the control experiments and the change in the beta stimulation experiments (relative change), which is an index of the magnitude of flux change attributable to beta stimulation, are approximately equal for influx and outflux. This difference or relative change is shown at the bottom of each column. The influx increased 0.65 μEq/cm^2 $\times$ hr relative to the control, and the outflux increased 0.56 μEq. This resulted in a net flux change which is approximately that of the control experiments. In other words, beta stimulation did not alter net sodium transport.

The large and equal increase in influx and outflux suggests that beta stimulation produces an increase in sodium permeability. However, if this increase in permeability occurred in the epidermal system for sodium transport previously discussed, an alteration in net flux or net transport should occur, for sodium permeability is a rate limiting factor in epidermal sodium transport inward (*see* Fig. 4). Therefore, the change in sodium flux must occur in another pathway for sodium movement. Beta stimulation causes mucous discharge by the skin (Watlington, 1965), and it may be that the mucous glands are the pathways for the increased sodium movement. It should also be noted (Fig. 5) that after beta stimulation, non-sodium current develops, and it has been postulated that this is the result of active chloride transport outward by the mucous glands (Koefoed-Johnsen et al., 1953).

The effects of epinephrine, which

produces both alpha and beta stimulation, is shown in Figure 6. The results are compared to the sum of the effects of alpha stimulation (pronethalol plus epinephrine, Fig. 3) and beta stimulation (isoproternol, Fig. 5). The changes in sodium flux, short-circuit current, and non-sodium current are all very similar in magnitude so that the separate alpha and beta effects well account for the changes produced by the combined alpha and beta stimulation produced by epinephrine.

Discussion

Figure 7 presents a hypothetical scheme of the nature of the alpha- and beta-adrenergic influences on sodium transport in frog skin. Alpha receptor stimulation decreases permeability of the epidermal system for sodium transport and hence reduces influx and outflux. The result is a decrease in net sodium transport. Beta-adrenergic receptor stimulation produces increased permeability of another pathway for sodium movement which is not involved in active transport of the ion, so that equal increases of influx and outflux occur. The effects with epinephrine, then, would be the resultant of these two opposing alterations in rates of sodium ion movement.

Alpha and beta stimulation produce opposite effects on smooth muscle contraction in most systems studied, including the arterioles (Ahlquist, 1965). Insulin release by the pancreas has been reported to be altered in opposite directions by the two stimuli (Porte, 1966). It is conceivable that opposing alterations in membrane permeability are fundamental to these and other physiologic changes produced by alpha- and beta-adrenergic receptor stimulation.

The possible role of cyclic 3′,5′-AMP, in the action of catecholamines on ion transport, merits discussion. This substance had been shown to be the mediator of epinephrine-induced activation of liver phosphorylase and has been proposed as the mediator of the action of catecholamines on other systems, as recently discussed by Sutherland and Robison (1966).

Strong evidence has been presented to implicate cyclic 3′,5′-AMP as the mediator of the increase in sodium and water permeability produced by vasopressin in toad bladder (Orloff and Handler, 1962; Handler et al., 1965). Vasopressin produces similar permeability changes in isolated frog skin (Koefoed-Johnsen and Ussing, 1953). An increase in tissue concentration of cyclic 3′,5′-AMP has been found in isolated frog skin treated with vasopressin, epinephrine, or isoproterenol (Watlington, Butcher, and Sutherland, unpublished). Beta blockade prevented the rise following the administration of epinephrine or isoproterenol. This suggests that the increase in cyclic 3′,5′-AMP concentration in tissue with catecholamines is a beta-adrenergic effect. It is probable that the increase in sodium and water permeability in frog skin produced by vasopressin is related to cyclic 3′,5′-AMP, as in toad bladder, in view of the marked similarities in the two tissues in regard to ion and water transport. The coincidence of an increase in sodium permeability and a rise in cyclic 3′,5′-AMP with beta-adrenergic stimulation in frog skin also suggests a causal relationship, although as previously discussed, the site of beta-adrenergic stimulation probably is other than that influenced by vasopressin.

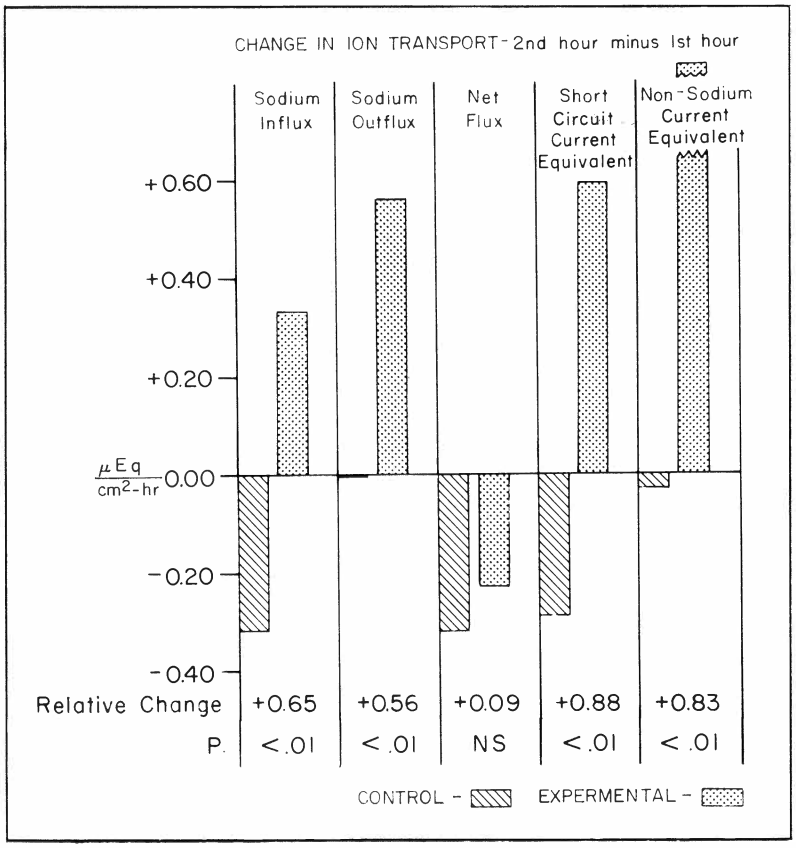

Fig. 5—Effect of beta-adrenergic stimulation (isoproterenol) on sodium flux and short-circuit current. *P* refers to *t* test comparing change in experimental group to change in control. *P* values greater than .05 are considered not significant. See text for meaning of "Relative Change."

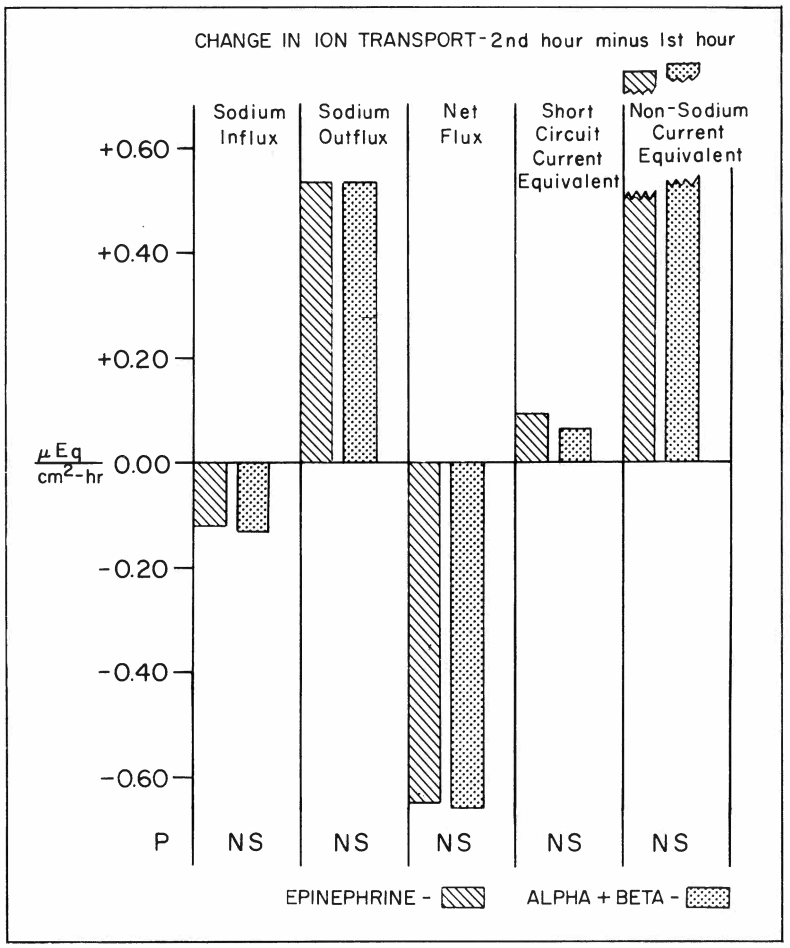

Fig. 6—Comparison of the effect of epinephrine and the algebraic sum of alpha and beta stimulation, separately produced, on sodium transport and short-circuit current. *P* refers to *t* test comparing change in experimental group to change in control. *P* values greater than .05 are considered not significant.

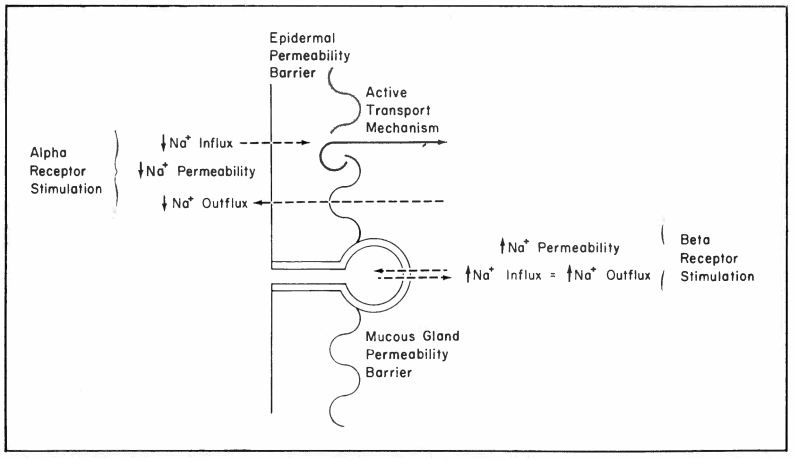

Fig. 7—Tentative scheme of the mode of action of alpha- and beta-adrenergic stimulation on sodium transport in isolated frog skin.

In view of the opposite effect of alpha-adrenergic stimulation on sodium permeability, it is conceivable that the permeability decrease is induced by a decrease in cyclic 3′, 5′-AMP levels. Sutherland (1963) previously considered the possibility that alpha-adrenergic stimulation may decrease tissue cyclic 3′,5′-AMP levels. Alonso et al. (1965) demonstrated a 50% decrease in short-circuit current following treatment of toad bladder with imidazole. This substance increases the tissue concentration of the phosphodiesterase which degrades cyclic 3′,5′-AMP. Thus, a decrease in tissue cyclic 3′,5′-AMP may have occurred and resulted in the decrease in short-circuit current secondary to a reduced sodium permeability of the system for active sodium transport.

Summary

The effect of catecholamines and a beta-adrenergic blocking agent on sodium flux and short-circuit current was evaluated in isolated frog skin. Alpha stimulation (pronethalol plus epinephrine) decreased net sodium flux and short-circuit current to an equivalent degree. Kinetic studies during alpha stimulation demonstrated a decrease in rate coefficient for entry into the skin transporting compartment but no change in the rate coefficient presumed to be related to active transport. Beta stimulation (isoproterenol) produced an equivalent increase in sodium influx and outflux with no change in net flux, and development of non-sodium current. The results suggest opposing effects of alpha- and beta-adrenergic stimulation on sodium permeability, although on different pathways for sodium movement, i.e., alpha stimulation decreases sodium permeability of the epidermal pathways for active transport, and beta stimulation increases permeability to sodium via another pathway. The beta effects may be related to mucous gland stimulation.

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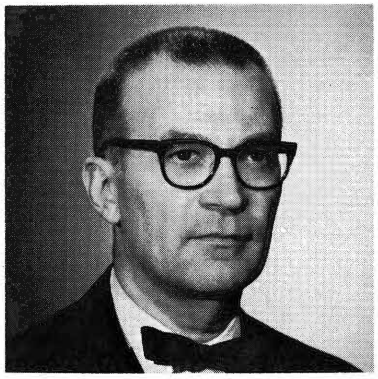

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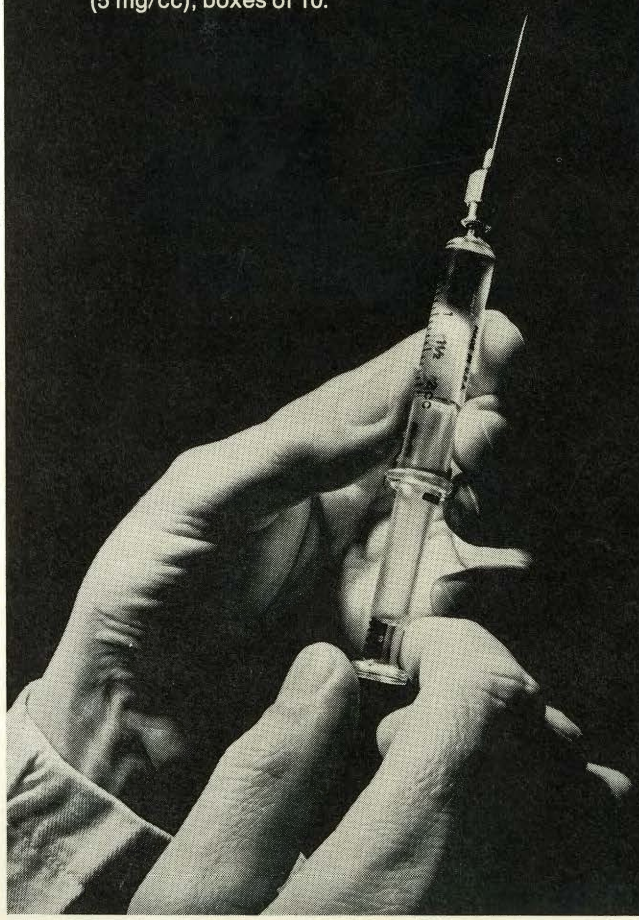

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INDICATIONS: Tension and anxiety states.

Psychoneurotic states, moderate to severe, where anxiety, apprehension or agitation exist alone or associated with depressive symptoms.

Somatic complaints which are concomitants of emotional factors.

Preoperative anxiety and acute stress reactions, used adjunctively in minor surgical procedures, gastroscopy, esophagoscopy.

Acute alcohol withdrawal.

Muscle spasm associated with cerebral palsy and athetosis.

CONTRAINDICATIONS: Infants; patients with a history of convulsive disorders, glaucoma, or known sensitivity to drug.

WARNINGS: Should not be added to parenteral fluids or be diluted. Not recommended for treatment of psychotic or severely depressed patients. Not to be administered to patients in shock or coma. Caution against hazardous occupations during therapy. Advise patients against simultaneous ingestion of alcohol and other CNS-depressant drugs during therapy. Abrupt discontinuance after prolonged overdosage may produce withdrawal symptoms similar to those noted with barbiturates and alcohol. Addiction-prone individuals should be under careful surveillance during therapy with Valium (diazepam) or other psychotropic drugs. Safe use in pregnancy and in children under age 12 not established.

PRECAUTIONS: Concurrent use with other psychotropics generally not recommended. Precautions indicated for severely depressed or patients in whom there is any evidence of impending depression. Observe usual precautions in impaired renal or hepatic function and in patients who may be suicidal. Not recommended for bronchoscopy, laryngoscopy, or obstetrical use. Since effect with narcotics may be additive, appropriate reduction in narcotic dosage is possible.

ADVERSE REACTIONS: Drowsiness, fatigue, ataxia. Also reported: blurred vision, changes in libido or salivation, confusion, constipation, depression, diplopia, dysarthria, euphoria, headache, hypoactivity, hypotension, incontinence, jaundice, nausea, skin rash, slurred speech, tremor, urinary retention and vertigo. Paradoxical reactions such as acute hyperexcited states, anxiety, excitement, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued. Periodic blood counts and liver-function tests advisable in long-term therapy. Changes in EEG patterns observed.

DOSAGE AND ADMINISTRATION: Individualize dosage. Usual initial adult dose is 2 to 10 mg I.M. or I.V. Lower doses (usually 2 mg to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. In minor surgical procedures, gastroscopy and esophagoscopy, 5 to 10 mg I.M. or I.V. 30 min. prior to procedure. Give injections slowly; take at least 1 min. for each 5 mg (1 cc). In acute conditions injection may be repeated within 1 hr., although interval of 3-4 hrs. is usually satisfactory; not more than 30 mg should be given within 8-hr. period.

Intramuscular: Deep intramuscular injection should be given slowly.

Intravenous: The solution should be injected slowly, taking at least one minute for each 5 mg (1 cc) given.

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