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Surgically implanted electronic devices for use in experimental physiology

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SURGICALLY IMPLANTED ELECTRONIC DEVICES FOR USE IN EXPERIMENTAL PHYSIOLOGY

by

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INTRODUCTION[1]

During the past several years great efforts have been expended on the development of systems which monitor functions of the mammalian body outside the conventional laboratory environment. The challenge of aerospace environment especially has stimulated the desire to observe bodily functions by means which do not interfere with normal activities.

Paramount to the development of this field of instrumentation are a few efforts in which sensing devices have been implanted within the bodies of experimental animals. New physiological information has been obtained from the observation of functions by chronically implanted devices in unanesthetized and lightly restrained animals. Some of these findings refute earlier concepts which developed from experiments conducted under extremely unphysiologic conditions. For example, the concept that increased cardiac output during exercise results from an increase of both stroke volume and heart rate was based upon the isolated heart-lung preparation of Starling. The normal control and function of the heart has been proven much more complicated than observed in the isolated preparation. By using implanted measuring devices,

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[1]This investigation was carried out during the tenure of a Postdoctoral Fellowship from the National Heart Institute, United States Public Health Service.

in intact, unanesthetized dogs, Rushmer (83) found that the stroke volume remained constant or only slightly increased during exercise. The incremented cardiac output was due solely to accelerated heart rate. Re-examination of other traditional concepts in physiology will continue as this field of instrumentation develops. Uses for operational transducer systems chronically implanted in experimental animals also can be found in the fields of pharmacology and pathology.

One of the greatest needs of experimental physiology is implantable transducers. Acceptable implantable transducers must have several attributes. First of all, they must be accurate and calibratible. Second, they should provoke minimum response in the tissues of the experimental subject. Last, but not least, the presence of the device should minimally alter the function being observed.

There is a paucity of information regarding tissue reactions to implanted transducer systems. Most of the reports about implanted electronic devices include no observations of tissue responses. In a few reports, sketchy comments have been made.

The objective of this investigation is a feasibility study. It involves the development of a system for monitoring selected aspects of cardiovascular and respiratory functions in dogs with chronically implanted electronic devices.

Several phases of this monitoring system have been studied. First studied were the gross and microscopic tissue changes invoked by implanted synthetic materials. Second, transducers that sensed cardiac and respiratory activity were designed, fabricated, implanted and evaluated. The durability of implanted electrical leads and body surface terminals also was investigated. Third, surgical procedures were devised for implanting transducers and leads. Last, a system which processed, amplified and telemetered transducer signals was designed, built and appraised.

BACKGROUND MATERIAL

Tissue Reactions to Implanted Synthetic Materials

A variety of synthetic materials have been employed as chronic implants in the mammalian body. Their principal use was to provide a substitute for malfunctioning or missing living tissues. The evaluation studies to find materials suitable for tissue replacement were spurred by the feasibility of restoring defective form and function in man. The synthetics have been used for the replacement of blood vessels, bile ducts, ureters, and as various soft tissue substitutes.

Foreign materials are inferior to living tissue in many respects and rarely become truly a part of the body. However, some of these substances will satisfactorily serve in place of living tissues.

Creech et al. (18) suggested desirable properties for a synthetic material embedded in mammalian tissue. One of these properties is that no physical modification of the material results from exposure to tissue fluids. Another is that it is both chemically inert and inert with respect to foreign body effect. It should be noncarcinogenic and nonallergenic. It should be cheaply and easily fabricated, and under continual mechanical stress should remain stable. Finally, adequate sterilization should be easily attained.

The above prerequisites apply as well to the synthetic materials which are used to coat surgically implanted electronic devices. Synthetic coverings must insulate chemically reactive components from the tissues and, in addition, protect the electronic components from the corrosive effects of tissue fluids. Reports of the value of various synthetic materials intended for implantation in man deal with their potential value as vascular and subcutaneous prostheses. Coincidentally for experimental physiological investigations these materials also are embedded in the soft tissues of the body or in contact with vascular elements. Enumeration of the reported tissue reactions in this section on background material will be restricted to those synthetic materials which were selected for use in this investigation. These materials are polyethylene, polyvinyl compounds, silicone compounds and teflon.

Polyethylene

Polyethylene tubing has been used in chronic implants for physiological studied by Jackson et al. (51) and Dziuk and Sellers (23).

Bing (10) reports that the reaction to intraperitoneally implanted polyethylene balls, 7 mm. in diameter, was greatest between the 11th and 38th days after implantation. During that period a capsule of connective tissue as thick as 2 mm.

encapsulated the implant. Polymorphonuclear leucocytes, macrophages and occasionally foreign body giant cells were present in this capsule of fibroblasts and collagenous fibers. The capsule had a lining of cells resembling vascular endothelium. The degree of connective tissue and foreign body responses was thought to be dependent upon the physical size of the implants rather than their chemical characteristics. This hypothesis was suggested by the observation that very small pieces of polyethylene film provoked a greater connective tissue encapsulation, with many foreign body giant cells, than did larger pieces.

Marlex, a polyethylene formed by catalysis under low pressure, was investigated by Usher and Wallace (94). Small pellets of this material placed in the intraperitoneal cavity of dogs did not cause adhesions. The gross reaction provoked by these pellets appeared to be less than that caused by particles of nylon, orlon, dacron or teflon.

Polyvinyl compounds

Two types of polyvinyl compounds have been embedded in living tissue and evaluated. The polyvinyl chloride sponges that were implanted by Brown et al. (11) proved to be either too friable or too reactive. Solid pieces of the material were heavy and not resilient. These investigators concluded that polyvinyl chloride was undesirable as an implant material.

Polyvinyl alcohol sponge[1], hardened by treatment with formaldehyde, has been found to be useful. Brown et al. also found that when it was implanted subcutaneously in mice that it was well tolerated. They stated that it might be useful for subcutaneous prostheses, although ulceration of the overlying skin would occur if it were implanted too shallowly. They also reported that the sponge did not appear to break down within 1 year after embedding, but that it lost resiliency after the open interstices of the sponge became filled with soft tissue. Bing (10) conversely reported that subcutaneously implanted sponge is partly reabsorbed, and microscopically appears "melted". Sponges implanted 1½ years in rabbits could not be found in tissue specimens examined both grossly and microscopically. Subcutaneous implants of polyvinyl alcohol sponge were invaded by collagenous fibers, fibroblasts, a few giant cells and occasional macrophages. Bing concluded that partial resorption of the sponge was accomplished by macrophages and giant cells, and that the spongy form of the material enhanced this process.

Grindley and Waugh (41) earlier had mentioned that the affinity for water exhibited by polyvinyl alcohol sponge enabled it to be rapidly penetrated by living tissue, or that

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[1]Ivalon. Clay-Adams Inc., 141 E. 25th St., New York, New York.

"cells follow water and what was inert becomes living". Shumway et al. (88) justified the use of polyvinyl alcohol sponge as an aortic grafting material partly because the porous graft is ultimately infiltrated by living tissue. Additionally they listed as other desirable properties its similarity in texture to aortic tissue, thus simplifying anastamoses by suturing, and its rapid ability to become bloodtight due to fibrin formation in the interstices. Jones et al. (53) found it to be suitable for grafts of all arteries greater than 7 mm. in diameter. But in long term experimental trials Harrison (46) found polyvinyl alcohol unsatisfactory as a substitute for large blood vessels because it underwent continuous degeneration and was replaced by fibrous tissue which was inadequate in tensile strength to prevent an aneurysm or rupture of the graft.

Jones et al. also successfully used polyvinyl alcohol sponge for the repair of tissue defects of the diaphragm and as a hemostatic agent in the repair of liver and kidney wounds. They reported, however, that this material was unsatisfactory as a substitute for large veins and small arteries because thrombosis occurred. They also reported its failure as an esophageal prosthesis. Eiken et al. (25) reported rupture of aortic grafts in 2, and thrombosis in 4, of 18 anastamoses of the aorta and other large arteries. Vineberg and Deliyannis (96) report the successful use of

polyvinyl alcohol sponge as a myocardial revascularization medium. Myocardial infarction was produced in a group of experimental dogs. Those dogs in which the sponge had been previously applied to the epicardium survived. Those receiving no treatment did not survive. Microscopic examination of the sponge and surrounding tissues showed that blood vessels of the pericardial sac appeared to unite with the blood filled sinuses of the sponge, and these in turn united with the myocardial blood sinusoids. Vineberg et al. (97) further reported that the blood-containing spaces of the sponge were lined with endothelial cells.

Silicone compounds

Silicone compounds are basically polymers of dimethyl-siloxane. A discussion of the uses of silicone materials in medicine is given by Brown et al. (11). The chemical structure of the dimethyl-siloxane polymers and the process of polymerization is briefly discussed by Brown et al. (14).

Solid silicone materials have been used for both vascular and soft tissue substitutes. Egdahl (24) used silicone rubber unsuccessfully as an aortic grafting material. He rejected it because of a high incidence of thrombosis in 10 experimental grafts in dogs. Another reason for rejection was the failure of a pseudointima to form.

Reports of success for silicones as soft tissue substitutes are numerous. Marzoni et al. (65) used several types

of closed cell silicone sponges in subcutaneous and subperiosteal implant studies. At both sites the sponge became encapsulated in a moderately thick layer of connective tissue. With the exception of 1 type, the air cells of the sponge were invaded by hyalinized connective tissue and focal accumulations of plasma cells and lymphocytes. The tissue reaction was that of fibrosis rather than foreign body reaction or exudation. The remaining type of sponge was encapsulated by a thin layer of connective tissue, but was not invaded by living tissue.

Solid forms of silicone rubber are resilient and are either clear amber or opaque white or tan in appearance. Brown et al. (12) have used these forms in both laboratory and clinical investigations. They report good results in the treatment of facial hemiatrophy and breast atrophy. Some of the difficulties encountered in the use and retention of these materials were infection, trauma, shifting of the implants and infiltration of open cell sponges with dense fibrous tissue. This infiltration gives the tissue an undesirably hard consistency. Additional clinical uses, reported by Brown and Ohlwiler (13), are as a nasal support following accidents, as a reconstructive agent for ears, and as a filler in cleft lip deformities.

There are several advantages of silicones as an implant material. Brown et al. (14) state that the material is

homogeneous and has good durability. Minimal tissue reaction is incited, and degeneration or calcification does not occur. Finally the material is easily obtained and fabricated, and can be repeatedly sterilized in an autoclave.

Polytetrafluoroethylene (teflon)[1]

Teflon is made by the polymerization of tetrafluoroethylene gas at high temperature and pressure. Brown et al. (12) state that there are no known solvents for the fluorocarbons and that they are stable over the range from -195 to +326°C. However, teflon can be etched. This process which prepares it for bonding to various silicone rubber compounds, can be accomplished by Tetra-Etch[2].

Teflon has a specific gravity of 2.1. This is relatively high compared to most other implantable synthetic materials. Harrison (45) reports that it is the least wettable of any of the plastics.

LeVeen and Barberio (58) reported that teflon is a semiflexible material, with a distinct waxy feel. It can be easily shaped with a knife and cannot be wet with water. This early report on the tissue reaction to teflon was based

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[1]DuPont de Nemours Company, Wilmington, Delaware.

[2]W. L. Gore and Associates, 487 Papermill Road, Newark, Delaware.

on an implantation procedure recommended by Miller and Sayers (67). This procedure, used for evaluating industrial dusts, consists of the intraperitoneal injection into guinea pigs of 2 cc. of a 5 per cent suspension of finely divided particles in saline. Examination of the peritoneal cavities of the experimental animals is performed at 14, 45, 90 days and up to 1 year after implantation. LeVeen and Barberio reported that finely divided teflon chips continued to lay free in the peritoneal cavity following implantation. There were no signs of acute inflammation or gross tissue reaction 3 days after implantation. After 70 days a thin fibrous sheath of mature fibroblasts lined with a thin layer of intact mesothelium was present. There was no sign of foreign body reaction surrounding the chips. The connective tissue capsule had not increased in thickness by the end of 6 months. It was emphasized that this synthetic material was unable to produce tissue changes and that the thin fibrous capsule actually developed as a result of trauma. Usher and Wallace (94) also reported favorably on intraperitoneal teflon implants.

In 1957 Creech et al. (18) reported that teflon and dacron woven fibers were satisfactory for aortic grafts. Pratt (78) used teflon for the replacement of aortic and arterial segments in man. He reported that 93 per cent of the implants were successful. He emphasized that teflon fabric

is very strong and that it does not lose strength while in contact with tissue fluids. Another great advantage of teflon was that the fibrin tube, which rapidly lines most vessel prostheses, was less than 1 mm. thick. Harrison (45) confirms this finding and additionally reports a very low incidence of occlusion.

Reports vary regarding success with teflon when used as a tubular graft material for other tissues of the body. Hallberg and Jonson (42), Myrin (69) and Kramish et al. (56) all reported good functional results following bile duct replacement with solid teflon tubing. There was no foreign body reaction. The fibrous sheath enveloping the graft was nonadherent. Warren et al. (98) reported failure of a woven teflon tubular graft as a replacement for the ureter. Hydronephrosis and hydroureter occurred when the anastamoses broke down. The woven material did not act as a scaffold for regeneration of the ureteral epithelium.

Brown et al. (12, 14) have found teflon suitable as a replacement for facial bone loss due to trauma, and for neoplastic and congenital defects. Pearson[1] has recently successfully augmented the medial lip of the patellar surface of

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[1]Pearson, P. T., Ames, Iowa. Comments on surgical uses of teflon. Private communication. 1961.

the canine femur as a treatment for traumatic and congenital patellar luxations.

Foreign materials implanted within the body have been known to incite tumor formation, either by their chemical irritative actions or by their physical bulk. It is pertinent here to include several references regarding the tumorogenic effects of polymers used in this investigation.

Oppenheimer et al. (71, 72) have reported the formation of various sarcomas in rats following implantation of polyethylene and polyvinyl chloride, silicone rubber, polyvinyl alcohol and teflon. In all cases the tumors which developed were of mesenchymal origin. The latent period usually exceeded 1 year. Confirmation of these tumorogenic tendencies have been reported for silicone rubber materials by Hueper (49) and for silicone rubber, teflon and polyvinyl chloride by Russel et al. (85). The relatively long latent period before tumor formation occurs in the relatively short-lived laboratory rodents points up the necessity for long term implantation studies to determine the sarcoma-producing tendencies of embedded polymers in the dog and man. A valuable study of the metabolism of the connective tissue sheath enveloping embedded plastics has been done by Oppenheimer et al. (73). They localized the uptake of $S^{35}O_4^=$ in the capsular tissue by the autoradiograph technique.

Methods for Detecting Selected Body Function Parameters

Heart potentials

Conventional methods for obtaining and interpreting electrocardiographic recordings from man can be found in texts such as that of Marriott (64). Those taken from dogs can be compared or interpreted by using information by Horowitz et al. (48), Lombard and Witham (60), and Hamlin and Smith (44).

The EKG (electrocardiogram) is a bioelectric event which conveys information about several aspects of cardiac function. From it can be determined cardiac rate, rhythm, conductive mechanisms and position. Roth et al. (82) enumerate the advantages of bioelectric events over other parameters of body function. They state that these events are easy to display, transmit and record, and that information is available in a short time without the delay encountered with other parameters involving chemical assays.

When skin contact electrodes or subcutaneously placed needles are utilized to pick up the cardiac potentials, the subject must ordinarily remain stationary and relaxed. This is to prevent aberrations of the recording by skeletal muscle action potentials and changes in the orientation of the electrodes with respect to the heart. The recording of heart potentials from a subject pursuing normal to vigorous

activity is subject to these artifacts. A partial solution to the problem is attained by placing electrodes in locations somewhat isolated from skeletal muscle action potentials. The magnitude of these potentials is large compared with body surface EKG potentials. Geddes et al. (37) suggest for EKG recordings from exercising subjects that small skin electrodes be positioned over bone areas such as found over the sternum. They recommend that an electrode be located at the cranial end of the sternum and another at the caudal end. The EKG waveform thus recorded would be unconventional when compared to standard lead systems. Even so it would contain the same information as conventional leads.

Barbato et al. (6) investigated the correlation between direct epicardial and thoracic EKG leads in man and concluded that there are corresponding points on the epicardium and on the body surface that respond with the same variations in potential during cardiac activity. Hamlin and Smith (44) state that it is possible to predict the configuration of an EKG recorded from any point on the body surface if 3 determinants are known. The first determinant is that the nature of the cardiac electrical generator be known. The second is that the propagation of waves of depolarization and repolarization through the conductive media of the body be known. The third is that the orientation between the point on the body surface and the boundary between the depolarized and nondepolarized myocardium be determined. If such is the case

it is logical to assume that a clinical interpretation of any EKG lead is theoretically possible. Nonconventional EKG lead systems thus have the same value as standard limb leads and precordial leads.

Nonconventional leads recently have been utilized for dynamic physiological studies of the heart activity of animals outside the usual laboratory situation. Graybiel et al. (39) implanted fine mesh platinum screen electrodes subcutaneously on the precordium and back of primates. These animals were subjected to ballistic space flights. Gorman (38) implanted an insulated stainless steel wire for an EKG electrode during animal investigations in biosatellite research. The bare end of the wire was secured around the posterior pectoral muscle of a mouse. The EKG recorded by radio telemetry from this lead placement appeared to be modulated by skeletal muscle action potentials. The baseline of the published recording is very unstable. Sines (89) also utilized subcutaneous wire electrodes for determining heart rate in the rat under laboratory conditions. Essler and Folk (29) reported the implantation of stainless steel wire electrodes in the abdominal cavity of the rabbit for radio telemetry of the EKG. Sullivan et al. (93) successfully recorded the EKG with hook electrodes inserted into the sternum and iliac crest of primates.

Many types of electrodes have been fabricated and used for cardiac stimulating electrodes to combat ventricular standstill. Cardiac arrest frequently develops following coronary occlusion and myocardial infarction. Especially promising results have been attained by using implanted cardiac electrodes and external or implanted electronic cardiac pacemakers. This instrumentation has successfully treated chronic atrioventricular dissociation and intermittent complete heart block (Stokes-Adams disease), both of which complicate recovery from cardiac septal infarctions. Various electrode types and combinations which were developed for use with cardiac stimulators are potentially useful in animal experimental physiology.

In 1952 Zoll (107) first reported the clinical use of an external cardiac pacemaker. The electrodes which he used were inserted subcutaneously over the rib cage. Rhythmic bursts of 130-volt, 2 millisecond pulses of 25 to 60 cycles per second successfully produced efficient cardiac contractions. Zoll et al. (108) used skin electrodes coated with saline jelly to stimulate the hearts of patients during Stokes-Adams attacks. The use of high stimulating voltages with subdermal or skin electrodes produced burns, contraction of axillary and thoracic muscles, and a disagreeable sensation in the human patients. Because of these effects these

electrodes were classed as undesirable except for emergency situations.

Starzl et al. (91) in 1955 reported the direct stimulation of the myocardium of dogs after surgically inducing complete heart block. They used a concentric bipolar needle electrode. They stated that the location of the site of ventricular stimulation with respect to the interventricular septum was not important. In this experiment the cardiac output was controlled by varying the rate of stimulation. Normal cardiac output could be regained after atrioventricular block was induced. It was attained by stimulating at the same rate as that existing before surgery. An anoxic myocardium was found to be incapable of responding adequately to external stimulation.

Weirich et al. (99, 100) were dissatisfied with the variable degree of success obtained by medical treatment of the hypotension resulting from ventricular bradycardia during complete heart block. They employed an external stimulator to control the cardiac rhythm in experimental dogs and human clinical cases. A direct unipolar electrode was implanted. It consisted of an active electrode of 0.009 inch diameter silver-plated, stranded copper wire inserted subepicardially in the right ventricular myocardium. To complete the circuit an indifferent electrode was placed on the surface of the body. The direct electrode reduced the adequate stimulus for ventricular contraction in the human heart to a range of 0.8

to 9.0 volts with an average of 2.25 volts. Undesirable skeletal muscle stimulation was eliminated by using this direct unipolar electrode at low voltages.

With the advent of transistorized cardiac pacemakers[1], which deliver a variable current of small magnitude, the unipolar-indifferent electrode combination proved unsatisfactory. This was so because the current delivered by the pacemaker was dissipated at the indifferent electrode at the body surface. An undesirable sequal to this phenomenon was inadequate current density at the direct cardiac electrode. Tissue reaction at the indifferent electrode increased electrical resistance at that point. After a period of time the current requirement for cardiac pacemaking was so greatly increased that skeletal muscle contractions were elicited.

Hunter et al. (50) developed a direct bipolar electrode which eliminated this disadvantage. The electrode consisted of 2 stainless steel pins, spaced 1.5 cm. apart, protruding from a silicone rubber patch. A coaxial cable lead was connected to these electrodes within the plaque. These electrode pins were inserted into the right ventricular myocardium. The patch was anchored to the epicardium. During experimental trials in dogs, the unblocked heart could be

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[1]Medtronic, Inc., 818 Nineteenth Ave. N. E., Minneapolis 18, Minnesota.

successfully paced by an external transistor pacemaker for as long as 5 months. The resistance between the electrodes was measured. It reached a plateau level of 500 to 600 ohms approximately 6 weeks after implantation. Hunter et al. reported successful results following implantation of the bipolar electrode in a 72 year-old man suffering from complete heart block.

The direct cardiac electrodes require open-chest surgery for careful placement. Unfortunately they would not be useful to treat acute ventricular standstill. For the emergency treatment of cardiac arrest, Ross and Hoffman (81) have recommended that a unipolar electrode of 0.015 inch diameter stainless steel wire be inserted directly into the myocardium through the closed chest wall. The wire is encased within a 3 inch, 22 gauge hypodermic needle for insertion. In order to minimize the chance for retraction of the wire from the myocardium they recommended that the wire be bent backwards at the tip of the needle prior to implantation. Bellet et al. (9) used 2 electrodes of this type inserted in a similar manner during experiments on dogs. They reported that the usual impedance range for stimulation was around 500 ohms, but made no mention of the technique for measurement. In addition they mentioned that the bent wire electrode that is inserted through the intact chest wall could easily be dislodged from the myocardium by movements due to respiration,

cardiac contractions and changes in position by the subject.

Lillehei et al. (59) reported the successful use of a transistor pacemaker in 66 clinical human cases, using either direct bipolar electrodes or a unipolar electrode. As for all previously mentioned reports on pacemakers, the rate of cardiac stimulation was predetermined by manually setting the pacemaker.

A unique variation was achieved by Kahn et al. (54). They utilized the atrial P-wave to efficiently trigger the pacemaker discharge to the ventricles. They used experimental dogs with complete heart block produced by ligating the atrioventricular bundle. Bipolar detecting electrodes were sutured to the atrial wall. The atrial depolarization potentials were detected and transmitted to the stimulator. After a timing delay, a 3 to 8 volt, 4 millisecond stimulatory discharge was delivered to a unipolar electrode sutured to the right ventricular wall.

An improvement in equipment for transistorized cardiac pacemakers has recently been reported by Chardack et al. (15). They developed an implantable pacemaker powered by long-lived mercury cell batteries. This compact stimulator was coated with room temperature vulcanizing silicone rubber[1].

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[1]RTV-502. Dow Corning Center for Aid to Medical Research, Midland, Michigan.

This material acted as an inert insulator. Bipolar electrodes were connected to this unit via leads covered with teflon. This instrumentation functioned satisfactorily in dogs with surgically induced complete heart block. The interelectrode resistance varied between 500 and 5000 ohms. The high values of impedance were thought to be due to the increased tissue resistance from scar tissue formation. Scar tissue is relatively avascular and appears less conductive than normal cardiac tissue. The rise in electrode resistance was not related to electrical stimulation. This same phenomenon was observed when the electrodes were not used for stimulation. The addendum to this report described the operation of the completely implanted system in several human patients. They estimated that battery replacement would be required after about 5 years in the implanted self-powered pacemaker. A surgical procedure would be necessary to accomplish the replacement.

Abrams et al. (1) developed an implantable pacemaker which derived its power externally. Inductively coupled power was transmitted through the intact skin to myocardial bipolar electrodes.

Blood vessel dimensions

Changes in the diameter of the aorta during the cardiac cycle have been measured by McDonald (61). He stated that

the thoracic aorta increased 15 to 20 per cent above diastolic diameter during the cardiac cycle and only 5 per cent in the abdominal aorta. Barnett et al. (7) using a caliper strain gauge in acute experiments confirmed that the aortic fluctuations fell within that range. They also investigated the relationship between mean blood pressure and mean diameter in the aorta. These were found to be essentially linearly related throughout physiological ranges of blood pressure (60-140 mm. Hg.). The pressure and diameter waveforms during a single cardiac cycle were almost congruent for mean blood pressures below 130 mm. Hg. A dynamic portrayal of pressure versus diameter on an oscilloscope produced a straight line. This also proved the linear relationship. Work by Lawton and Collins (57) confirmed this linearity. They found that elastic forces predominated in the aorta and that the extensibility of the vessel was moderately decreased by norepinephrine, a vasoconstrictor drug. Rushmer (83) earlier had conducted chronic studies on the relation between pressure and circumference in the aorta. He found that these 2 parameters tended to fluctuate together, but that the waveforms differed slightly in configuration. He suggested that this difference might be explained by technical artifacts altering the phase relations between the records, by active contraction of the smooth muscle or by changes in length of the aorta during each cardiac cycle.

If the relation between pressure and diameter in the aorta is predictable, some means for determining flow rate may be feasible. Hamilton and Remington (43) compared the cardiac stroke volume in dogs as measured by a dye injection method with the central pressure pulse. A rough correlation ($r = 0.78$) existed between stroke volume and pulse pressure. When stroke volume was compared against a calculation based upon pressure pulse contour, pulse propagation time and arterial distensibility, good correlation ($r = 0.994$) was found. McDonald (62) investigated the relation of pulsatile pressure to flow in the femoral artery of dogs. He found that the observed values for flow curves agreed, within limits of observational error, with the values calculated from the equations suggested by Womersley (104, 105). These observations by investigators in this field of cardiology and angiology appear to establish the value of efforts to develop micrometer transducers for chronically monitoring blood vessel diameters. The reports of Remington (80), Alexander (3), and Patel et al. (75) on aortic mechanics are helpful for determining the configuration of pressure and dimension waveforms at various levels of the aorta.

The micrometer of Barnett et al. (7) consisted of hinged brass leaves upon which a strain gauge was attached. This arrangement was both accurate and linear, but would be unsuitable for chronic implantation. In 1955 Rushmer (83)

reported the use of a mercury-in-rubber strain gauge to detect circumferential changes in the aorta. The device consisted of a length of fine bore latex tubing filled with mercury. It was sealed with metal plugs to which lead wires were attached. The gauge was wrapped around the aorta and the terminals anchored together so they would not become shorted. The cyclic fluctuations of aortic diameter varied the resistance of the thin column of mercury. The resistance change was detected by a Wheatstone bridge circuit and recorded. This strain gauge was an adaptation of a gauge used by Whitney (101, 102) to detect changes in the volume of human limbs. Ancillary information about the operation and optimization of this type of transducer system can be found in the reports of Elsner et al. (26) and Lawton and Collins (57).

Another type of transducer for sensing changes in heart and blood vessel dimensions involves variable reactance principles. Adams and Corell (2) reported the use of a capacitive micrometer for indirectly detecting blood pressure in human limbs. Both occlusion pressures and pulse waveforms could be suitable detected and recorded from a transducer placed on the forearm. They found that arterial volume varied with pressure in a nearly linear relationship over a large range of pressures. Wilson (103) reported the measurement of left ventricular dimensions utilizing a transducer

which operated on the mutual inductance principle. This system operated at a frequency in the audio range.

The long term detection of blood vessel dynamics with transducers impinging upon, or constricting the vessel, must allow for the effect of the transducer. The health and operating efficiency of the vessel and body functions in general might be altered by the transducer. Shipley and Gregg (86) found no fixed relationship between the per cent reduction in luminal or external vessel dimensions and the per cent reduction in blood flow. Prochnik et al. (79) found that the pressure to bilateral carotid occlusion in dogs depended upon pre-existing mean arterial pressure in the range over 60 mm. Hg. Gagnon et al. (35) reported transient changes in glomerular filtration rate and renal plasma flow following complete occlusion of the aorta distal to the renal arteries. Olmsted (70) commented about the use of a flowmeter implanted around the aorta in dogs. He found that the implant did not work satisfactorily until tissue reaction fixed the device and vessel in constant relation. However, his device eroded through the aortic wall in 3 to 10 weeks.

Heart sounds

Heart sounds are a reflection of the dynamic blood flow pattern in the heart. Abnormal function can be related to abnormal sounds. The discrepance between the frequency response

of the human ear and that of the transducers which detect heart sounds has made arduous the scientific evaluation of abnormal sounds. Various systems for recording have been developed to increase the value of PKG (phonocardiogram) information. Craige (17) reported the use of phonocardiography for detecting interventricular defects. A bell and a diaphragm head were used to detect low and high frequency components, respectively. The recording system which equalized the recorded sounds to the frequency response curve of the human ear had a logarithmic frequency response. McKusick (63) summarized his work in spectral phonocardiography, a method for quantitizing and analyzing both normal and abnormal heart sounds.

Implantable PKG transducers have been investigated by Sullivan et al. (93). They were unable to find any which met requirements for size, response, moistureproofing or system compatability. Douglas and Seal (21) described a semiconductor strain gauge acceptable for detecting both heart sounds and intrathoracic pressure which functioned well for short term studies. The long term stability of this device was not evaluated.

Respiratory movements

The state of the art of transduction and recording of various respiratory function parameters from unrestrained

exercising subjects falls far short of the elegance found in the stationary system described by Geddes et al. (36). However, compatible sensing systems have been devised for situations in which the subject wears a helmet or face mask. To measure respiration rate, Graybiel et al. (39) positioned a thermistor bead in the airway adjacent to the nostril of primates in ballistic space flights. Sullivan et al. (92) employed sensors positioned in the airway leading to a pressure suit. These devices detected flow pattern, oxygen consumption and tidal volume. From the last parameter the minute volume, ventilation rate, and respiration rate were secondarily derived. Douglas and Seal (21) utilized an implanted semiconductor strain gauge which detected respiration rate in an acute experiment.

Telemetering Physiological Information

A description of conventional methods for obtaining physiological information from acute animal preparations can be found in the manual of physiology by Hoff and Geddes (47). In this type of experiment the animal cannot be considered to be functioning in a normal environment. A conscious animal responds emotionally to the unfamiliar laboratory situation. Allen (4) found that the blood pressure of dogs changed because of an emotional response to the application of a sphygmomanometer cuff. Fuller (33) in 1948 reported that

heart rate and respiration rate in conscious dogs varied greatly depending upon the presence or absence of an experimenter, simple restraint, and loud auditory stimuli.

If the experimental animal is anesthetized it is subjected to other complicating influences. Among them are anesthetic drugs, surgical procedures and abnormal body position.

An improvement in the accuracy of physiological data can be attained in chronic experiments. Examples of this type of experiment have been described by Kolin (55), Rushmer and Smith (84), Page and Olmsted (74) and Greiss and Barefoot (40). In chronic experiments the transducers are implanted in the experimental animals. The animals are then allowed to recover from the results of anesthesia and surgery before experimental trials are made. During the course of repeated recording sessions, the animals' emotional responses to the experimental procedures tend to decline. A similar experimental situation using man as the subject is reviewed by Wood (106) and Geddes et al. (36). Under these circumstances the subject was required to remain relatively stationary with respect to the instrumentation. The transducers were not chronically implanted.

The epitome of instrumentation techniques in physiological experiments would be a system which divorced the subject from the laboratory environment. For animal

experiments the treatment could then be applied in the environment to which the animal is normally adapted. Likewise human subjects could be examined in a normal situation. Gone would be the confusing array of apparatus and the presence of distracting personnel. These factors often stimulate emotional responses which alter the function that is being observed.

Contemporary attempts to achieve this level of instrumentation have been successful. The subject has been liberated from the great bulk of equipment by radio telemetry. Radio telemetry optimally provides a link, without lead wires between the subject and the processing and recording equipment. Various degrees of achievement have been attained in recent attempts at this type of instrumentation.

In 1948 Fuller and Gordon (34) used an FM radio transmitter to telemeter human finger pulse, carotid artery pulse and pneumogram, and canine pneumogram. The sensors which modulated the radio transmitter operated on the inductive principle. They were pneumatic devices. This work proved the feasibility of the concept. The distance that data were telemetered was less than 100 feet. Following this first attempt, many accounts of data transmission over relatively short ranges have been reported. The reports of Jacobson and MacKay (52) and Farrer et al. (31) are examples of the early and present states of the art for endoradiosondes. These

devices have been used to transmit intraluminal pressure, temperature and pH from the digestive tract to nearby recorders. Examples of the application of radio telemetering of physiological data from laboratory animals, free to move about in cages, have been reported by Essler (28), Sines (89) and England and Pasamanick (27). In each of the above cases and in that reported by Gorman (38), the transducers were implanted within the body of the animal. The entire radio transmitter with power source (batteries) was implanted by Essler, and England and Pasamanick. A similar implant was made by Sullivan et al. (93) for primates in biosatellite research.

Radio telemetering of the EKG over greater distances, using a single radio link, has been achieved by Dunn and Beenken (22) using human subjects. Intraruminal pressure in cattle has been transmitted by Payne (76). Human heart rate has been radio telemetered by Shipton (87). Transmission of data several hundred feet was regularly done by these workers. Mattson and Ulstad (66) described a system capable of delivering 3 channels of physiological information from a dog over a distance as great as 1 mile. This system was phase modulated and exhibited 95 per cent accuracy. The input requirement was 0 to 100 millivolts. It was accurate within 5 per cent over the frequency range of 0 to 100 cycles per second. The input impedance was 100 kilohms.

Another type of system has been developed which greatly extends the range over which data can be transmitted. Two radio links are employed in this system. The first transmitter, very low powered, is employed to transmit signals from the subject across a short distance (i.e., cabin in an airplane or space capsule) to a receiver and second radio transmitter within the vehicle. This second transmitter is high powered and can transmit over great distances. Instrumentation using this system for handling physiological data from man and animals has been described by Graybiel et al. (39), Gorman (38), Ettelson and Pinc (30), and Cooper and Beaupre (16).

The types of function parameters which can be handled by this type of telemetry are many. Barr and Voas (8) have radio telemetered EKG, electroencephalogram, pneumogram, galvanic skin response, and skin and core body temperatures. Morrell (68) reports successful transmission of nerve action potentials.

MATERIALS AND METHODS

Implant Materials

There are 2 general types of materials used in surgically implanted electronic devices. The coating materials and electrical insulators make up 1 group. Electrical conductors comprise the other. Under some circumstances the latter might become exposed to the tissues. Some members of this group are toxic.

Fourteen different types of materials were implanted in the experimental dogs. Table 1 indicates the type of materials used and the number of dogs in which each material was implanted.

Coating materials and electrical insulators

In most instances these materials serve as both coatings and insulators. Ideally they should be perfect electrical insulators, with a low dielectric constant. They should be impermeable to tissue fluid and water vapor. In addition they should be biologically inert and should meet requirements set forth for implantable synthetic materials.

Polyethylene Regular grade polyethylene is translucent to opaque and is moderately pliable. The dielectric constant is 2.25 to 2.35. It has a specific gravity of about 0.92. Chemically it is resistant to weak acids and alkalis, strong alkalis and organic solvents. It is attacked by

strong oxidizing acids. Under 66 pounds per square inch pressure the heat distortion point ranges from 105 to 121°F. Under atmospheric pressure the material begins to distort at 212°F. Thus sterilization by steam under pressure in an autoclave is precluded. Water absorption after 24 hours immersion is less than 0.015 per cent.

There is a special high density form of polyethylene having greater resistance to chemicals and a heat resistance point of 250°F. This material can be autoclaved.

The polyethylene used in this study was the regular grade. This is available in the form of tubing and as a dielectric material in some coaxial electrical cables. It can be sterilized by immersion in a chemical disinfectant such as a 0.02 per cent solution of chlorhexidine[1]. Polyethylene is classed as being biologically inert.

Polyvinyl compounds Two types of materials are available in this group. Both types were surgically implanted in this investigation.

Polyvinyl alcohol sponge The sponge material is made by foaming nitrogen gas through polymerizing vinyl alcohol. A soft material is formed which is later hardened by treatment with formaldehyde. The sponge is white in

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[1]Nolvasan. Fort Dodge Laboratories, Fort Dodge, Iowa.

appearance and its cut surface resembles a slice of bread. The cells are of the open type, that is, interconnecting. When dry, ivalon sponge is hard and rigid, but it is resilient and soft when moist. When first boiled in water it shrinks slightly. Further shrinkage does not occur on repeated boilings. Ivalon is very easily penetrated by water. This property perhaps explains the ease with which tissue cells invade it. It is easily formed. Thin slices can be made by slicing it while wet and frozen. It can be sterilized by autoclaving, after first being boiled.

Polyvinyl chloride This substance is available in the form of tubing[1] and as such is useful as an implant material. It is quite flexible and is transparent to opaque. The heat resistance point is 175°F. It therefore must be chemically sterilized. The specific gravity is approximately 1.2. The dielectric constant is 5.0 to 6.0. It is commonly used as an electrical insulator, under the name of "thermoplastic insulation". Tygon is not affected by weak or strong acids or alkalis but is soluble in some organic solvents. In the body it is not inert. Tissue reactions possibly may be due to plastisizing agents which have been incorporated.

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[1]Tygon. U. S. Stoneware Company, Plastics and Synthetics Division, Akron 9, Ohio.

Silicone compounds Several forms and types of materials of potential usefulness are available. Some are produced in a medical grade. Silicones in general are biologically inert and do not incite foreign body reaction when embedded in tissues. Adherence to tissue is slight. Chemically they are resistant to acids, alkalis and organic solvents. The dielectric constant is about 3.0. They are efficient electrical insulators and are used as "potting" material for electronic devices. The specific gravity is about 1.1. These materials are quite heat resistant and can be sterilized by autoclaving. Silicones are flexible and resilient. Molded forms hold their shapes.

Silicone rubber tubing[1] This material possesses the properties listed above. It is available in a large variety of diameters and wall thicknesses.

Silicone rubber solid stock[2] A variety of thicknesses and shapes are available. The pure material is somewhat friable. When greater tensile strength is required however, a special formulation can be used. This type of the silicone rubber has been calendered on either straight weave or knitted dacron.

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[1]Silatube. Ronthor Reiss Corporation, Ronsil Products Division, Little Falls, New Jersey.

[2]Silastic X-30146. Dow Corning Center for Aid to Medical Research, Midland, Michigan.

Room temperature vulcanizing silicone rubber

These materials are available from two sources[1,2]. They possess the conventional qualities of the medical grade silicone rubbers, and have the advantage of vulcanizing at room temperature. This property makes custom fabrication very convenient. The uncatalyzed form is a viscous liquid and should not be placed in contact with body tissues. After polymerization is completed, however, the product is a resilient solid which is biologically inert. Both open and closed cell types of sponge are also available.

Medical adhesive[3] This is a bonding agent used to adhere silicone rubber to itself or to many other substances including metals and glass. It has the consistency of an ointment when fresh. Exposure to air and humidity rapidly cures it to a rubber. In the process of curing, acetic acid is liberated so it should not be placed in contact with tissue before curing. After curing, however, it is as inert in tissues as the other silicone rubbers. It provides an especially good bond between surfaces that have been

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[1]RTV-502 and others. Dow Corning Center for Aid to Medical Research, Midland, Michigan.

[2]RTV silicone rubber. General Electric, Silicone Products Department, Waterford, New York.

[3]Silastic Type A. Dow Corning Center for Aid to Medical Research, Midland, Michigan.

cleaned and pretreated with a primer.[1]

Silicone varnish[2] This material is available as a fluid for dip-coating objects. After curing at 150°C. for 4 to 6 hours in an oven it becomes a smooth brittle film. It is not a medical grade product.

Silicone impregnated fiberglass This fabric, in the form of a tube, forms the outer jacket for some types of coaxial cable[3]. Though not purported to be medical grade, it is mentioned here because of its potential usefulness as an implantable covering for electrical conductors.

Halogenated carbons These materials are the most chemically and biologically inert materials known. Teflon and Kel F[4] have found use in surgical applications. Teflon is not affected by weak or strong acids, alkalis or organic solvents. It can be sterilized by autoclaving. It has a dielectric constant of 2.0. Teflon does not absorb water. It is flexible only in thin forms. The surface is waxy and slippery. It is best shaped by machining or whittling.

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[1]Dow A-4094. Dow Chemical Company, Midland, Michigan.

[2]980 Varnish. Dow Chemical Company, Midland, Michigan.

[3]Amphenol 196/U. Amphenol-Borg Electronics Corp., S. Harlem Ave. at 63rd St., Chicago, Illinois.

[4]Kel F (polytrifluoromonochloroethylene). Minnesota Mining and Manufacturing Company, 900 Bush Ave., St. Paul, Minnesota.

Additional properties of this material have been mentioned earlier.

Electrical conductors

These can be used to deliver an electrical current from a source within the body to an external point. There are 2 reasons for using inert synthetic coatings for metallic conductors implanted in body tissues. The first is that effects deleterius to tissues result when common electrical conductors made from copper, tin and lead are implanted in the mammalian body. Venable and Stuck (95) reported tissue necrosis as a result of galvanic action from implanted metals. They also gave a brief history of the use and results of various kinds of metallic implants in medicine. Conductor materials which may be implanted in the body are few in number. They are limited to the noble metals (silver, gold and platinum) and various stainless alloys. The second important reason for employing inert substances is that body fluids corrode metals. Small wires can either break or become poor conductors.

Metallic conductors Platinum and silver wire, and especially platinum-iridium alloys are able to withstand continuous flexing movement. However, they are quite expensive. In addition, the necessity for electrical insulation of implanted leads minimizes their desirability.

Several stainless metals are recommended for embedding in tissues. Wires made from tantalum or special alloys of stainless steel are routinely buried in tissue. Tantalum is too brittle to make a good electrical lead. Of the surgical stainless steel alloys, SMO 18-8 type 316 is the least affected by mechanical stress. Another alloy acceptable for metal prostheses is vitallium[1]. It is available through surgical supply houses. A commercially available conductor[2], made for high temperature operation, consists of stranded stainless steel wire which has been copper and silver plated.

Nonmetallic conductors A semiconductive silicone rubber[3] which is quite extensible is available. It has a volume resistivity of approximately 60 ohms per cm. This unique substance shows some promise as an implant material.

Development of Implantable Transducers

Transducers designated for operation when implanted within the body must possess other attributes in addition to those enumerated by Fry (32) for transducers used for physiologic purposes. Fry first states that physiologic

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[1]Austenal Laboratories. New York, New York.

[2]Amphenol #414-004. R F Products, 33 E. Franklin St., Danbury, Connecticut.

[3]Silastic S-2086. Dow Corning Center for Aid to Medical Research, Midland, Michigan.

transducers should have static accuracy. That is, they should be able to reliably detect extremely slowly varying events. Secondly, they should have dynamic accuracy, the ability to detect with fidelity rapidly occurring events. To meet this specification the device should not be responsive to nonphysiologic "noise" of electrical, mechanical and thermal origins. Finally, Fry recommends that the device should not be physiologically reactive. That is to say, by its presence it should neither alter the morphology of the organism, nor disturb the normal flow of mass and energy at the site of detection.

Additional qualifications which should be requested deal with the ability of transducers to operate efficiently in an unfriendly environment. Chronically implanted transducers are subjected to great mechanical and chemical stresses by body movement and tissue fluids. It is possible that in order to develop implants able to function in the presence of these stresses, some compromise of attributes for accuracy may be required. One of the main objectives of this thesis was the investigation of implantable transducers.

Electrodes for cardiac potentials

In the initial investigation to determine the tissue reaction to various synthetic materials, teflon and silicone rubber were found to be the most inert. Since teflon

insulated electrical conductors are readily obtainable, teflon was selected as the insulation for electrode leads in this study. Stainless steel lead wires and electrodes were implanted.

Epicardial electrodes Two types of electrodes were developed for direct attachment to the epicardium. A preliminary trial in a dog demonstrated the impracticality of attaching a thin electrode to the surface of the heart. This electrode consisted of a 1/2 inch segment of a blunted surgical stainless steel suture needle. It was soldered to 0.010 inch #302 surgical stainless steel lead wire. The needle eye terminated the electrode. It was anchored to the epicardium with a nonmetallic suture. The shaft of the needle also was anchored to the epicardium by sutures. The lead wire was inserted into white teflon tubing obtained by removing stranded copper wire from commercially available hookup wire[1]. Failure of this type of electrode to remain attached to the epicardium was due to insufficient support of the device.

A different type of electrode implant was fabricated. It consisted of a 5 mm. loop of 0.010 inch #302 stainless steel wire at the end of lead wire encased in teflon. The

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[1]Belden 8324, 24 gauge. Allied Radio Corp., 100 N. Western Ave., Chicago, Illinois.

loop was embedded in a wafer of ivalon sponge which was 2 mm. thick and 15 mm. square. On the surface of the wafer opposite the electrode loop, was cemented a 15 mm. by 30 mm. piece of Silastic X-30146 sheet, 0.005 inch thick, using Dow Type A Medical Adhesive. The overlapping portion of silicone rubber sheet was cemented around the teflon wire insulation. This type of electrode is shown in Figure 1. The ivalon plaque was incorporated in the design to provide a synthetic matrix into which cells of the epicardium could penetrate, immobilizing the implant. The silastic sheet, in addition to strengthening the union between electrode and plaque, would provide a slick nonadhering surface and prevent adhesion of the cardiac implant to the pericardial sac.

Two electrodes of this type were implanted in each of 4 dogs. One plaque was applied directly to an auricle, and the other to the corresponding ventricle. The plaque was sutured to the epicardium in 3 of the 4 dogs with a vetafil[1] suture. In the remaining dog the plaques were not anchored. The ends of the electrode leads were brought out through the skin through a teflon or a silicone rubber grommet. The impedance between the electrodes was measured with an impedance meter[2]

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[1]Fort Dodge Laboratories, Fort Dodge, Iowa.

[2]Z - angle meter type 301 A. Technology Instrument Corporation, Waltham, Massachusetts.

at appropriate intervals following implantation. The dogs were sacrificed at 64, 123, 140 and 372 days following implantation. Gross observations were made of the transducers and tissue reactions. Tissue specimens were saved for microscopic examination.

EKG electrodes implanted in bone The objective of this phase of work was to devise an EKG lead system which minimized the artifacts produced by skeletal muscle action potentials. An additional objective was to find an electrode placement which minimized the change of electrode position with respect to the heart that occurs during locomotion. Insulated lead wires with terminals secured in bone seemed best to achieve this. Even so the electrode-heart orientation would vary cyclically because of respiratory and cardiac movements. Bone electrodes would neither possess the fixed relation, nor detect as large potentials, as epicardial electrodes. However they could be implanted in dogs by a relatively simple surgical procedure.

An acute experiment in 1 dog confirmed the magnitude and relative stability of the heart potentials detected by electrodes attached to the rib cage. In chronic experiments a total of 10 pairs of bone electrodes were implanted in 10 dogs. Several combinations of teflon insulated stainless steel lead wires and electrodes were used. One type of electrode attachment in bone was made by passing a lead wire

through a small hole drilled into the sternum at the level of the 5th rib. Another electrode was inserted in a similar fashion in the dorsal process of the 9th thoracic vertebra. Each wire was then knotted. The other type of attachment was a small stainless steel bone screw[1] inserted into a 1/16 inch hole drilled into the same location. The second type of electrode is shown in Figure 2. The lead wire has been wrapped around the screw. In the 6 dogs with the electrodes consisting of wire knotted around bone, 2 pairs of leads were made with 0.010 inch #302 wire, and 4 pairs were made with #414-004 wire. In 4 dogs the electrodes were bone screws, and the leads were #414-004 wire. The other end of each electrode lead was attached to the receptacle above the skin grommet. Recordings of EKG were taken daily for the first few days postoperatively and twice weekly thereafter. At variable intervals, depending upon the operation of the electrodes and other implanted devices, the 10 dogs were sacrificed. Gross observations were made of the implanted devices and the surrounding tissues.

Piezoelectric PKG transducer

The type of heart sound transducer which produces the highest output voltage without an external power source is

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[1]#337. Zimmer Mfg. Co., Warsaw, Indiana.

the crystal microphone. For this reason contact microphones[1] were obtained for use as implanted PKG transducers. The d.c. (direct current) resistance of these units ranged from about 1 to 20 megohms. Each unit was coated with RTV-502 silicone rubber after connecting the lead wires to terminals in the skin grommet. These units were implanted subcutaneously in 10 dogs. Immediately following implantation the voltage output generated by heart sounds was measured. It fell in the range of from 1 to 5 millivolts. The first and second heart sounds were distinguishable on the recordings. One disadvantage of the transducer was a relatively poor response to low audio frequencies. Recordings of heart sounds were made following the same schedule as for EKG recordings. For several of the implants the d.c. resistance across the terminals of the PKG transducer was measured periodically. At the end of each implant experiment the implanted microphone was removed and examined for defects. The amount of tissue reaction around the transducer and leads was observed and tissue specimens were taken for microscopic examination.

Epivascular micrometers

Several types of transducers for detecting diameter changes in large arteries were fabricated. They were first

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[1] PA-14 contact microphone. Lafayette Radio, Jamaica 33, New York.

tested and evaluated on simulated arterial models. Studies in dogs during acute and chronic experiments followed.

Fluid strain gauges This type of transducer, first used by Whitney (101,102), was adapted for use as a chronically implanted transducer. Three different conductive media in silatube were tested. Silicone rubber tubing was utilized rather than latex tubing because it is much less reactive in tissues.

Several mercury-in-silicone rubber strain gauges were made. Each consisted of a 5 cm. length of 1/32 inch inside diameter silatube, filled with mercury. The ends of the tube were plugged with inserts adapted from press-fittings[1]. Holes 0.015 inch in diameter and 1/8 inch deep were drilled into 1 end of the plug. This arrangement was utilized to facilitate connection with electrical leads during surgery. The end of 0.010 inch #316 stainless steel wire was inserted into the hole and a union made by crimping the plug. This made it possible to avoid making soldered connections during surgery.

The performance of this type of gauge with increments of stretch was observed using a Wheatstone bridge. The resistance of the gauge before tension was applied was approximately 0.3 ohm. A linear relationship existed between resistance and gauge length when the gauge was stretched from 110 to 150

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[1]Type 69001-8302. Garlock, Inc., Camden, New Jersey.

per cent of its resting length. Several of these devices exhibited this characteristic. The data derived from the test of 1 of the gauges are plotted in Figure 3.

This transducer was tested around the thoracic aorta of 2 dogs during acute experiments. Following this 3 implants were made for chronic studies. The crimped union of transducer and leads was a failure in the 2 acute experiments. For the chronic implants solder connections were made using aseptic technique. Observations of function were made following implantation until the transducers ceased to function. The usual gross and microscopic observations were made.

A disadvantage of the mercury-in-silicone rubber strain gauge was low sensitivity. This was due to the low resistance of the Wheatstone bridge detector circuitry required by the transducer. To improve this 2 other fluid media were investigated. Both were characterized by high volume resistivity. Aqueous solutions of sodium chloride or copper sulfate in tubing were used to make 50 kilohm transducers. These transducers were unsatisfactory because water vapor was lost through the walls of the silatube. Evaporation caused discontinuities in the fluid column of the gauge. An additional defect of these transducers was resistance instability. The resistance was unstable even when pure copper electrodes were used to contact the copper sulfate solution, and a 400 cycle a.c. (alternating current) voltage was applied to the

bridge. Investigation of these 2 transducers was stopped.

Capacitive micrometer This phase of investigation of implantable transducers deals with a 2 plate capacitor placed around a large pulsating artery.

Theoretical considerations Changes in vessel diameter cause corresponding variations in the capacitance of the transducer by changing the spacing between the plates. Unfortunately, practical dimensions for an implantable transducer limit the capacitance of the device to less than 50$\mu\mu$f (micromicrofarads). However by energizing the transducer with VHF (very high frequency) oscillations through a coaxial transmission line of proper length, the impedance at the input end of the transmission line may be converted to a convenient magnitude.

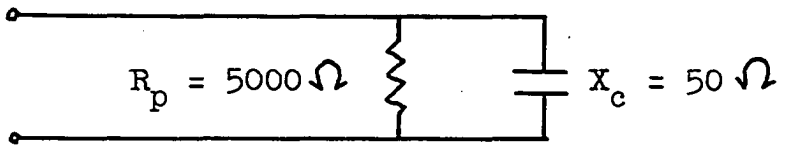
A capacitive implant around the aorta of a dog would have a capacitance of approximately 30$\mu\mu$f. The impedance of this device at a frequency of 100 megacycles would then be,

$$X_c = \frac{1}{2\pi f C} = \frac{1}{6.28 \times 10^8 \times 30 \times 10^{-12}} \qquad (1)$$

or approximately 50 ohms.

The characteristic impedance of this device would not be pure reactance. The transducer plates can be embedded in a thin shell of a highly insulating serumproofed material and implanted around an artery. In this situation the equivalent

circuit for the device would be as shown below.



These values would give a quality factor, Q, of 100 for the transducer. The admittance of this device can be written as,

$$Y_1 = \frac{1}{Z} = \frac{1}{R_p} + \frac{j}{X_c} = \frac{j}{X_c}\left[1 - j\,\frac{X_c}{R_p}\right] . \qquad (2)$$

If $\frac{1}{Q} = \frac{X_c}{R_p} = \delta$,

$$Y_1 = \frac{j}{X_c}\left[\,1 - j\,\delta\,\right] . \qquad (3)$$

Since impedance Z_1 is the inverse of admittance Y_1,

$$Z_1 = \frac{-\,j\,X_c}{1 - j\,\delta} = -\,j\,X_c\left[1 + j\,\delta - \delta^2 - j\,\delta^3 + \ldots\right] \qquad (4)$$

However, terms of second order and higher can be ignored, since they will be very much smaller than the term

$\left[\,1 + j\,\delta\right]$ thus,

$$Z_1 = -\,j\,X_c\left[\,1 + j\,\delta\right] . \qquad (5)$$

The capacitance of 2 parallel plates is inversely proportional to the spacing between them. It is therefore

permissable to assume that the capacitance of this device may fluctuate approximately 20 per cent. McDonald (61) reported a 20 per cent fluctuation in diameter of the thoracic aorta in the dog. The impedance of the transducer can then be said to vary $\pm$ 10 per cent from some value midway between systolic and diastolic values. If K represents the instantaneous fractional change from the average diameter, the value for impedance can then be represented by,

$$Z_1 = - j X_c \left[1 + j\delta \right] \left[1 + K \right] , \qquad (6)$$

$$\text{where} \quad - 0.1 \leq K \leq +0.1 \quad .$$

By expanding the expression and eliminating second order terms,

$$Z_1 = - j X_c \left[1 + K + j\delta \right] \qquad (7)$$

$$Z_1 = X_c\delta - j \left[X_c - \bar{X}_c K \right] \quad . \qquad (8)$$

The formula for the input impedance, Z_{in}, of a radio frequency transmission line is,

$$Z_{in} = Z_o \frac{\left[\frac{Z_1}{Z_o} + \alpha l \right] + j \left[\left(1 + \frac{Z_1}{Z_o} \alpha l \right) \tan \beta l \right]}{\left[1 + \frac{Z_1}{Z_o} \alpha l \right] + j \left[\left(\frac{Z_1}{Z_o} + \alpha l \right) \tan \beta l \right]} \qquad (9)$$

where Z_o = line impedance (ohms)

Z_1 = load impedance (ohms)

α = attenuation of the line (nepers/cm.)

ℓ = length of transmission line (cm.)

$\beta = \frac{2\pi}{\lambda}$ (radians/cm.)

λ = wavelength (cm.) at the specified frequency.

For ease in calculation, it will be assumed that $\ell = \lambda/8$.

Thus, $\tan\beta\ell = \tan \frac{2\pi}{\lambda} \cdot \frac{\lambda}{8} = \tan \frac{\pi}{4} = 1.0$ and the formula for Z_{in} reduces to,

$$Z_{in} = \frac{\left[\frac{Z_1}{Z_o} + \alpha\ell\right] + j\left[1 + \frac{Z_1}{Z_o}\right]}{\left[1 + \frac{Z_1}{Z_o}\alpha\ell\right] + j\left[\frac{Z_1}{Z_o} + \alpha\ell\right]} \quad . \qquad (10)$$

For this investigation a coaxial cable was used which has a Z_o = 50 ohms and an attenuation factor of 0.125 db (decibels) per foot[1]. A $\lambda/8$ length of this cable at 100 megacycles per second therefore has a total attenuation, $\alpha\ell$, of 0.0117 nepers. Substituting equation (8) in equation (10), and substituting in the numerical values for $\alpha\ell$, X_c and Z_o gives,

$$Z_{in} = 50 \frac{(0.0234 + \delta) + j\,K}{(2 - K) + j\,\delta} \qquad (11)$$

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[1] Amphenol 174/U.

Values of Z_{in} for a $\lambda/8$ transmission line at 100 megacycles per second at selected values of K and δ are plotted in Figure 4. The characteristically low impedance of this capacitor-terminated transmission line resembles that of a series circuit around the resonance point. The addition of a $\lambda/4$ segment of transmission line to this system converts the impedance characteristic to that resembling a parallel circuit near the resonance point. This system would have a much higher peak impedance value.

Changes of the impedance of the capacitor-transmission line system were detected by a locally built special VHF Wheatstone bridge, or with the circuit shown in Figure 5. Changes in the input impedance of the transmission line could be made by changing the length of the line. The desired impedance values, whether they appear purely resistive, capacitive or inductive, can be calculated from equation (9) or estimated by using a Smith chart.

Construction of a capacitive transducer There are several requirements for a transducer which is to function over a period of time while implanted around an artery. First, it should be coated with an inert material, so that the danger of vessel occlusion by chemical irritation is minimized. Second, the implant should fit snugly around the vessel so as to accurately follow cyclic dimensional changes. Third, it should not mechanically incite an occlusive tissue

reaction. Finally, the characteristics (both mechanical and electrical) of the transducer must remain constant, or at least predictable unless a means for repeated calibrations can be devised.

Several prototypes of the capacitive transducer were fabricated and tested during acute experiments in dogs. The sites of implantation were the thoracic and abdominal aorta and the carotid artery. Blood pressure and EKG or pneumogram were recorded simultaneously with diametric changes. The final form of the transducer system consisted of 174/U coaxial transmission line terminated by the capacitor. The capacitor consisted of 2 - 1 cm. by 2 cm. pieces of 0.005 inch brass shim stock, each soldered to short leads from the cable. The plates were then cemented to a rolled piece of silastic X-30146 which had been calendered on straight weave dacron. This stage of fabrication is shown in Figure 6. This device was then fixed onto a 0.375 inch diameter glass rod and inserted into a cylindrical paper tube with a diameter slightly larger than the transducer. Freshly catalyzed RTV-502 was then poured into the form and allowed to solidify. When the vulcanization was complete the form was disassembled and the excess rubber trimmed away. The finished product, which is shown in Figure 7, is an overlapping split ring.

This type of transducer was implanted in 4 dogs for

chronic studies. At appropriate intervals following implantation recordings of the transducer operation were made. The dogs were euthanized 14, 16, 27 and 42 days after implantation. The condition of each transducer was observed and the tissue at the implant site was examined.

Inductive micrometer A second type of epivascular transducer utilizing VHF transmission line theory was investigated. It consisted of a single 0.45 inch loop of #30 enameled copper wire connected to the end of a length of 174/U coaxial cable. This was incorporated into one side of an RTV-502 silicone rubber split ring. A shorted single turn loop of wire 0.45 inch in diameter was incorporated on the opposite side of the ring. This inductive micrometer was driven by oscillations in the VHF range. Fluctuations in the spacing varied the mutual inductance between the 2 loops. In turn changes in the inductance of the unshorted loop were induced. These variations were reflected by impedance changes at the other end of the transmission line.

This transducer was tested on the aorta of 1 dog in an acute experiment.

Respiration rate transducers

Mercury-in-silicone rubber strain gauge A transducer identical to those used around the aorta was employed. The operation of this type of transducer was observed in 1 acute

experiment before being implanted on a chronic basis in 2 dogs. Recordings and observations were taken intermittently following implantation until the transducers ceased to function. The usual examinations were made at necropsy.

Capacitive transducer In the investigation of epivascular transducers on the thoracic aorta, it was noticed that some of the fluctuations in the d.c. level of the record correlated with respiratory efforts. It was postulated that this artifact was due to changes in the dielectric constant of the medium adjacent to the transducer. With each respiration the gaseous content of the lung was changed. This in turn altered the distribution of the lines of flux in the fringe area around the capacitor plates. In order to test this hypothesis a fixed 2 plate capacitor with a silicone rubber dielectric was made in the form of a thin wafer. It was coated with RTV-502. This device was implanted intercostally between the parietal pleura and intercostal muscles. Postoperative recordings of transducer operation indicated respiratory rate. The rapid fluctuations of small magnitude appear to be due to contractions of the heart.

Conductive silicone rubber strain gauge This transducer detected changes in intercostal spacing. It consisted of a 2 inch length of conductive silicone rubber rod, 0.05 inch in diameter. A teflon insulated stranded stainless steel lead wire was attached to each end of the rod. A wafer

of teflon served to immobilize each terminal of the transducer. Several stages in the fabrication of this unit are shown in Figures 8, 9, and 10. The wafer was attached to a rib with a small stainless steel screw. When the transducer was placed under tension across several ribs, the expansion of the thoracic cage, which accompanied respiratory efforts, changed the length of the silicone rod. The resistance of this strain gauge changed as its length changed. The response of the silicone material was much too slow to record faithfully the changes in length of the strain gauge. Therefore a quantitative relationship between resistance and rib cage dimensions could not be developed. Nevertheless this device did give an indication of respiratory rate. It had a d.c. resistance of 50 kilohms. Changes in resistance were sensitively detected by the Wheatstone bridge circuit shown in Figure 11. The transducer was first tested in an acute experiment. It appeared to function satisfactorily. Similar units were fabricated for chronic studies and were implanted in 2 dogs. Recordings of the operation of each transducer were made. At necropsy the physical and operative conditions were observed. Tissues were taken for gross and microscopic examination.

Implantation Procedures

Implanted objects were placed in 8 locations in the experimental dogs. Table 2 indicates the locations in which implants were embedded and the number of dogs used for implants in each location.

Selection and care for experimental dogs

Forty-three dogs of mixed breeding were used in this study. Twenty acute experiments and 35 implantation experiments were conducted. Implantation experiments were designed to evaluate materials, tissue reactions, transducers, and surgical procedures. Dogs of various weights and sexes, and indeterminate ages were used. Most of the chronic experimental dogs were mature but were less than 2 years of age. Only dogs judged to be in good health by a physical examination were selected for chronic studies. Some of these were vaccinated for canine distemper and canine infectious hepatitis before experimentation.

The cages in which the dogs were housed were made of galvanized iron. They were cleaned twice daily.

Water and dry commercial dog food containing 24 per cent protein and 6 per cent fat were fed ad libitum to the experimental dogs.

Preparations for surgery

All materials which were used in implantation procedures for chronic studies were sterilized by 1 of 2 methods. Steam sterilization under pressure was used for surgical instruments, gloves, linens and implantable materials which could withstand 121°C. The array of general operating instruments is shown in Figure 13. Chemical disinfection by immersion in aqueous 0.02 per cent chlorhexidine provided the means for disinfecting materials with low heat tolerance, or instruments with sharp cutting edges which become dulled by repeated autoclaving.

Anesthetization of the dogs used in surgical procedures was accomplished by the intravenous administration of sodium pentobarbital solution given to effect. The dose was approximately 30 milligrams per kilogram body weight. Solid food was withheld for at least 12 hours prior to surgery. Hair over and adjacent to the surgical field was removed using an electric clipper with a #40 blade. The skin was then prepared for surgery by repeated scrubbings with a 25 per cent aqueous germicidal detergent which contained 0.6 per cent benzethonium chloride[1]. The lather was removed with cotton after each scrubbing. If thoracic surgery was contemplated,

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[1]Germicidal Detergent. Parke, Davis and Co., Detroit, Michigan.

an endotracheal catheter with cuff was inserted into the trachea. The cuff was inflated. The tube then was taped to the upper jaw to prevent accidental dislodgement. The catheter was attached to an artificial respiration apparatus[1] and the oxygen pressure set for 11 to 14 centimeters of water.

The hands and arms of the surgeon were repeatedly scrubbed with the 25 per cent aqueous germicidal detergent and then rinsed with tap water. After completing the scrubbing, the surgeon dried his hands and arms with a sterile towel and donned a sterile full length operating gown. He then put on dry, sterile surgical gloves.

The animal was then draped with sterile cloths leaving the surgical field exposed. Adjacent areas of hair and skin were securely covered.

Surgical procedures

There are 4 principles of good surgical technique which, if observed, enhance chances for successful results. These principles are devoted to minimizing undesirable sequalae to tissue injury. The success of an implantation procedure especially hinges upon these principles. This is

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[1]PR-3 Prothoracic Respirator with breathing bag. Professional Veterinary Service, 819 S. W. 12th Avenue, Miami, Florida.

because a foreign material is introduced into the tissues. Some materials might be irritating. Others might serve as an ideal medium for infection to develop.

These principles are first, aseptic technique, or preventing the introduction of infectious organisms into the field of surgery. This is accomplished by using sterile equipment and avoiding contamination. The second is atraumatic technique, or minimizing unnecessary devitalization of tissue. Careful dissecting technique helps to minimize trauma. The third requirement is hemostasis, or the control of hemorrhage during the operative procedure. The last requirement is careful closure of exposed tissues. This is achieved by accurate apposition of divided parts and by meticulous suturing technique.

Subcutaneous implants A pilot study was designed to obtain information about the tissue reaction to the synthetic materials used in the implantation trials. A lateral thoracic site for implantation was selected. This location was chosen because many of the devices which were to be implanted later in the investigation would be implanted in, or would traverse, this area.

Strips of regular polyethylene, polyvinyl chloride tubing, silicone rubber tubing, teflon insulated wire and siliconized fiberglass were inserted subcutaneously in 3 dogs.

A 3 inch length of each synthetic material was implanted. The diameter of each varied from 1/16 to 1/4 inch, depending upon the anticipated size of later implants. To avoid undue tissue response from disruption of tissue by incisions into the implant bed, the sterile implants were inserted into a tunnel in the subcutaneous tissue. This tunnel was made by inserting a trocar and cannula through a small incision in the skin. This cannula is shown in Figure 12. This operative technique later proved useful for advancing electrical leads through tissues without incisions. The general surgical instruments used for implanting devices are shown in Figure 13.

Each implant was palpated daily to ascertain gross reaction. At 1, 3 and 6 weeks following surgery, 1 of the dogs was anesthetized and, using aseptic technique, the implant beds were examined. Gross tissue reaction to each material was recorded and a small specimen of tissue was removed for microscopic examination.

As other likely synthetic materials became available, subcutaneous implant studies were conducted. During chronic trials to evaluate transducers and lead systems, more observations of tissue reactions were made. Whenever possible, tissue specimens were removed for microscopic examination, from subcutaneous as well as from other locations within the body.

The PKG transducers were implanted subcutaneously or intermuscularly on the left side of the thorax of 10 dogs. They were positioned at the level of the atrioventricular valves in the 4th intercostal space. For implantation, a short skin incision sufficed to allow the manipulation of the transducer through a subcutaneous tunnel originating near the site of the skin grommet. Figure 14 shows the skin incisions that were made for the implantation of a skin grommet and receptacle and the EKG, PKG and pneumograph transducers and leads.

Three types of respiration transducers were used in this study. The procedure for the implantation of the capacitor-type sensor has already been described. The mercury-in-silicone rubber transducer was implanted under the skin on the left side of the thorax in 2 dogs. Both ends were joined by a loop of vetafil in silicone rubber tubing. This loop was inserted around the rib cage using the trocar and cannula. Lead wires from the transducers traversed subcutaneously to the terminals in the skin grommet.

The conductive silicone rubber respiration transducer was attached to the left 6th and 9th ribs in 2 dogs. It was inserted under the intact latissimus dorsi muscle by blunt dissection. Stainless steel bone screws were used to secure the ends of the device to the ribs.

The function of this last type of transducer was

monitored by measurement of the d.c. resistance of the strain gauge and recording of the pneumogram of the dog. The usual necropsy examination procedure was conducted.

Skin prostheses and basic transducer harnesses Two types of synthetic grommets were developed. These were designed to provide a serumproof channel for the exit of implanted electrical leads. Attached to it is a connector for the long multiwire cable of the telemeter equipment. This long cable made it possible to position the recorder some distance away from the experimental dog. In turn this allowed the dog more freedom of movement.

One type of skin prosthesis proved impractical. It consisted of a circular silicone rubber insert, molded from RTV-502. The device had a T-shaped longitudinal section. The body of the "T" was 1/2 inch in diameter. The circular wafer forming its top was 1/8 inch thick and 1 inch in diameter. This grommet was implanted in an inverted position by inserting it up from below through a 1/2 inch circular incision in the skin. The subcutaneous entry was made through an accessory skin incision. Development of this device was terminated when the material proved too friable to withstand abuse. It tended to break apart. The ensuing skin infection was impossible to control with the device in place.

Another prosthetic skin grommet which was developed and successfully used in this study is shown in Figure 15. It

was adapted from a type used by Kolin (55). This device, however, is made of teflon rather than lucite. Also unlike Kolin's grommet, it was designed to conduct 4, rather than 1, pairs of electrical leads. The dimensions of the threaded washers are 3/4 by 3/4 by 1/8 inch. The center hole was threaded with a 1/4 by 20 tap. The 1/4 inch cylindrical rod, which was 1 inch long, was threaded with a 1/4 by 20 die. An 1/8 hole is drilled down the center of the rod.

Originally this device was inserted in the skin of 6 dogs. The implantation procedure was similar to that for the RTV-502 grommet, except that a 3/16 inch round hole was made in the skin, rather than 1/2 inch. However, as development of the lead-through system progressed, a cable connector[1] was incorporated on the device (shown in Figure 16). A further modification was the fabrication of an integral unit composed of transducers, leads and grommet. This arrangement is shown in Figure 17. The receptacle, grommet and lead wires were infiltrated with freshly catalyzed RTV-502. The serum-proofed device is shown in Figure 18. This coating minimized the accumulation of tissue fluids within the grommet and receptacle. This latter type of implant was made in 10 dogs. As before, the circular incision was made using the specially adapted cork borer shown in Figure 12. An accessory incision

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[1]Amphenol type 126-122.

was made so it joined the circular incision. The device was then inserted into the skin and subcutaneous tissues. The deeper tissues were carefully sutured with vetafil. The lead wires coming from the integral multiple transducer implant, as shown in Figure 18, were then carefully sutured to the surrounding connective tissues. A purse string suture of vetafil was then placed in the skin around the grommet to support the tissues during the healing period. The accessory incision was also sutured.

Physical examination of the gross tissue reaction around the grommet was made during the healing period. As various experiments were terminated, the tissue reaction around the grommet was evaluated by gross and microscopic examinations.

Electronic leads to the base of the heart Two procedures for the implantation of leads and transducers to the heart and aorta were evaluated. One method, entailing a transpleural inlay of the lead wires, was rejected because of the extreme amount of adhesions which formed. A thick tube of connective tissue invested the teflon insulated lead wires. The lungs, pericardial sac and parietal pleura had adhered to it. This excessive reaction was deemed undesirable because it impaired vital functions.

Another method was devised whereby the leads were not introduced into the pleural cavity. By dissections on

embalmed cadavers, a satisfactory route for implantation was found. This procedure was successfully employed in 9 dogs. For the implantation of devices in or on the heart, a left or right thoracotomy is performed through the 4th intercostal space. If exposure of the thoracic portion of the descending aorta (aorta thoracica) is desired, the approach is best made through the left 5th or 6th intercostal space. The devices which were implanted within the thorax in this study were epicardial electrodes (in 4 dogs) and aortic epivascular transducers (in 3 dogs). The devices were installed in a manner to be described later. The lead wires were brought out through a tunnel in the dorsal mediastinum. The passage was dissected by inserting either the trocar and cannula or the small curved cannula shown in Figure 12. The insertion was made starting downward from a point in the subcutaneous tissue approximately 2 inches lateral to the skin grommet. The grommet previously had been placed in the skin on the dorsal midline of the body. Its location was 1 to 2 inches caudal to the posterior angles of the scapulae, or at the level of the 7th thoracic vertebra. The cannula was passed down between fibers of the latissimus dorsi, serratus ventralis and dorsalis and iliocostalis dorsi muscles through the membranous septum between the longissimus dorsi and iliocostalis dorsi muscles. At this point an entrance is made into the 6th intercostal space. The cannula then was

carefully inserted subpleurally into the dorsal mediastinum. A small nick in the pleura near the transducer provided an opening through which the lead wires could be inserted into the bore of the cannula. Removal of the cannula left the coated wire embedded within the mediastinal tissue. With this method of insertion the pleural cavity was not traversed by foreign material.

Epicardial electrodes These were implanted in 4 dogs for the study of direct cardiac potentials. Dummy implants were made in 2 additional dogs to observe tissue reactions. Following surgery measurements of interelectrode impedance and cardiac potentials were made. At appropriate intervals the dogs were sacrificed. Observations were made of the electrodes and tissues. The epicardial implant procedure was relatively simple. An incision was made in the pericardial sac, avoiding the phrenic nerve. Two plaques were then sutured to the epicardium, 1 on the ventricle, the other on the auricle. Lead wires emerged from the pericardial sac into the mediastinum. The pericardial sac was sutured.

Epivascular implants Mercury-in-rubber strain gauges were chronically implanted around the thoracic aorta of 3 dogs. The gauge was inserted into a small tunnel around the artery. It was then placed under slight tension. The ends were tied together with vetafil suture. Lead wires were installed so that they traversed the dorsal mediastinum and

intercostal space as described previously. The connections between the lead wires and the transducer were soldered at this time. Care was taken to avoid burning adjacent tissue.

The chronic implantation of capacitor transducers was accomplished by a similar technique. A transducer, with 1 cm. by 2 cm. plates, was slipped around the aorta of 1 dog posterior to the renal arteries. Several small segmental arteries were ligated in order to dissect free a piece of the aorta sufficiently long to accept the transducer. Once installed around the artery, the transducer was self retaining. The lead wire was brought out through the body wall and connected to the skin receptacle.

Small capacitive transducers, having plates 2.0 by 0.3 cm., were placed around the left common carotid arteries of 4 dogs. The surgical approach was through the skin and muscles overlying the trachea on the ventral midline. The artery was exposed by careful incision of the carotid sheath connective tissue. The transducer was slipped around the artery. The connective tissue sheath was then closed with size A nylon thread. Lead wires were passed into a cannula inserted anteriorly and ventrally through the subcutaneous tissue of the left side of the neck. They were connected to the receptacle on a skin grommet located on the dorsal aspect of the thorax. The operation of the transducers was recorded postoperatively. At appropriate intervals following

implantation the dogs were sacrificed and observations made of the condition of the transducers and surrounding tissues.

Intravascular implants The feasibility of maintaining implanted devices in contact with the blood was investigated by 2 methods. In the first, a thin piece of thermoplastic tubing coated with Dow 980 silicone varnish was implanted in the right external jugular vein of 4 dogs. To insert the device the vein was occluded and a small puncture wound was made. The implant was inserted and the incision in the wall of the vein was sutured with 5-0 silk to prevent seepage of blood.

The second approach involved the implantation of a simulated pressure transducer in the left ventricle of 1 dog. A 1/4 inch diameter aluminum dummy, 3/4 inch long, was attached to a coaxial cable and was coated with silicone varnish. It was inserted through a puncture wound in the wall of the left ventricle, and fixed there with a purse-string suture. The implant was examined 25 days postoperatively.

Bone EKG electrodes Two types of EKG electrodes were implanted in 10 dogs. The design of this phase has been recorded in the discussion of electrode materials. To attach the dorsal electrode the dorsal spine of the 9th thoracic vertebra was exposed through a skin incision which crossed the midline. Sharp dissection down through the underlying

connective tissues bared the bony process. For implanting the ventral electrode, the sternum, at the junction with the 5th rib, was exposed through an extension of the incision made for embedding the heart sound microphone. Blunt dissection under the lateral edge of the rectus abdominus muscle accomplished the exposure. Necropsy examination was conducted at the end of each trial to determine if the electrodes were still fixed in bone. Observations of gross tissue reaction were made.

Postoperative care of dogs

The care of the dogs following implantation procedures was intentionally kept to a minimum. Antibiotics were not routinely given following surgical procedures. Bandaging was not found necessary. Each dog was examined daily. The condition of skin and subdermal implants was determined by visual observation and palpation. If infection was developing around a skin prosthesis, an antibiotic containing neomycin and polymyxin B[1] was injected into the site of infection and occasionally intramuscularly. The crusts of exudate which formed postoperatively around the skin prostheses were removed. An antibiotic wound powder[2] was

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[1]Daribiotic Injectable. S. E. Massengill Co., Veterinary Division, Bristol, Tennessee.

[2]Keraspray. S. E. Massengill Co., Veterinary Division, Bristol, Tennessee.

applied daily until the normal process of healing sealed the skin around the grommet. Figure 19 shows a healed skin grommet implant 656 days after implantation. Figure 20 shows a similar implant 89 days after implantation.

Telemetry

The transmission of physiological information from transducers implanted within the bodies of dogs to the recorders was accomplished directly by using multiconductor connectors and cables. An overall view of the typical recording situation is seen in Figure 21. Twelve feet of cable leading from the dog to the electronic equipment enabled the dog to move about within a limited area.

The leads from the implanted transducers terminated at the 9-pin receptacle attached to the teflon skin grommet. This receptacle is shown in Figure 16.

Recordings were taken for evaluating the function of implanted EKG electrodes and the heart sound transducer. The information was relayed from the transducers through the cable to a junction box that distributed the signals to the recorder preamplifiers. The junction box and associated cables are shown in Figure 22. The circuitry for this distribution system is shown in Figure 24.

A processing and amplifying device was designed and built on 1 chassis. This device was meant to be attached to

a harness and carried by a dog. Attached to the opposite side of the harness would be the radio telemeter transmitter described by Mattson and Ulstad (66). The processor itself is capable of handling inputs from implanted electrodes, heart sound transducers or the conductive silicone rubber respiration rate transducers. It can deliver an output compatible with the specifications for the telemeter apparatus designed by Mattson and Ulstad. The device measures 1 1/2 by 2 by 6 3/4 inches and weighs 335 grams, including batteries. It is shown in Figure 23. The circuitry of this device (Figure 25) has switching circuits to handle the 3 parameters. Amplification is obtained from 2 miniature transistor amplifiers[1]. An amplifier circuit similar to that recommended by the manufacturer for a 0 to 20 kilocycle bandwidth was utilized. Unfortunately the output of each amplifier contained a -1.1 volt d.c. offset. It was therefore necessary to capacitor-couple the stages to assure proper operating bias.

The 75 μf capacitor-coupling between the 60 ohm output impedance of the first amplifier and the 10 kilohm input impedance of the second amplifier gave a simple 0.75 second high pass RC characteristic. An additional 2.25 second

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[1]Model 207 G. Taber Instrument Corporation, North Tonawanda, New York.

simple high pass RC filter eliminated the d.c. bias from the output of the second amplifier. Oscilloscopic examination of the output from the amplifier driven by a sine wave generator showed faithful reproduction of waveform from 5 to 500 cycles per second. Near the high frequency end of this range the output signal lagged the input by about 8°. Calculation of the lower frequency limit from circuit component values gives a frequency of 0.212 cycles per second for the frequency at which the response is 3 db down.

This circuitry was also designed to deliver either unamplified or amplified signals from the 3 implanted transducers to the junction box and from there to the recorder. Simultaneous recording of the EKG, PKG and respiration rate could then be made. In Figure 21 the equipment is functioning in that capacity.

Incorporated in the mobile amplifier circuit was a Wheatstone bridge designed to work with the conductive silicone rubber strain gauge. The bridge is designed to balance using a transducer with a minimum resistance of 34 kilohms. Operating values for the implanted strain gauges ranged upward from 50 kilohms. The circuit of the bridge is shown in Figure 25.

Recording Systems

The pen recorder used for recording the EKG potentials, heart sounds, respiratory rate and diametric blood vessel

fluctuations was a Physiograph[1]. The preamplifiers of this recorder are capacitor-coupled and have a time constant of 2 seconds. This value meets the minimum requirement suggested by the American Medical Association Council on Physical Medicine (5) for EKG recordings of man. The pen driving amplifiers are direct-coupled. Their high frequency response is limited by the pen motors to approximately 40 cycles per second.

A dual beam oscilloscope[2] was used for monitoring the performance of transducer systems when a permanent record was not required.

For recording d.c. levels, a 2 channel recorder[3] with direct coupled amplifiers was employed.

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[1]E & M Instrument Company., Division of Air Shields, Incorporated, Houston, Texas.

[2]Type 502. Tektronix, Inc., Portland, Oregon.

[3]Twin-Viso Model 60. Sanborn Company, Waltham 64, Massachusetts.

RESULTS AND DISCUSSION

This feasibility test program had 2 goals. They were to observe tissue reactions, and to design and test transducers and lead systems. Several combinations of synthetic materials and types of instrumentation were implanted in most experimental dogs. The results and discussion of the implants therefore can best be compared and related by an anecdotal presentation.

Gross and Microscopic Observations of Reactions to Implants

An important goal for physiologic experiments with chronically implanted instrumentation is that the devices do not alter, or minimally alter, the function of the body. Ancillary to this goal should be the desire to invoke the least possible discomfort upon the animal and still obtain desired information.

Of the tissues of the body, the connective tissues proper, especially those tissues interspaced between the organs and those masses of tissue with specific and vital functions, are best prepared to tolerate the presence of foreign bodies. Here occurs the least disturbance to the normal body functions. It is these tissues which have great powers of regeneration. They regenerate in kind, or with cells and tissues related to the original types.

These tissues were intentionally invaded in this project. They include the subcutaneous, intermuscular and subpleural connective tissues as well as blood and bone.

Each tissue specimen prepared for microscopic examination in this report was removed from the animal immediately after sacrifice. Euthanasia was performed by an overdose of sodium pentobarbital. The tissue was fixed and stored in buffered neutral 10 per cent formalin. Each specimen was trimmed and then embedded in paraffin. Sections 7 to 10 microns thick were cut and mounted. Each specimen was stained with Harris' Alum Hematoxylin according to Davenport (20) and precipitated Eosin according to Pearson (77) or the Crossman (19) modification of the Mallory Triple Stain.

A microscopic view of normal subcutaneous connective tissue from the lateral thoracic wall stained with hematoxylin and eosin is seen in Figure 26. This specimen consists mainly of spaces that once contained fat. The fat was removed during the preparation of the sections. There is a delicate framework of collagenous fibers arranged in connective tissue septa. A few small blood vessels can be recognized.

In contrast, Figure 27 shows a specimen of subcutaneous connective tissue from the lateral thoracic wall in which a foreign body was inserted, in this case a soldered joint between 2 bare copper wires. This specimen was removed 127

days after implantation. An enormous amount of tissue reaction is present. The innermost layer of cells consists of relatively undifferentiated mesenchymal cells, rounded in outline and with hyperchromic nuclei. Adjacent to this is a zone of actively proliferating fibroblasts and aggregations of red blood cells and macrophages. Some capillaries are present. There is a rather distinct junction between this layer and the next. The next zone is relatively thin and consists mainly of immature fibroblasts and collagenous fibers. Peripherally there is a vascular zone containing many dense irregularly arranged collagenous fibers. Probably an inner layer of loose debris coated the wire which was removed from the tissue specimen prior to fixation. The whole process can be described as a "walling-off" reaction to an irritating foreign body. It represents the most severe type of subcutaneous reaction found in this study. The relatively inert synthetic materials provoked less reaction, unless body movements mechanically stimulated the surrounding tissues.

Polyethylene

The tissue reaction to subcutaneously embedded polyethylene was classified as moderate. Seven days following embedding, the implant was surrounded by a thin layer of primitive mesenchymal cells. Next to this membrane was a

thin zone of proliferating fibroblasts interspersed with macrophages and lymphocytes. At 3 weeks the fibroblast layer was vastly thickened. Mature fibroblasts appeared in the peripheral zone while more primitive types occurred in the middle zone. The layer of mesenchymal cells remained constant in thickness. Occasionally plasma cells could be found under the lining layer. At 6 weeks, as can be seen in Figure 28, maturation of the encapsulating connective tissue was in progress. Dense collagenous fibers and maturing fibroblasts encircled the middle zone consisting of immature fibroblasts and a delicate meshwork of collagenous fibers.

Polyvinyl compounds

Polyvinyl chloride Subcutaneously implanted tygon tubing provoked a great reaction. One week after implantation a thick layer of primitive mesenchymal cells in intercellular ground substance could be seen. Numerous polymorphonuclear leucocytes appeared in the adjacent zone which was showing early fibroblastic activity. Figure 29 shows the reaction 3 weeks after implantation. A moderately thick zone of primitive mesenchymal cells is resting upon a very thick layer of actively proliferating fibrous connective tissue. Accumulations of lymphocytes and numerous small blood vessels are seen in the outer portion of this layer. At 6 weeks this fibrous connective tissue had matured and condensed. A zone

of dense areolar connective tissue surrounded the 2 inner layers. The middle layer consisted of immature fibroblasts and collagenous fibers. The inner zone was a thick layer of mesenchymal cells supported by immature fibroblasts.

The tissue reaction to polyvinyl chloride, ascertained by palpation through the skin, was marked especially during the 2 weeks following implantation. Of the synthetic implants, the polyvinyl chloride material induced the greatest amount of subcutaneous tissue reaction.

Formalinized polyvinyl alcohol sponge Epicardial implants of ivalon sponge were examined 10, 50, 64, 123, 140 and 372 days after implantation. The amount of sponge invasion by, and adherence to, the epicardial tissue was quite variable. Six pairs of plaques were implanted. Only 1 pair did not adhere to the epicardium satisfactorily. All the remaining plaques adhered firmly to the surface of the heart. The shear strength of the bond between the sponge and epicardium of a 50 day implant was determined to be approximately 2.5 pounds per square inch.

The epicardial implants did not appear to cause discomfort in the experimental dogs. However, these animals were not subjected to strenuous activity. The gross appearance of 4 of the 6 pairs of implants revealed a massive response to the foreign body. Although the plaques (which had an

outer cover of silastic sheet) did not adhere to the pericardial sac, small quantities of fibrin had deposited on the fixation sutures. Scarification of an 1/8 inch zone of epicardium occurred around the perimeter of 1 plaque. In 3 dogs the myocardium beneath the implants appeared thickened on palpation. In 4 dogs the implants provoked considerable proliferation of the epicardium. A pocket of purulent material accumulated between the sponge and the heart wall in 1 of the 4 dogs.

In 2 of the dogs the gross reaction to the implants was very slight. The plaques adhered to the heart without visible signs of scarring. There was no thickening of the myocardium. The implant was in place for 372 days in 1 case. It appeared benignly situated at the surface of the heart.

On the basis of gross observation, it was concluded that this type of implant would not meet the specification of low physiologic "reactance" for implants used to monitor normal physiologic activity.

Microscopic examination of the sponge-epicardial zone revealed a progressive invasion of the open spaces in the ivalon with tissue fluid and cells. Ten days following implantation the spaces were loosely filled with a sparse matrix of young proliferating fibroblasts, free erythrocytes, lymphocytes and a few neutrophils. Lymphocytes accumulated in the junction zone external to the hyperplastic serous

layer of epicardium. The underlying myocardium appeared normal.

In Figure 30, the response to the implant after 64 days can be seen. A sheet of tissue, mostly lymphocytes and neutrophils, lays external to the hyperplastic epicardium, which consists of several layers of rectangular cells. The cardiac muscle fibers lying immediately beneath the junction zone appear degenerate. They are swollen and their striations and intercalated discs appear less prominent than those in deeper fibers. The sponge itself has become densely infiltrated with fibrous connective tissue. The spaces are invaded by collagenous fibers and both mature and immature fibroblasts. Erythrocytes are present. They appear within channels lined with endothelial-like cells.

Silicone compounds

Silicone rubber tubing Lengths of silatube implanted subcutaneously provoked moderate tissue reaction. No swelling at the implant site was detected following surgery. Microscopic examination of tissue around the implant 1 week after implantation revealed a single layer of undifferentiated mesenchymal cells setting upon a thin zone of immature fibroblasts. At 3 weeks the layer of mesenchymal cells was several cells thick. The immature fibroblast layer contained some lymphocytes and plasma cells. Figure 31 shows a view

of the inner portion of a thick zone of reaction. The reactive tissue is lined with mesenchymal cells. A meshwork of young proliferating fibroblasts interspersed with macrophages, erythrocytes, lymphocytes and a few plasma cells can be seen underlying the inner zone. Beyond this zone is a distinct zone of dense fibrous connective tissue with many blood vessels in the outer portion.

Implantation of silatube in the external jugular vein was unsuccessful. Two days after implantation the vein was found to be occluded. Microscopic examination of the vein revealed the lumen occluded with a thrombus. The intimal layer had lost its continuity. The intima and media were infiltrated by large numbers of neutrophils and lymphocytes.

Room temperature vulcanizing silicone rubber RTV-502 implanted subcutaneously provoked less tissue reaction than did polyethylene or polyvinyl chloride tubing. The reaction was greater than for silastic, silatube or teflon however. Figure 32 shows the tissue reaction after 1 week. There is considerable vascularity in the zone immediately adjacent to the implant. Fragments of the lining of undifferentiated mesenchymal cells can be seen. This rather loose tissue is supported on a framework of fibroblasts.

The degree of maturity of the fibroblasts and the concentration of collagenous fibers, increased from the inner zone to the periphery. Tissues examined a month or more

after implantation were characterized by a thin layer of undifferentiated mesenchymal cells surrounded by a thick zone of mature fibroblasts and collagenous fibers. In later studies, heart sound transducers coated with RTV-502 were implanted in subcutaneous tissue. The thickness of the tissue reaction around the transducers was visibly greater than that around the small diameter lead wires encased within silatube or than the RTV-502 implants in the pilot study.

The RTV-502 skin grommets provoked an intense reaction. The process was dominantly suppurative in nature. Suppuration occurred because of the contamination of the deeper tissues that ensued following breakdown of the molded prostheses. Inflammatory changes were very marked. In both cases where silicone rubber grommets were originally implanted, teflon grommets were substituted later.

Epivascular devices covered with RTV-502 appeared to make acceptable implants. Of the 4 cases in which capacitive transducers were implanted around the left common carotid artery only 1 transducer failed to remain in position. The inside diameter of this particular device was too small. Pulsations of the vessel probably forced the implant away from the vessel. One other transducer was chronically implanted around the abdominal aorta of a dog. The plates of the good implants, examined <u>in situ</u> at the time of sacrifice, appeared to be responding to the pressure pulse. Their

performance following implantation probably changed as the connective tissue response developed. All of the implants were surrounded by a membrane of connective tissue. In addition there was similar tissue between the artery and inner surface of the micrometers. In each case, however, vessel pulsations expanded the transducer.

Figure 33 shows the zone of tissue immediately surrounding a carotid capacitive transducer 14 days following implantation. A fragmented lining, 2 or 3 cells thick, of undifferentiated mesenchymal cells can be seen along the inner surface of the section. Adjacent to it is a zone of actively proliferating fibroblasts, loosely arranged and interspersed with macrophages and neutrophils. Peripheral to this zone is a layer of densely packed fibroblasts and and collagenous fibers, containing focal accumulations of neutrophils. Another tissue section of a 27 day implant showed a similar distribution of cell types. There were many small blood vessels in the area directly subjacent to the undifferentiated mesenchymal layer. A few eosinophils could also be found in this zone.

Examination of the tissue intervening between the transducer and the artery revealed a similar reaction. The tissue growth was composed mainly of proliferating immature fibroblasts. In addition there was a matrix of collagenous fibers containing both blood vessels and, in the center of

the zone, accumulations of free erythrocytes.

Silicone rubber sheet material Silastic X-30146 was implanted subcutaneously to ascertain tissue reactivity prior to using it as a covering on the outer surface of the epicardial ivalon plaques. This material is made for medical use. Figure 34 shows the tissue reaction at 50 days to a 3 inch long thin strip, 1/4 inch wide, of 0.10 inch sheet material. The tissue reaction consisted solely of a filmy, nonadherent membrane. The cells in the reactive tissue were less active than the cells in any of the other specimens which were examined. Lining this filmy capsule is a zone of undifferentiated mesenchymal cells several cells thick. The most primitive cells are located centrally. The outer rows of cells have differentiated into regularly arranged fibroblasts with collagenous fibers. Mature fibroblasts are present in the outermost layer. The thinness of the reaction and the relative inactivity of the cells in this localization reaction suggest that the implant was inert.

Thin 0.005 inch sheets of this material were cemented to the ivalon sponge plaques that were attached to the epicardium of 6 dogs. Following implantation adherence of the silastic material to the pericardial sac did not occur. Where vetafil sutures had been inserted through the plaque into the myocardium loose strands of fibrin had deposited, however.

Silicone varnish The evaluation of this material for surgical use has not been reported to the author's knowledge. The thin, extremely slick surface that it forms after it cures in an oven would be advantageous as a coating for implants. Figure 35 shows a specimen of subcutaneous tissue surrounding a 15 day varnished implant. The inner zone of the reaction consists of intercellular ground substance and undifferentiated mesenchymal cells. Next to this is a zone of loosely arranged immature fibroblasts interspersed with macrophages, lymphocytes and a few plasma cells. Numerous blood vessels are present. The most peripheral layer is dense and consists of mature fibroblasts and collagenous fibers irregularly arranged. This material thus appeared to be moderately reactive when embedded in subcutaneous tissue.

Thin pieces of polyvinyl tubing coated with silicone varnish were implanted in the right external jugular veins of 4 dogs. Following implantation this vein remained patent in only 1 dog. In this case the duration of the implant was only 2 days. Those veins containing the other 3 implants were found to be occluded by thrombi at 2, 7 and 14 days following implantation. A microscopic section of a vein which was occluded 2 days postoperatively is shown in Figure 36. The intimal lining of the vessel is greatly hyperplastic and has been invaded by neutrophils, many of which are immature. The lumen is filled with cellular

aggregations of erythrocytes, leucocytes and detached intimal cells. The varnish coating of 2 intrajugular implants had cracked. The cured varnish was very brittle and did not withstand flexion. This is a serious disadvantage for a coating material on objects which are not rigid.

The potential value of the silicone varnish as a coating for intravascular devices still might be suggested by the results obtained in another implantation experiment. A simulated pressure transducer was implanted within the left ventricle of 1 dog. There was no deposition of fibrin on it 25 days after implantation. The lining of the left ventricular chamber appeared normal with only a small piece of granulomatous tissue projecting into the ventricular lumen alongside the silicone varnished coaxial cable. The myocardium around the cable, however, was greatly thickened by connective tissue. Immediately next to the cable the cardiac muscle had been replaced by a zone of immature fibroblasts infiltrated by neutrophils. Collagenous fibers were present in this tissue.

Siliconized fiberglass This material is available as the outer jacket for 196/U coaxial cable. The reputation of the silicones for inertness, plus the easy availability of an electrical conductor covered with a potentially inert coating material, prompted the evaluation of this material in the pilot study. Siliconized fiberglass produced a

relatively mild reaction 7 days after implantation. A thin membrane composed of intercellular ground substance and undifferentiated mesenchymal cells had interposed between the implant and adjacent adipose tissue. However, this adipose tissue was infiltrated by many macrophages and lymphocytes. This may suggest that the implant was not inert. At 3 weeks a moderately thick intermediate zone of immature fibroblasts and small blood vessels had developed. By 6 weeks this zone had become quite thick and the outer layers were composed primarily of collagenous fibers and mature fibroblasts.

Teflon

The teflon materials used in this study were of 2 sizes. The first type was a relatively thin (less than 0.07 inch) tubing which served as the insulation for lead wires. It was either firmly bonded to stranded steel wire or it served as a covering into which 0.010 inch stainless steel wire loosely fitted. The second type of teflon implant, the skin grommet, was comparatively large and bulky.

Subcutaneously implanted teflon tubing provoked a low grade walling off reaction. At 7 days the surrounding tissue consisted of several cell thicknesses of undifferentiated mesenchymal cells, supported on a relatively thin layer of maturing fibroblasts and collagenous fibers. At 6 weeks the type of reaction was the same, but the thickness slightly

greater. Figure 37 shows the thin inner zone of mesenchymal cells and immature fibroblasts, surrounded by a layer of mature fibroblasts and collagenous fibers. The adjacent adipose tissue appears to be unaffected.

A similarly benign reaction resulted in 2 dogs from teflon insulated wire implanted in the dorsal mediastinum. The tissue reaction, when examined at 64 and 177 days respectively, consisted of a single layer of flattened mesenchymal cells underlaid by a zone of immature fibroblasts several cells thick. Peripherally there was a zone of densely packed collagenous fibers interspersed with mature fibroblasts. This thick zone of fibrous connective tissue probably was not a response to chemical irritation, but appeared similar to the type of reaction reported by LeVeen and Barberio (58) to be due to mechanical stimulation. Trauma to mediastinal tissues, produced by the cyclic movement of lead wires attached to the heart, probably induced the excessive connective tissue proliferation. The teflon tubing used for both of these investigations was very smooth and it easily slipped from the embedding tissues at necropsy. The comparatively rough teflon wire insulation implanted subcutaneously in the original pilot study, and later in multiple transducer implant studies, slipped less easily from the thin tube of connective tissue.

Teflon skin grommets produced gross changes in the skin in all of the 16 dogs. The prostheses were implanted for periods ranging from 8 to 656 days. In each case the device was surrounded by a thickened ring of indurated skin. The tissue adjacent to the teflon threaded rod and subcutaneous disc appeared to be friable. The markedly altered gross appearance of the tissue was not surprising. The grommet itself was large, and its mass, accelerated by body movements would exert considerable trauma to the surrounding tissues. Varying tension exerted upon it by the buried lead wires would also contribute to the traumatic affect. Furthermore another factor would be the inflammatory response to microbial contamination which occurred following some of the implants. Various degrees of inflammation, both hypertrophic and hyperplastic in nature, accompanied infection. Antibiotic therapy, however, usually controlled the infection.

Figures 38 and 39 show tissue reactions to teflon grommets which had been in position for 33 and 656 days, respectively. Both dogs retaining these grommets required very little surveillance. After the initial healing period of 2 to 3 weeks, providing infection did not intervene, tissue grew into the threaded portion of the device, effectively preventing serum seepage. Consequently there was no exudation around the grommet. Neither animal was

discomforted by the device. Of the 16 dogs implanted with the teflon grommet, only 2 appeared to be discomforted by its presence. In both of these cases the implantation of the device was faulty because the threaded portion did not lie perpendicular to the skin. This caused the lower disc to apply pressure and to wear against the skin. Mutilation of the skin grommet was prevented by inserting it in the dorsal thoracic skin. This location was found to be inaccessible for licking or scratching.

Figure 38 shows a small portion of the cellular reaction immediately adjacent to a skin grommet. The device had been in place for 33 days. At the time the tissue specimen was taken, an acute infection existed. Present in this tissue are large numbers of polymorphonuclear leucocytes and eosinophils. Immature fibroblasts have appeared and are proliferating next to this zone of free cells. Macrophages, eosinophils, and a few multinucleated giant cells and cells resembling mast cells were found in this zone. Numerous blood vessels are visible. In the subcutaneous portion of this tissue specimen, undifferentiated mesenchymal cells appeared next to the teflon grommet, in place of the diffuse zone of phagocytic and blood cells shown here. The peripheral zone of reaction in this specimen consisted mainly of maturing fibroblasts with collagenous fibers and focal accumulations of lymphocytes. This specimen represents the

greatest reaction to a skin implant, as judged by clinical, gross and microscopic examinations.

In contrast is shown Figure 39, a low power view of the tissue response to a skin grommet 656 days after implantation. The gross superficial appearance of the implant at this time is shown by Figure 19. The reactive tissue here appears to be exclusively mature fibrous connective tissue with scattered accumulations of lymphocytes. Undifferentiated mesenchymal cells are absent at the surface adjacent to the teflon, as seen here, but may have been lost during sampling. The extremely thin lining of the specimen adjacent to the teflon appeared friable and mucilaginous in vivo. In another portion of this specimen, near the juncture of the scar tissue with stratified squamous epithelium, numerous neutrophils, erythrocytes, macrophages and lymphocytes appeared to be scattered throughout a loose network of immature fibroblasts. Considerable amorphous debris is present at that junction.

Minimum tissue reactions followed the subcutaneous implantation of teflon and several of the silicone rubber materials, notable medical grade silastic and RTV-502. It would be advisable to choose from either group, a material to coat implantable devices that are irritating. However, considerations other than minimal tissue reaction may govern the final choice of coating materials. For example, where

flexibility is desired for electrical leads, teflon may be too stiff, except for wires of small diameter (24 gauge and smaller). Silicone rubber tubing or a coating of RTV-502 are both quite flexible in diameters as great as 3/16 inch. Silatube however is known to be pervious to water vapor, and therefore would be unsuitable as an insulator for reactive metals or high impedance devices. RTV-502 also exhibits this permeability to water vapor. Therefore unless a primer coating of waterproof material is utilized, the best insulating material might be polyethylene or tygon. Both are waterproof, though moderately reactive in tissues.

An extremely smooth, inert surface may be desirable to minimize the formation of a thrombus around an intravascularly implanted device. Dow 980 varnish may be acceptable if the implanted device is rigid and can tolerate the heat for curing the varnish. If the object is flexible however, a teflon coating would serve best. Unfortunately, fabrication of snug teflon coatings with shiny unblemished surfaces would be difficult. Conversely, for extravascular implants, a rough textured inert surface may be desirable. It would be more firmly embedded in the tissue thus minimizing gravitation of the implant.

In general then, each implanted device and/or lead system presents a unique problem. Selection of an acceptable

insulating and coating material depends both upon preserving electronic specifications while still observing the desirability for an inert substance. For some applications a moderately reactive material might prove useful. Fragile lead wires tend to fatigue and break when subjected to flexing movements. The protective stiffness of a moderately thick tube of connective tissue decreases the extent of this flexing movement.

LeVeen and Barberio (58) and Miller and Sayers (67) state that the degree of reaction to an implanted substance is proportional to, discounting other factors, the surface area of the foreign material. Thus the response to a quantity of powdered material would be much greater than to the same quantity in a solid piece of the same material. Other factors, however, such as movement and inertial effects of the implant, were found to greatly influence the degree of tissue reaction in this investigation. Comparatively large implants incited disproportionately greater reaction than did small implants.

Operation of Implanted Lead Systems

Malfunctions occurred at 3 locations in the implanted sensing systems. Failure at 1 or more of these locations usually disrupted the flow of information. The data frequently was altered so that interpretation of recordings was

difficult. The trouble locations were at the transducer, in the implanted electrical leads, and within the terminals at the body surface.

Terminals

Corrosion of the terminals in the multiconductor receptacle attached to the teflon skin grommet occurred in 3 of the 10 EKG and PKG transducer implants. Tissue fluids entered the receptacle via insufficiently waterproofed channels and produced a low impedance shunt path between the connector terminals. Waterproofing failure at the receptacle was due to incomplete filling of the receptacle and grommet with the silicone rubber. Tissue fluid seeped into the defects from the underlying tissues by capillary action. Body movement probably enhanced this penetration. Another source of moisture in 3 of the implants was the teflon tubing around the monofilament stainless steel wire. As an open channel existed between the tubing and the wire, the fluid entered the lead at the electrode end and penetrated directly to the terminal in the receptacle. In the case of the EKG and PKG this effect at the terminals inactivated the system. This can be seen in Figure 40. Compare this recording with the properly operating implanted EKG and PKG systems in Figure 41. The high impedance heart sound microphones were shorted by moisture. The efficiency of implanted capacitive

transducers in another dog was eventually nullified by a decrease in impedance caused by serum leakage into the skin receptable.

Leads between transducers and skin terminals

Disruption of the continuity of leads between transducers and skin terminals occurred consistently in wires made of either copper or #302 monofilament stainless steel. In 2 of the animals where copper wire leads were implanted in the mediastinum, the wire was fragmented at points which were disintegrated by electrolytic reaction. Number 302 stainless steel lead wire was used with the epicardial electrode plaques in 4 dogs. These plaques remained in position throughout the study, but the lead wires became disrupted at 7, 24, 33 and 35 days following installation. The discontinuities were signalled by a sudden change in interelectrode impedance and phase angle.

Disruption of stainless steel wire did not occur in the 3 dogs with multiple transducer implants using #316 wire leads. Prolonged continuity may have been due to the increased strength and durability possessed by this alloy.

Similarly, stranded stainless steel wire with snug teflon insulation remained intact. Where bare wire was exposed, however, breakage did occur.

All soldered connections which became moistened by

tissue fluids invariably disintegrated from electrolytic action. This type of discontinuity occurred in the leads for 3 of the 10 heart sound transducers. Because of the construction of the microphone case it was impossible to make lead connections inside the case. The transducer leads had to be connected on the outside. Penetration of the connections by fluid caused a short in the system, and no transducer signal could be recorded.

Several types of materials, or combinations of them, were employed to moistureproof transducers and leads in this investigation. Due to the superior tissue tolerance for silicone rubber, various forms of silicone rubber materials were selected to coat implanted reactive materials. Soldered electrical connections and reactive materials such as the PKG transducer case were dip-coated with RTV-502. In addition, RTV-502 was utilized to waterproof the junctions between the grommet and lead wires, and between the lead wires and transducers. This method for waterproofing was not successful in most cases especially where teflon parts were used. Two reasons for this failure are apparent. First, the silicone material failed to bond unless the teflon had been etched and treated with Dow A-4094 primer. Etched teflon-silicone rubber junctions pretreated with Dow A-4094 primer were made for sealing the grommets of the last 2 multiple

transducer implants. No evidence of moisture penetration of the receptacles was found at the termination of the experiments. However the output for each PKG transducer gradually deteriorated following implantation, probably because of moisture in the microphone case or leads. Failure of unetched teflon and RTV-502 to adhere left an interface through which fluid penetrated to the underlying parts. Primer coats of polyvinyl or lucite liquid plastic or epoxy cement[1] failed to adhere to teflon. The primers did adhere to the copper lead wire and plastic microphone case. The second reason is that despite the impermeability of silicone tubing and RTV-502 to water, they are penetrated slightly by water vapor. The vapor apparently is transmitted through to the inner surface of the silicone rubber. The accumulation of moisture in the microphone case and cable was noted for 7 of the 10 implanted heart sound transducers.

Adequate protection of leads and transducers from tissue fluids proved difficult to achieve. Best results were obtained where the bond between unlike materials was sufficiently strong to withstand the stress of body movements. Best results were also obtained when thick coatings of

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[1]Devcon Corporation, Danvers, Massachusetts.

RTV-502 were bonded to well primed materials but not including unetched teflon.

Operation of Implanted Transducers

Epicardial electrodes

The changes in interelectrode impedance with time for epicardial electrodes are shown in Table 3. The variations in impedance resemble the resistance changes reported for myocardial electrodes by Hunter et al. (50) and Bellet et al. (9). In those experiments pure resistance was the only parameter measured. In this experiment complex impedances were recorded. Direct correlation of results cannot therefore be made because of the difference in parameters.

The magnitude of the direct cardiac QRS potentials, as detected by the epicardial electrodes, did not exceed 10 millivolts for any of the 4 dogs. The relatively low output plus the high physiologic reactance induced by this implant, negated the usefulness of the device.

EKG electrodes implanted in bone

In preliminary trials the QRS complex measured across properly operating electrodes ranged from 2 to 5 millivolts. Potentials of this magnitude were sufficient to drive the preamplifier at the required level of output. Consequently this type of electrode implant was utilized for the multiple

transducer systems. Satisfactory tracings of EKG potentials were recorded for the entire length of trial for 7 of the 10 implants. The longest interval was 89 days. Figures 41 through 49 illustrate EKG tracings taken at various intervals following implantation. Typical EKG recordings show a steady baseline modulated slightly by respiratory efforts. A summary of operating characteristics for the electrode and lead systems is shown in Table 4. Of particular interest is the high incidence of electrode detachments from bone. Apparently most types of stainless steel wire, when kinked or tightly wound, will fatigue and break when exposed to tissue fluid and mechanical stress. Venable and Stuck (95) report that there are no stainless steel alloys which can completely resist electrolytic action in tissues. Stress and deterioration apparently occurred with these implanted electrodes. In the dogs where electrode detachments occurred, the terminal end of the wire was securely embedded in connective tissue reaction. Accordingly, electrode movement was very slight. The EKG recorded in this situation showed occasional baseline shifts which were not attributable to respiratory fluctuations.

Piezoelectric PKG transducers

A summary of the operating characteristics of the 10 implants is shown in Table 5. Only 1 of these transducers

functioned throughout the entire length of the trials. Deterioration of output was due primarily to shorting of the high impedance crystal by moisture. The shunting effect caused by moisture occurred either within the transducer case or in the leads or skin receptacle. Figures 44 through 48 illustrate the progressive deterioration by moisture of an implanted heart sound transducer system utilizing a piezoelectric crystal. Table 6 shows the progressive decrease with time of the d.c. resistance of several of the PKG transducers. Detachment of the lead wires at the microphone case occurred in 3 implants.

On the basis of this investigation, the implantation of transducers having a high impedance is deemed impractical, unless moistureproofing in the entire system is infallible.

Epivascular micrometers

Mercury-in-silicone rubber strain gauges Figure 51 illustrates the waveform obtained during an acute experiment from a strain gauge placed under tension around the thoracic aorta of a dog. This record compares favorably with those obtained by Rushmer (83). Recordings from chronically implanted transducers in 3 dogs were defective because the lead connections at the transducers became detached. Further discouragement with this particular transducer system resulted with the sudden death of 2 of the dogs, 8 and 28 days

following implantation. Death was due to rupture of the aorta at the implant site.

Capacitive micrometers This type of transducer functioned intermittently. The primary drawback with this device appeared to be the extreme sensitivity of the transmission line to movement. This line connected the transducer on the pulsating artery with the external electronic circuitry. Respiratory movements of anesthetized dogs frequently caused distortion of the pulse diameter recording. The aberrations consisted of shifts in the d.c. level of the recording, and distortion of pulse diametric waveform. The latter discrepancy can be seen in Figure 52. There is a possibility that this effect might be due to either changes in longitudinal tension of the artery or slippage of the transducer with respect to the vessel. Both factors could correlate with respiratory movements.

Figures 50 and 53 illustrate the potential value of the epivascular micrometer. Figure 53 shows a recording of aortic diametric fluctuations in an acute experiment. Electrical stimulation of the right vagus nerve produced cardiac arrest. The 2 ventricular contractions which occurred during stimulation were due to the vagal release phenomenon. Aortic diameter changes closely followed blood pressure changes during this interval. Slow compensatory shifts in the level of the epivascular transducer output are artifacts caused by

condensor-coupling in the Physiograph preamplifier. The rapid changes in aortic diameter during vagal stimulation are genuine evidence of the fidelity of the sensor. Aortic diameter seems to correlate fairly well with blood pressure changes here. The response to intravenously administered epinephrine was also investigated in 2 acute experiments. Equally confirmatory recordings were obtained during this maneuver. Because the recorder preamplifier was not direct-coupled, a relationship could not be established between mean blood pressure and mean artery diameter. However, by plotting the pulse diametric change versus diastolic blood pressure, a curvilinear relationship was found. The greatest change in vessel diameter caused by the pulse pressure occurred at diastolic pressures within the normal range, while smaller dimensional changes occurred at both high and low blood pressures.

Figure 50 shows a recording taken 1 day after implantation of a capacitive transducer around the abdominal aorta. A rather unique phenomenon occurred while this dog was under sodium pentobarbital anesthesia. Every 4th beat of the heart resulted in a pulse deficit. QRS complexes marked with arrows on the recording are abnormal. The QRS magnitude is greater than that of intervening contractions. The duration of the QRS interval is longer. Both features are commonly found with idioventricular contractions. These ectopic beats

are frequently too poorly organized to eject blood into the aorta. This recording of aortic diameter exhibits the pulse deficit. Each abnormal QRS complex is followed by a corresponding "decay" in aortic diameter. There is accurate synchronization of the deficit phenomenon with the ectopic QRS complexes. There is no correlation between the deficit and respiratory movements.

The effect of respiration on the level and waveform of the capacitive transducer system can be seen in Figure 54. While the level of the carotid blood pressure recording holds constant, the level and waveform of the carotid diameter recording fluctuate synchronously with the inspiratory phase of respiration.

This device could be calibrated. A direct coupled recorder was connected to the detector circuit. Several different spacings between the capacitor plates were obtained by placing the transducer around glass rods of known diameter. The level of detector output was recorded for the various spacings. The results of the calibration of 1 transducer are shown in Figure 57. The relationship of spacing to output is not linear. The calibration curve shows a simple relation, though.

There are promising aspects of the epivascular capacitive transducer. Occasionally, creditable recordings of aortic dimensional changes were obtained. Tissue tolerance

to implants indicated the suitability of this type of implant. However this transducer system appeared to have this insurmountable disadvantage, the undesirable sensitivity of the transmission line emanating from the transducer. Stacy (90) mentions the transmission line problem as a deficiency of capacitive micrometer systems. Investigation of the capacitive transducer system was stopped at this stage because of this unwanted feature.

A supplementary acute experiment in the phase of transducer design involved a transmission line terminated with an inductive load. The terminal device was a flat coil. It was embedded on 1 side of a transducer similar to the one shown in Figure 7. Its impedance varied with changes of the mutual inductance between it and a shorted wire loop which was located on the other wing of the implant. This system used the detector circuit shown in Figure 5. Changes in aortic diameter were easily detected, but this system also proved sensitive to movements of the transmission line. This phase of the study was also terminated.

Respiration rate transducers

Mercury-in-silicone rubber transducers proved to be unsatisfactory as chronic implants. The maintenance of electrical lead connections was impossible. The copper plugs in the tubing eventually came into contact with tissue fluids.

The resulting electrolysis provoked considerable tissue reaction. Figure 55 shows a recording made while using this type of transducer. The larger fluctuations give a qualitative indication of respiratory rate, while the small, more rapid fluctuations are due to contractions of the heart.

Figure 56 shows a recording made while using the capacitive transducer that was implanted external to the parietal pleura. The only information available from this recording is respiratory rate. The advantages of this type of transducer are that it is simple in construction, and can be implanted easily. It is a sensing device which cannot be dislodged by an experimental animal. It, however, provides no more information of respiratory mechanics than does the thermistor bead transducer described by Graybiel et al. (39).

The conductive silicone rubber strain gauge proved to be feasible as a chronic implant. Installation of the device was relatively simple. The teflon end tabs were anchored to bone by stainless steel screws. They were not easily dislodged. The transducer remained fairly stable following implantation, as can be seen in the data for dog 56 in Table 7. Another transducer in another dog ceased to function when 1 end of the strain gauge became detached from the lead wire. Figure 42 shows the EKG, PKG, and pneumogram recorded 7 days after implantation. The Wheatstone bridge and transistor preamplifiers which are incorporated in the portable

processing unit were used to record the pneumogram. Respiration and heart rate are clearly sensed by this transducer. Again a nonquantitative recording is obtained. Tissue reaction to this transducer was minimal. Pain at the implant site seemed to reduce intercostal expansion for several days postoperatively.

Portable Wheatstone bridge and preamplifier

This device functioned efficiently. Figure 49 shows a simultaneous recording of 2 EKG channels. Channel 1 was amplified exclusively by the Physiograph system. Channel 2 was preamplified by the home-built unit and then fed into the Physiograph system. Both waveforms compare closely, when the differences in magnitude of waveform are considered. A gain of approximately 400 is obtained by the portable processing unit.

This unit also functioned satisfactorily for amplifying the respiratory variations detected by the Wheatstone bridge, as can be seen in Figure 42.

For amplifying the output from the heart sound transducer the device was unsuccessful. The input impedance of the transistor preamplifier proved to be too low for the piezoelectric crystal. This reduced the magnitude of the crystal output to the microvolt range. The output was buried in electrical noise. The gain of the transistor preamplifier

when used for PKG amplification was insufficient to meet the input requirements for a radio telemetering system.

SUMMARY AND CONCLUSIONS

The trials to evaluate tissue reaction to implanted synthetic materials demonstrated that the response of the body to an implant depended upon at least 2 factors. The first factor was the chemical nature of the implanted object. Of the solid materials tested, teflon appeared to be the most chemically inert, as judged by gross and microscopic examinations of tissues. Medical grade silicone rubber products exhibited almost the same degree of inertness, followed closely by a nonmedical silicone product. Polyethylene was only moderately inert, and polyvinyl chloride proved to be quite reactive in tissue. These solid implants were invariably encapsulated by zones of proliferating connective tissue. The thickness and the proliferative activity of the reaction were generally inversely proportional to the chemical inertness of the implant. The open cell sponge made of polyvinyl alcohol was infiltrated, rather than encapsulated, by living tissue. Epicardial plaques made of this material were invaded by cellular components, with the end result being complete filling of the open spaces by fibrous connective tissue. Dissolution of the sponge did not occur in the epicardial implants. The second factor was the size of the implant. Large implants appeared to induce disproportionately thick tissue reaction. This phenomenon was ascribed to the

increased traumatic effect of a large mass accelerated by body movements. Tissue reactions to the relatively inert teflon and silicone rubber compounds were especially great when the implant was continually shifted with respect to surrounding tissues by muscular activity. This was notable for teflon coated lead wires implanted in the mediastinum, where a thick but low grade tissue reaction developed. This effect was also seen for the teflon grommets in the skin. Bacterial contamination was an additional stimulatory factor for this type of reaction, however.

Practical surgical procedures and implantable devices were developed and used for embedding devices in several locations in the dog. Deep subcutaneous and superficial osseous locations were found desirable for embedding transducers. These locations permitted easy installation and maintenance of EKG, PKG and respiration transducers. Chronic implants around large arteries and within the left ventricle were found feasible. Minimal pleural tissue reaction was achieved by embedding electronic lead wires within the dorsal mediastinum. Intravascular implants in large veins were unsuccessful. The maintenance of teflon skin prostheses proved feasible for periods as long as 20 months.

Maintaining implanted electronic lead systems was found difficult. Metallic conductors developed discontinuities from mechanical fatigue and/or electrolytic disintegration by

tissue fluids. The length of time that lead wires remained intact was longest when teflon insulation was imperviously bonded to the wires so that the conductors stayed dry. Two types of stainless steel conductors were found to be durable. They were Amphenol #414-004 stranded wire and #316 surgical wire. In some of the implants, where a relatively large amount of tissue reaction developed to support the leads, disruption of lead wires due to mechanical fatigue appeared to be minimized. Implanted soldered connections between conductors and at terminals consistently disintegrated from galvanic action when moistened by tissue fluids.

Moistureproofing of terminals, connections and high impedance circuits proved to be a difficult problem. Tissue fluid penetration was the major cause for electrical shorts and chemical corrosion in embedded electronic parts. A successful solution to this problem was not found. Better results were obtained, however, after a procedure to etch teflon surfaces was carried out before sealing implants with room temperature vulcanizing silicone rubber. It is concluded that better waterproofing could be attained if there was available a flexible, completely water and water vapor proof, universally adherent, inert coating material. Inertness would not be necessary if the material could be used as a primer before coating with a biologically inert substance.

The development and testing of implantable transducers

were the most provocative phases of the investigation. The transduction of each physiological parameter presented unique problems. The combination of electronic and biologic specifications for implantable devices having minimal biological and physiologic reactance created manifold limitations. On the basis of results obtained during implantation trials, some desirable characteristics for implantable transducers were formulated.

Electrodes implanted in the bones of the thoracic cage proved to be satisfactory for detecting cardiac potentials. EKG recordings were acceptable despite the fact that some electrodes broke at the point of attachment to bone during the postimplant period. The cause for detachment was determined to be fatigue from mechanical and chemical stress. An attribute for a durable electrode would be that the electrode and the lead wire be a continuous piece of material.

High impedance PKG transducers were found to be impractical implanted devices. Although heart sounds would be satisfactorily recorded for a short time following implantation, the magnitude of the transducer output invariable declined with time. This decrease was due to electrical shorting by moisture accumulation in the transducer or lead wires. Very low impedance devices would be preferable to minimize the effect of moisture.

Two types of epivascular micrometers were implanted

and tested. The first type, mercury-in-silicone rubber strain gauges, was found to be unsatisfactory. The maintenance of lead connections to the transducers proved difficult. Because the tubing was installed under considerable tension, it eroded through the aorta. The second type of transducer proved feasible from the biological standpoint. Chronically implanted capacitive micrometers in dogs induced moderate tissue reaction around the aorta and carotid artery. The electronic lead system for these devices, however, proved undesirably sensitive to changes in position, and produced artifacts in the recordings of blood vessel dimensions. These types of transducers would be valuable instrumental devices in animal experimental research if the transmission line problem could be eliminated.

One unsuccessful and 2 successful types of respiration rate transducers were developed and implanted. Disadvantages of the mercury-in-silicone rubber strain gauge for respiration were the low sensitivity and the discontinuity problem in the electrical leads. The capacitive and conductive silicone rubber transducers both qualitatively sensed respiratory rate.

The implantation of electronic sensors within the bodies of dogs proved feasible in many respects.

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TABLES

Table 1. Numbers of chronic implantation procedures listed by materials implanted

Implanted material	Number of dogs
Polyethylene tubing	3
Polyvinyl chloride tubing	3
Polyvinyl alcohol sponge	5
Thermoplastic insulation	1
Teflon insulated wire	29
Teflon skin prosthesis	16
Silicone rubber tubing	11
Room temperature vulcanizing silicone rubber	15
Silicone varnish	5
Conductive silicone rubber	2
Copper wire and solder	3
Stainless steel wire (#302)	4
Stainless steel wire (#316)	3
Stainless steel wire (#414-004)	8
Stainless steel screws	4

Table 2. Numbers of chronic implantation procedures listed by locations of implants

Implant locations	Number of dogs
Cutaneous	19
Subcutaneous	19
Mediastinal	9
Transpleural	5
Epicardial	6
Intracardial	1
Intravascular	4
Epivascular	4

Table 3. Epicardial interelectrode impedance values[a] following implantation

No. of days after implantation	Dog no. 21		Dog no. 22		Dog no. 24		Dog no. 29	
	Z[b]	θ[c]	Z[b]	θ[c]	Z[d]	θ[e]	Z[d]	θ[e]
0			1100	-30	396	-33	378	-25
1			1000		271	-34		
2			741	-35	247	-36	333	-26
3			710					
4			580	-34			340	-24
5			600	-30				
6			610	-34	230	-32		
7					270	-36		
8	2950	-52			270	-36		
9	2950	-52			295	-23	330	-24
10					290	-32		
12							375	-24
14	2940							
15					280	-34	379	-25
16	4000	-48						
21					290	-32		
23	7100							
24					270	-32		
26							413	-26
33							564	-34
35	19600							

[a]Measured with a Type 301-a Z-angle meter. Technology Instrument Corporation, Waltham, Massachusetts.

[b]Impedance in ohms measured at 60 cycles per second.

[c]Phase angle in degrees measured at 60 cycles per second.

[d]Impedance in ohms measured at 400 cycles per second.

[e]Phase angle in degrees measured at 400 cycles per second.

Table 4. Performance of implanted electrocardiograph (EKG) electrodes

Dog no.	Duration of experiment[b]	Transducer operational life[b]	First appearance of defects[b]	QRS magnitude Start[c]	QRS magnitude End[d]	Comments[a]
37	8	8		4.5	3.0	Leads attached
38	89	89		1.0	2.0	Leads attached
39	31	9	9	4.0	2.5	Leads detached
42	14	14	12	5.0	0	Leads detached, receptacle corroded
45	27	27	11	7.5	0.3	Leads detached, receptacle corroded
46	42	42	20	6.5	2.5	Leads attached
50	33	33		2.0	2.0	Leads detached
51	35	35		3.0	3.0	Leads detached
56	18	11	11	4.5	3.5	Leads detached
58	12	12		1.5	1.5	Leads detached

[a]Findings at end of experiment.

[b]Days.

[c]Millivolts output after implantation.

[d]Millivolts output at end of experiment.

Table 5. Performance of implanted phonocardiograph (PKG) transducers

Dog no.	Duration of experiment[a]	Transducer operational life[a]	First appearance of defects[a]	Output voltage[b] Start	Output voltage[b] End	D. C. resistance[c] Start	D. C. resistance[c] End	Locations where moisture found[d]
37	8	8		4.5	.04		0.290	Case
38	89	7		10.0	0		9.5	
39	31	10		6.0	0		0.120	Leads
42	14	1	12	0.35	0		0	Leads, receptacle
45	27	1	4	1.5	0		0.011	Case, leads
46	42	5	8	4.0	0		0.4	
50	33	14	21	4.0	0	5,000	20	Case, leads
51	35	21		6.2	0	4,500	60	Case
56	18	11		0.2	0	90,000	140	
58	12	5		0.15	0	42,000	120	Leads

[a]Days.

[b]Millivolts.

[c]Kilohms.

[d]Examined at end of experiment.

Table 6. Phonocardiograph (PKG) transducer d.c. resistance values[a] following implantation

No. of days after implantation	D.C. resistance[b]			
	Dog no. 50	Dog no. 51	Dog no. 56	Dog no. 58
0	5000	4500	90000	42000
1	2000			5000
3	500	1250	9500	
4			400	
5				1600
6	420			
7		900	140	
11	500	700	200	
12				120
13	150			
14	40	200		
18	30	100	140	
21	10	100		
25	20	80		
28	45	20		

[a]Measured with a Heath vacuum tube voltmeter. Heath Company, Benton Harbor, Michigan.

[b]Kilohms.

Table 7. Performance of implanted conductive silicone rubber pneumograph transducers

Dog no.	Duration of experiment[c]	Transducer operational life[c]	First appearance of defects[c]	D.C. resistance[a] Start	End	Comments[b]
56	18	18		50	75	
58	12	1	1	55	400	Lead wire detached

[a]Kilohms.

[b]Findings at end of experiment.

[c]Days.

ILLUSTRATIONS

Figure 1. Stainless steel epicardial electrode and ivalon plaque

Figure 2. Stainless steel bone screw electrode

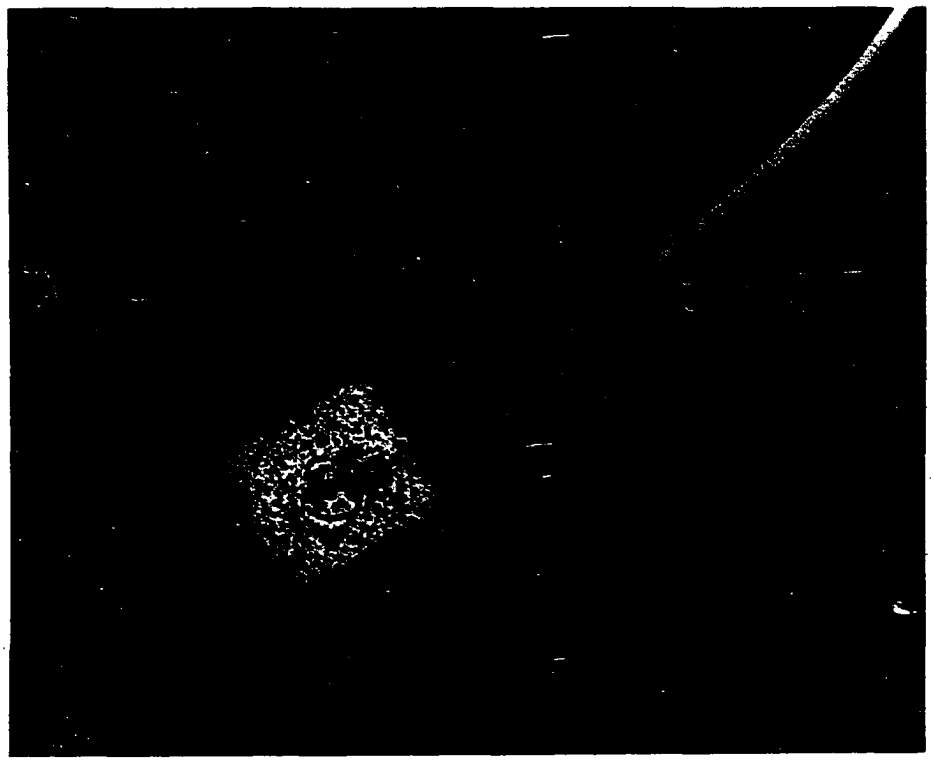


Figure 3. Plot of calibration data for a mercury-in-silicone rubber strain gauge

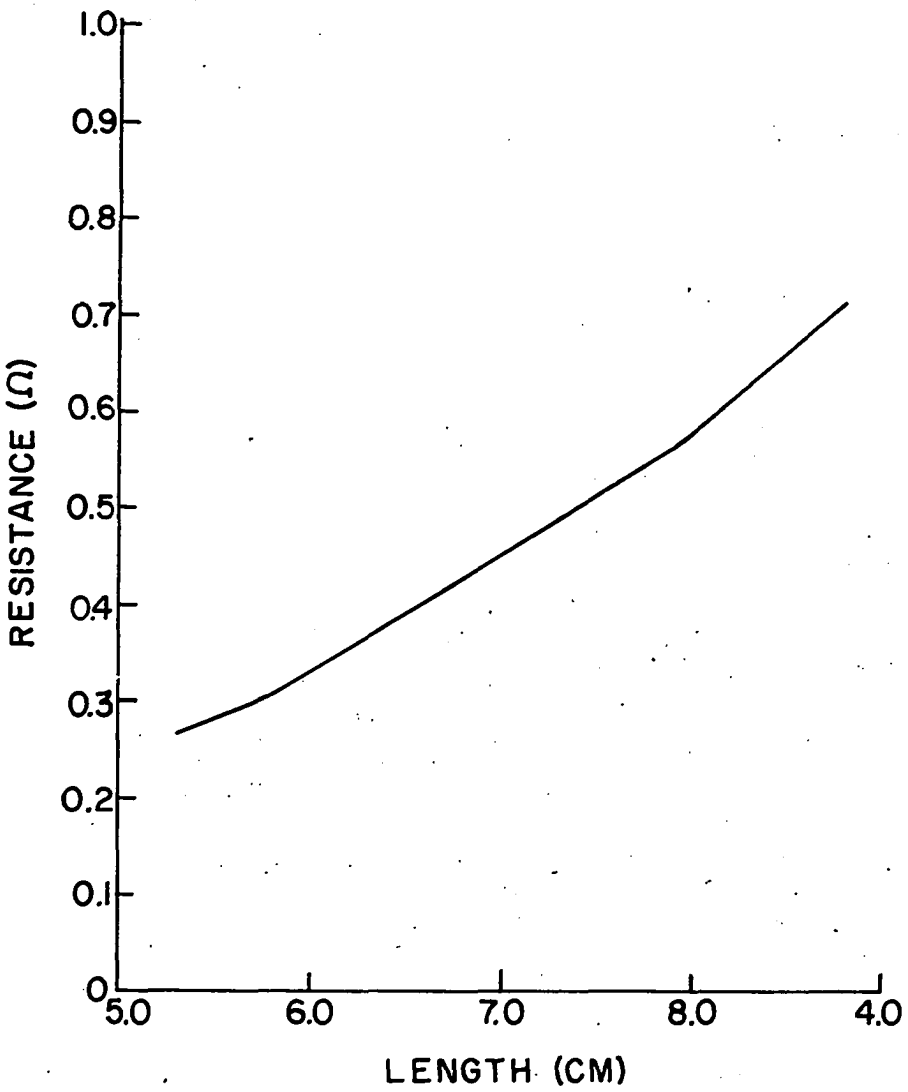

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
RESISTANCE (Ω)
5.0
6.0
7.0
8.0
4.0
LENGTH (CM)

Figure 4. Plot of calculated values for input impedance and phase angle versus change in plate spacing for a $\lambda/8$ transmission line terminated by a capacitive epivascular micrometer

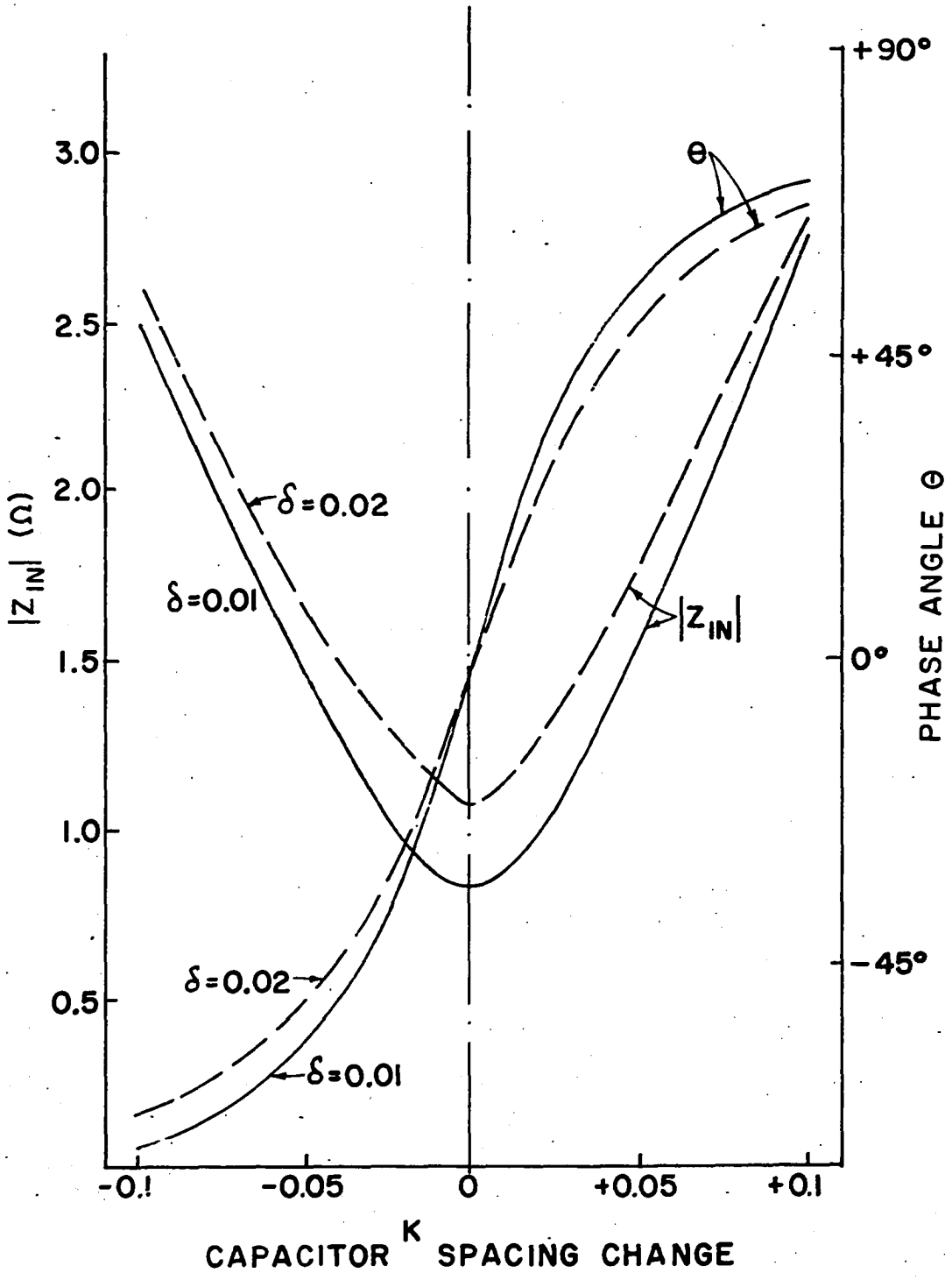

+90°
3.0
θ
2.5
+45°
2.0
δ=0.02
δ=0.01
|Z_IN| (Ω)
1.5
|Z_IN|
0°
PHASE ANGLE θ
1.0
-45°
δ=0.02
0.5
δ=0.01
-0.1
-0.05
0
+0.05
+0.1
CAPACITOR K SPACING CHANGE

Figure 5. Electronic circuit design of the detector unit for capacitive or inductive epivascular micrometers

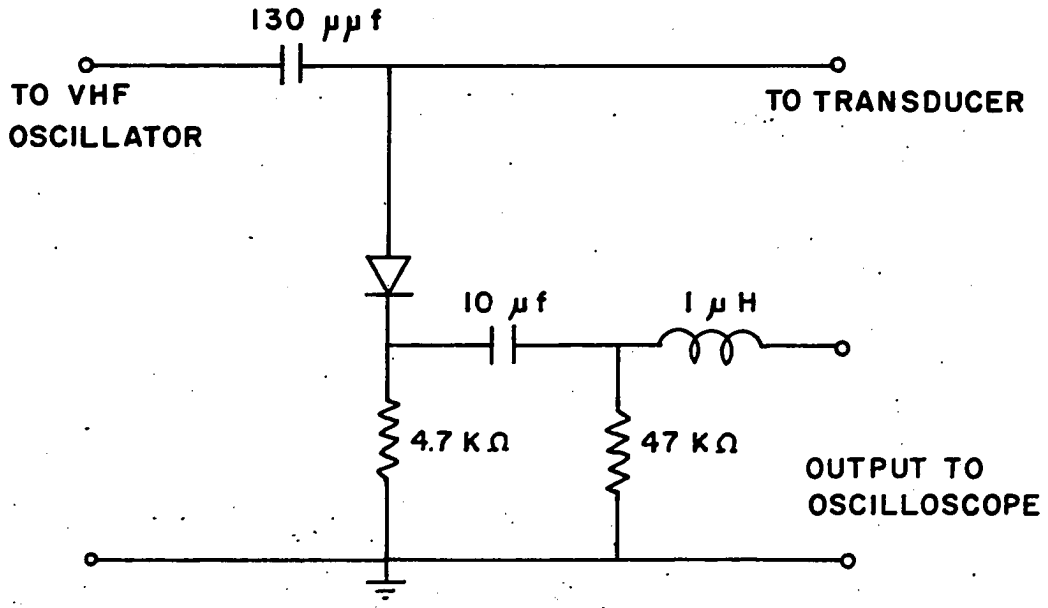
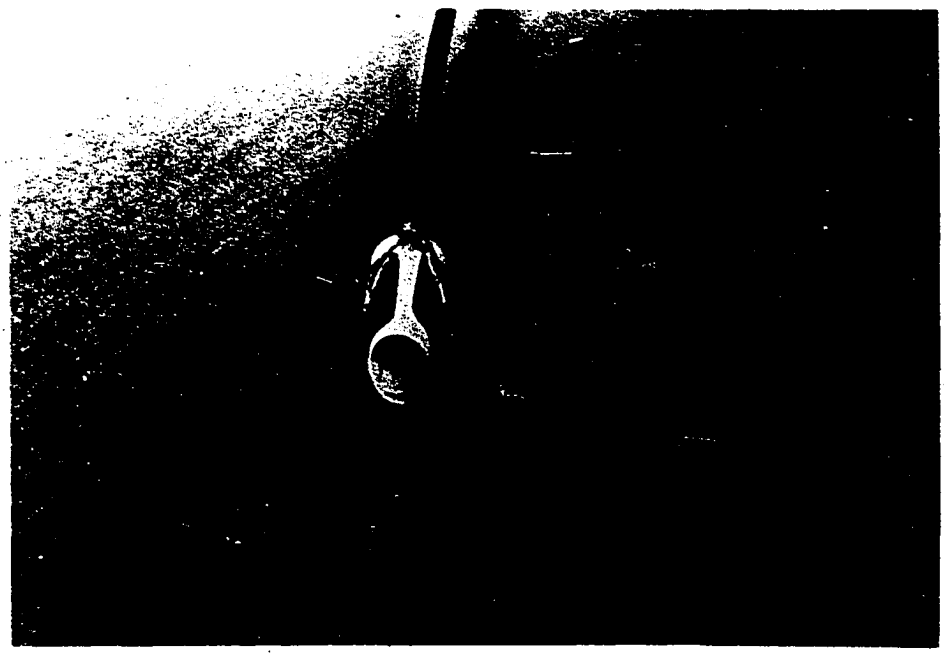

130 μμf
TO VHF
OSCILLATOR
TO TRANSDUCER
10 μf
1 μH
4.7 KΩ
47 KΩ
OUTPUT TO
OSCILLOSCOPE

Figure 6. Capacitive epivascular micrometer during construction

Figure 7. Capacitive epivascular micrometer after coating with RTV-502



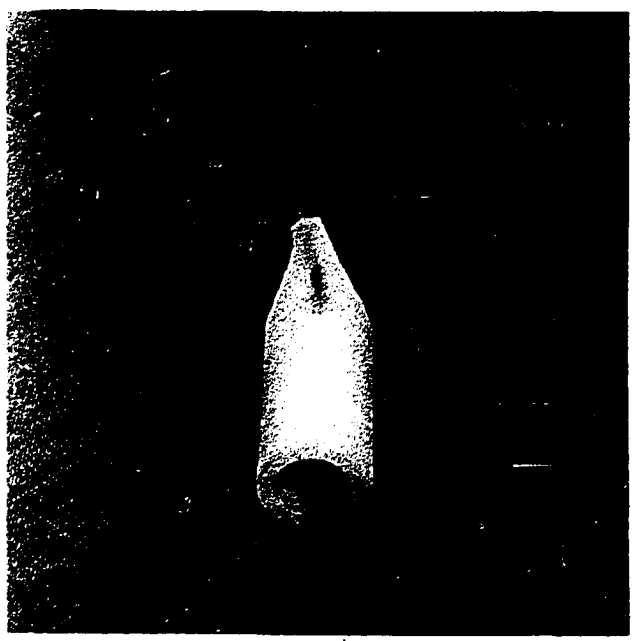
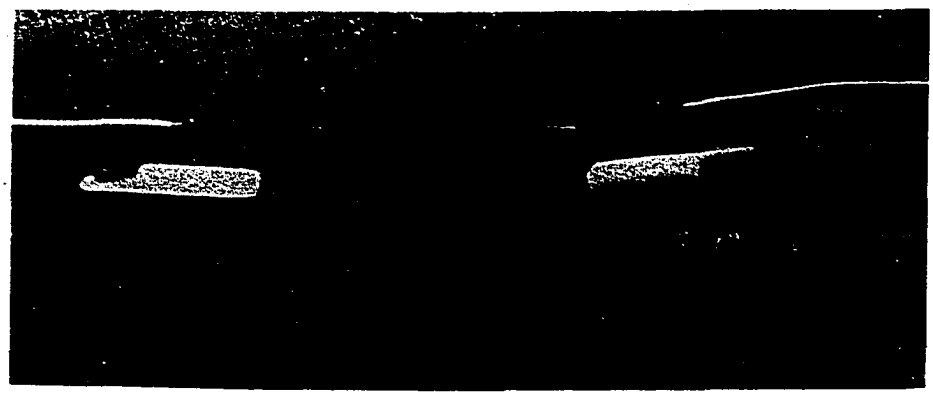


Figure 8. Conductive silicone rubber respiration transducer (unassembled)

Figure 9. Conductive silicone rubber respiration transducer (assembled)

Figure 10. Conductive silicone rubber respiration transducer (coated with RTV-502)



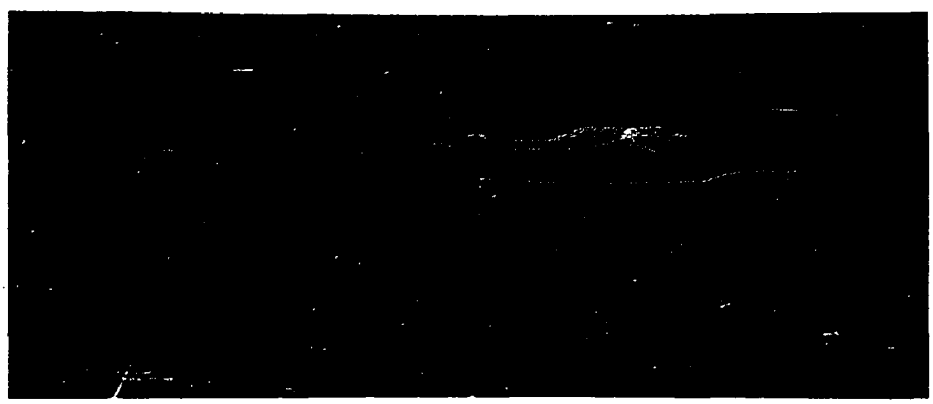


Figure 11. Electronic circuit design of the Wheatstone bridge detector for the conductive silicone rubber pneumograph transducer

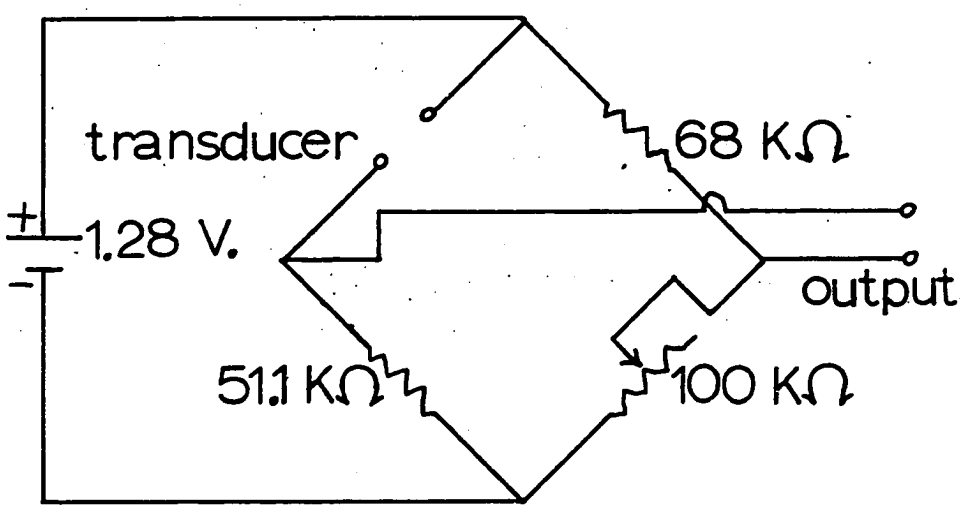
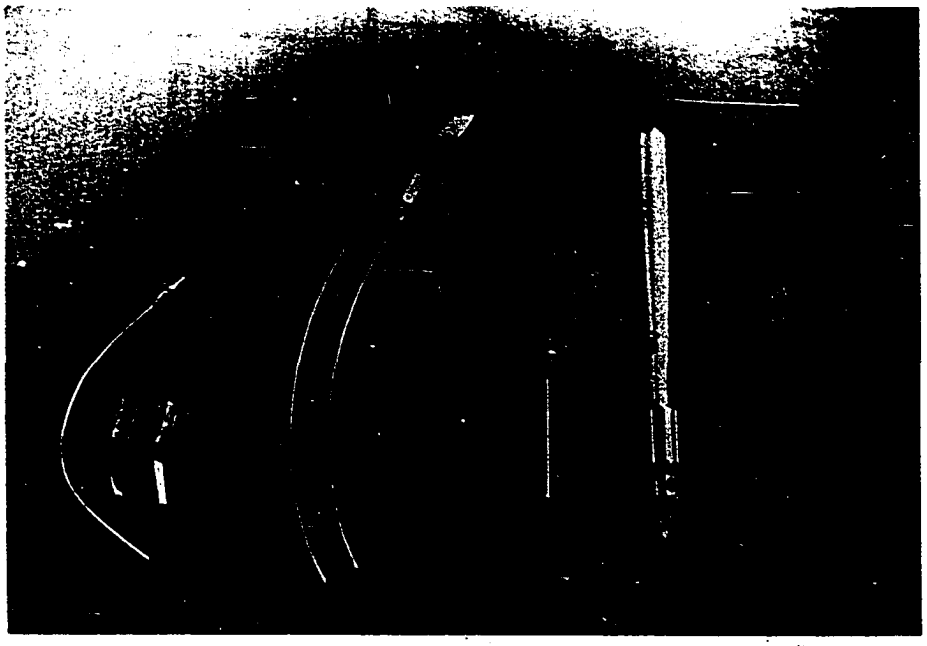

transducer
68 KΩ
+
1.28 V.
−
output
51.1 KΩ
100 KΩ

Figure 12. Special surgical instruments used for implanting transducers and electrical lead systems

a. Small curved cannula
b. Bulldog clamps
c. Trocar and cannula
d. Screwdriver
e. 1/16 inch drill
f. Skin boring instrument
g. Intramedullary pin chuck

Figure 13. General surgical instruments used for implanting transducers and electrical lead systems



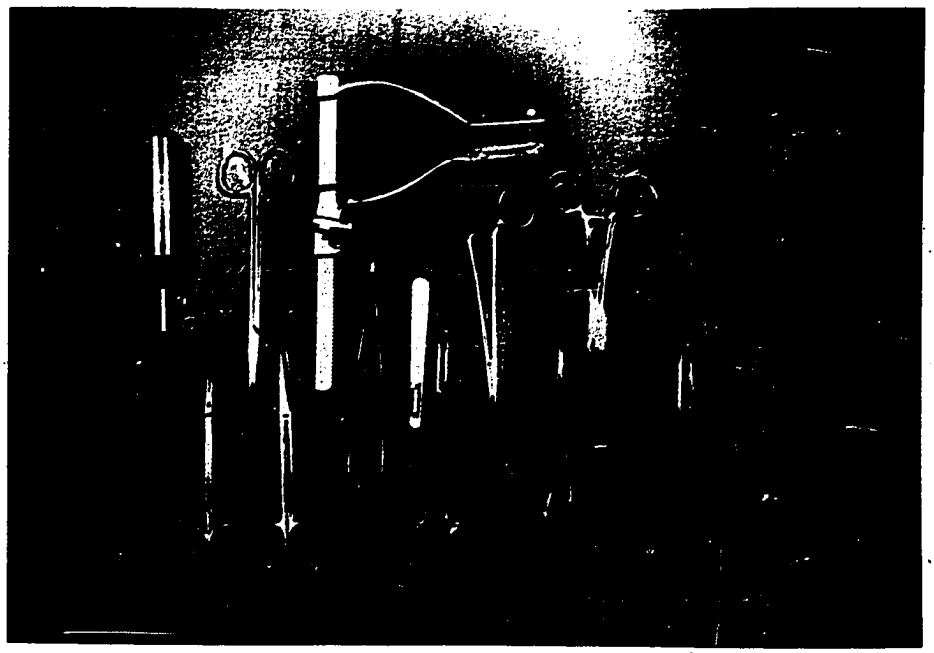
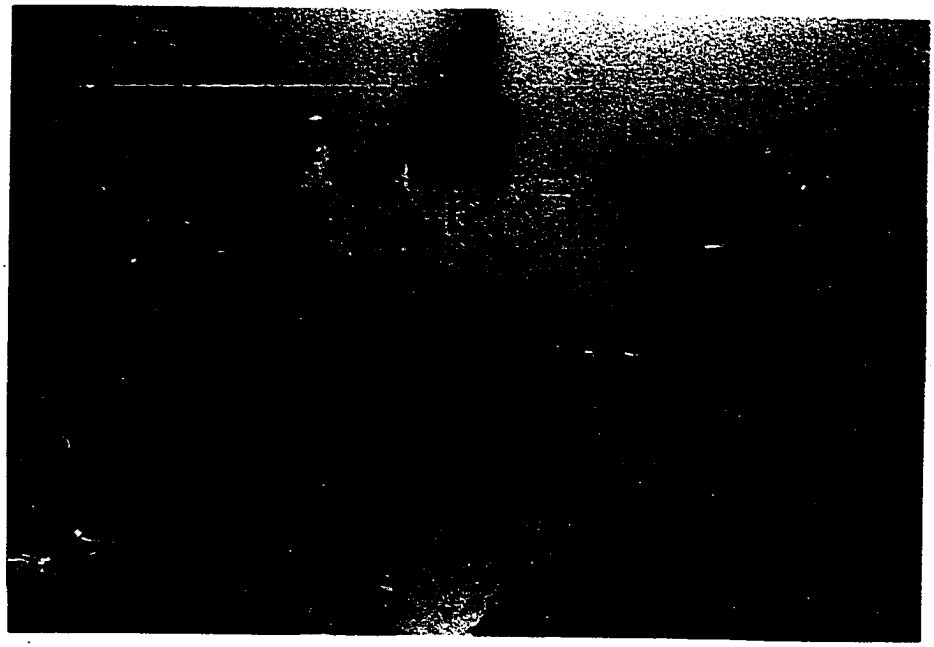


Figure 14. Dog 56 on 4th postoperative day showing location of skin incisions for integral multiple transducer and lead system

a. Teflon grommet and receptacle
b. Skin incision over EKG electrode
c. Skin incision over PKG transducer and EKG electrode
d. Skin incision over conductive silicone rubber respiration transducer

Figure 15. Teflon skin grommet



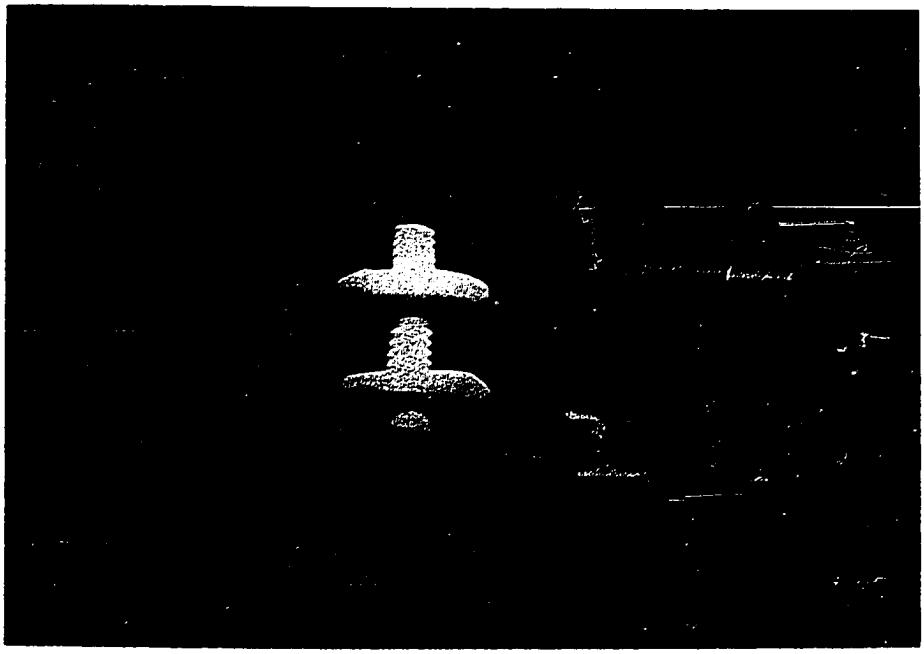


Figure 16. Teflon skin grommet with Amphenol 126-122 receptacle

Figure 17. Integral multiple transducer and lead system (assembled, before coating with RTV-502)

a. Receptacle
b. Teflon skin grommet
c. Teflon insulated Amphenol #414-004 wire
d. Conductive silicone rubber respiration transducer
e. EKG bone screw electrodes
f. Piezoelectric PKG transducer

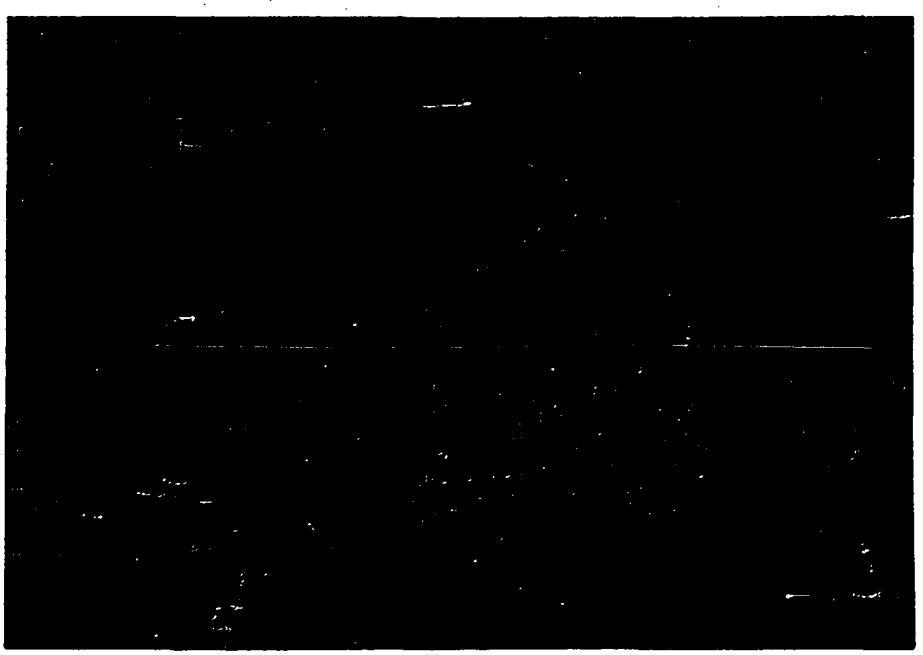


Figure 18. Integral multiple transducer and lead system (coated with RTV-502)

Figure 19. Appearance of teflon grommet and skin of dog 6 after 656 days

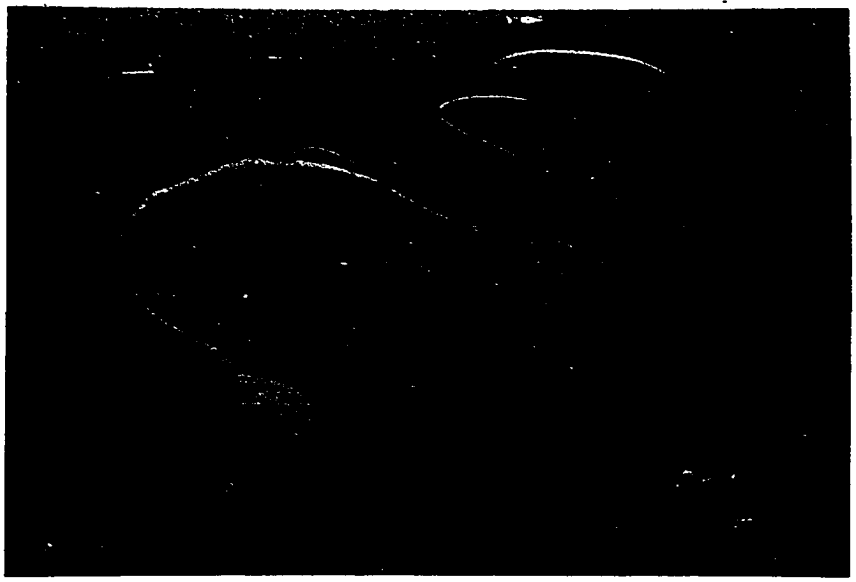
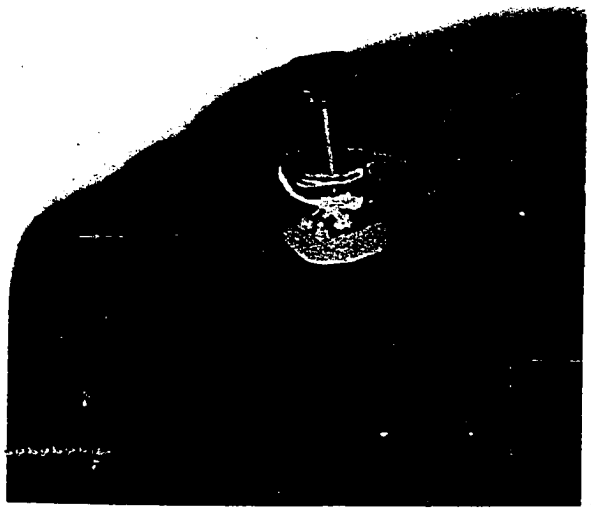


Figure 20. Appearance of teflon grommet and skin of dog 38 after 89 days

Figure 21. Recording situation for monitoring operation of multiple transducer implants

a. Multiconductor cable
b. Bridge preamplifier
c. Junction box
d. Physiograph preamplifiers
e. Physiograph recorder



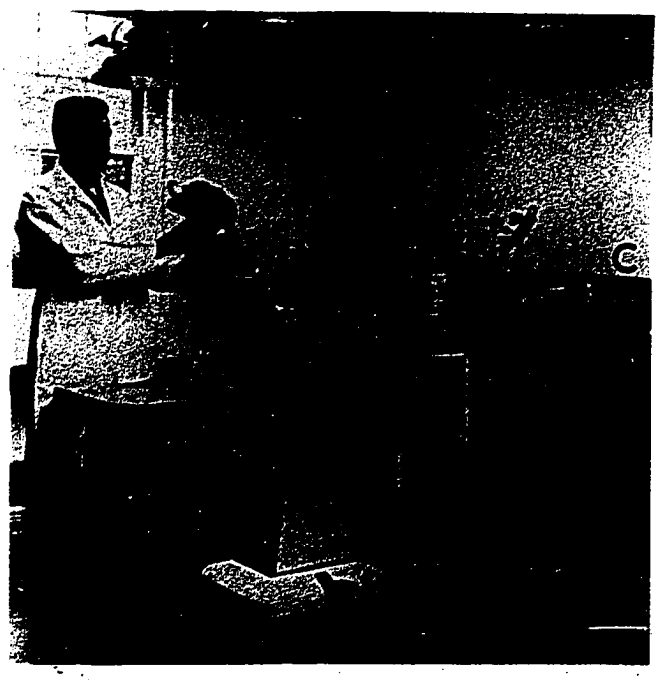
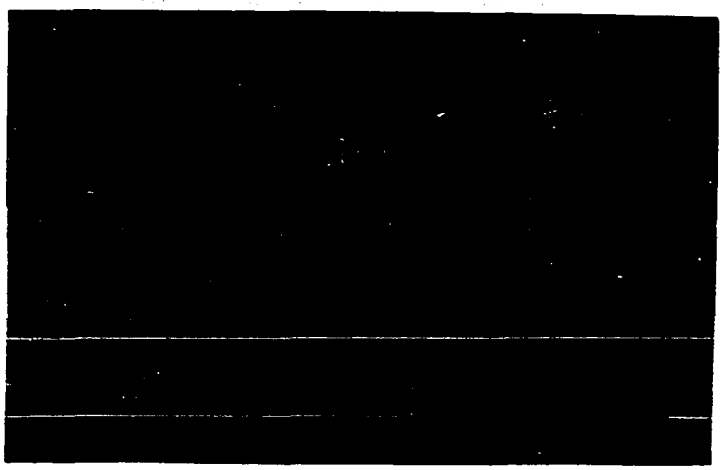


Figure 22. Telemeter system for relaying physiological information from the experimental dog to the pen recorder

a. Cable from dog
b. Bridge-preamplifier
c. Junction box
d. Cables to recorder

Figure 23. Portable Wheatstone bridge-transistor preamplifier



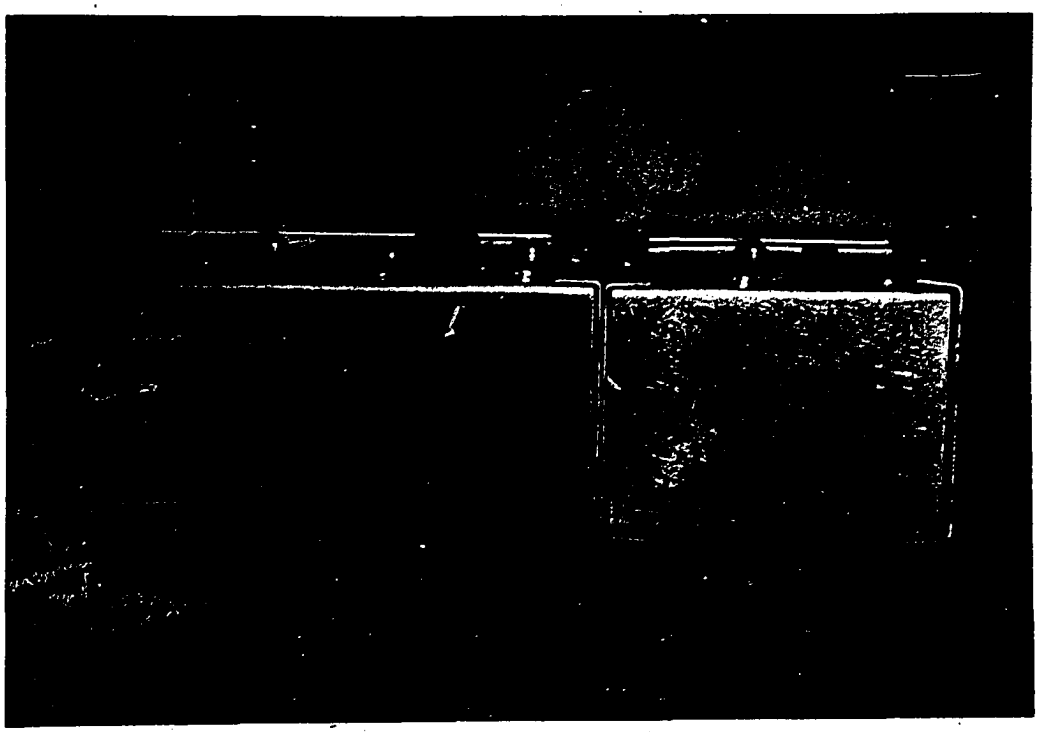


Figure 24. Electrical circuit design of the junction box distribution system

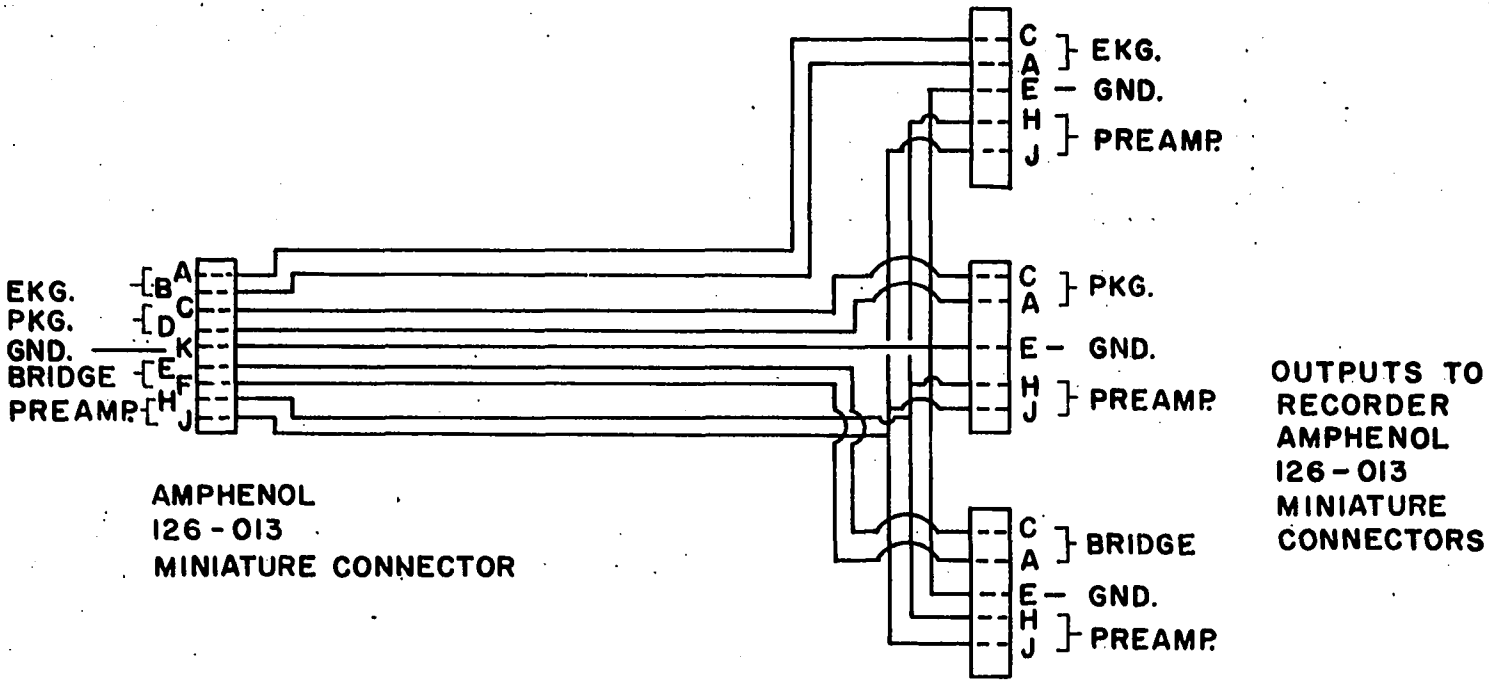

EKG.
PKG.
GND.
BRIDGE
PREAMP.
B
A
C
D
K
E
F
H
J
AMPHENOL
126 - 013
MINIATURE CONNECTOR
C
A
E
H
J
EKG.
GND.
PREAMP.
C
A
E
H
J
PKG.
GND.
PREAMP.
C
A
E
H
J
BRIDGE
GND.
PREAMP.
OUTPUTS TO
RECORDER
AMPHENOL
126 - 013
MINIATURE
CONNECTORS

Figure 25. Electronic circuit design of the combined Wheatstone bridge-transistor preamplifier unit for processing and amplifying information from electrocardiographic, phonocardiographic and pneumographic transducers

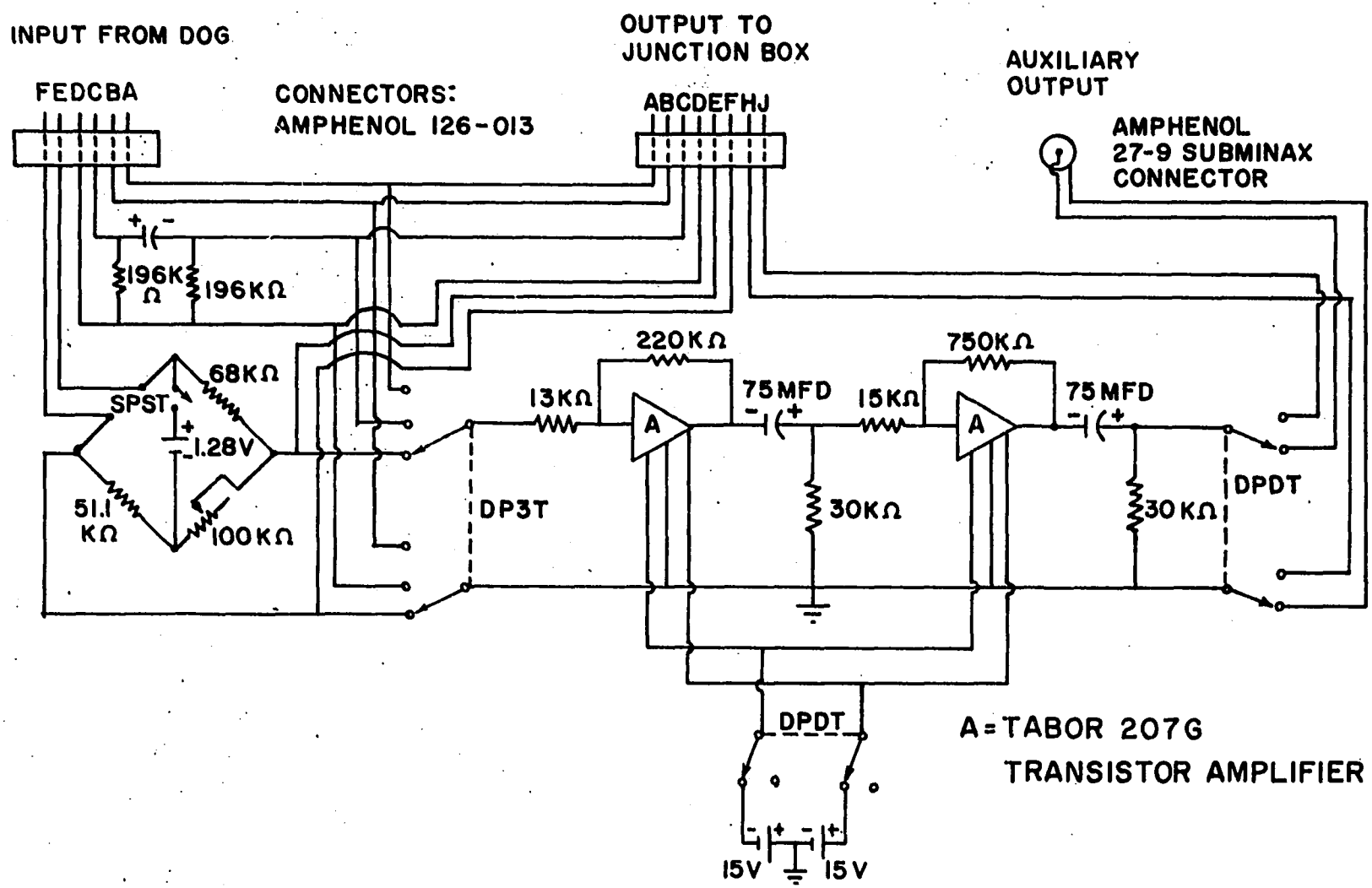
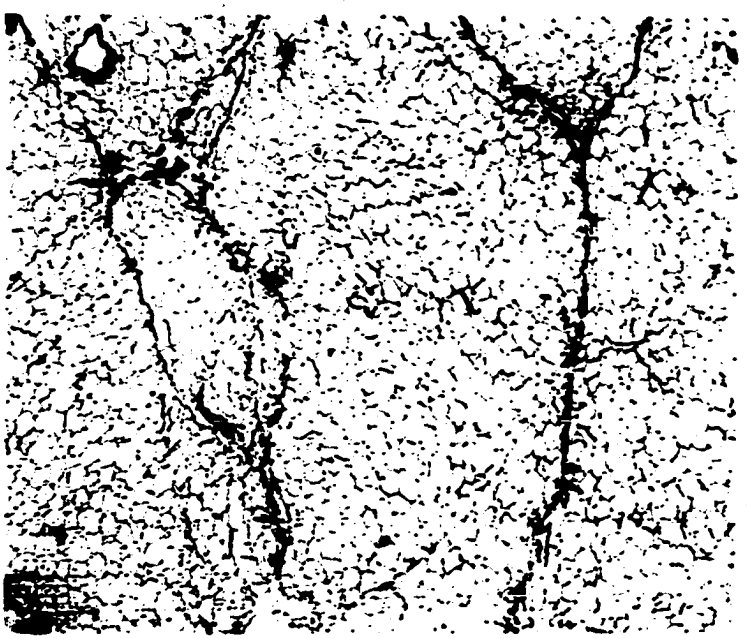

INPUT FROM DOG
FEDCBA
CONNECTORS:
AMPHENOL 126-013
OUTPUT TO
JUNCTION BOX
ABCDEFHJ
AUXILIARY
OUTPUT
AMPHENOL
27-9 SUBMINAX
CONNECTOR
196KΩ
196KΩ
68KΩ
SPST
1.28V
51.1
KΩ
100KΩ
DP3T
220KΩ
13KΩ
75MFD
30KΩ
750KΩ
15KΩ
75MFD
30KΩ
DPDT
DPDT
15V
15V
A=TABOR 207G
TRANSISTOR AMPLIFIER

Figure 26. Section of normal subcutaneous tissue from the lateral thoracic wall of dog 18 fixed in buffered neutral formalin and stained with hematoxylin and eosin 36X

Figure 27. Section of tissue reaction after 127 days around soldered copper wire implanted in the lateral thoracic wall subcutaneous tissue of dog 7, fixed in buffered neutral formalin and stained with hematoxylin and eosin 95X

a. Zone of undifferentiated mesenchymal cells
b. Zone of actively proliferating fibroblasts
c. Zone of immature fibroblasts and collagenous fibers
d. Zone of irregularly arranged collagenous fibers



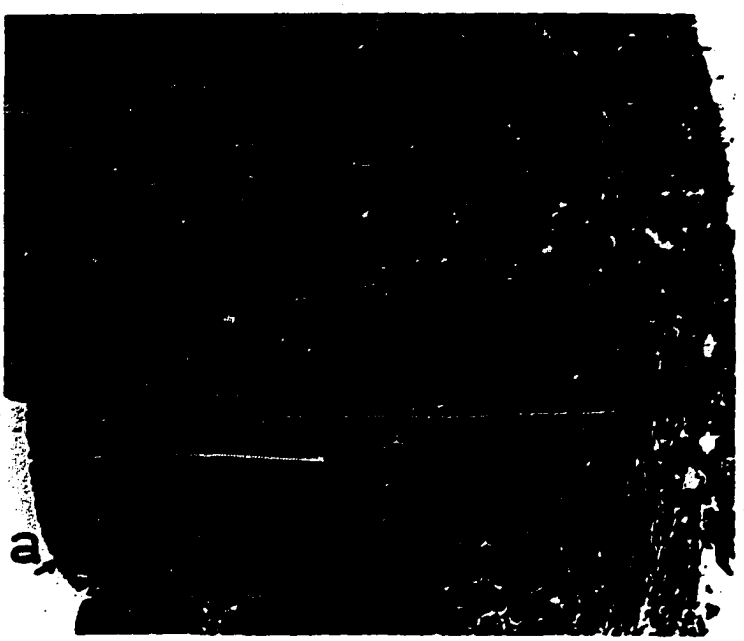

a

Figure 28. Section of tissue reaction after 40 days around polyethylene tubing implanted in lateral thoracic wall subcutaneous tissue of dog 2, fixed in buffered neutral formalin and stained with hematoxylin and eosin 95X

Figure 29. Section of tissue reaction after 20 days around polyvinyl chloride tubing implanted in lateral thoracic wall subcutaneous tissue of dog 3, fixed in buffered neutral formalin and stained with hematoxylin and eosin 95X

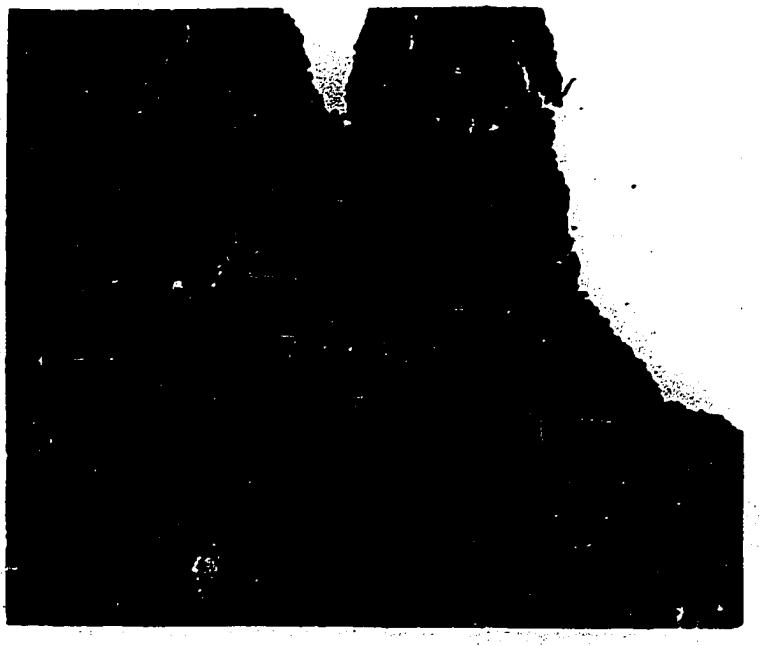
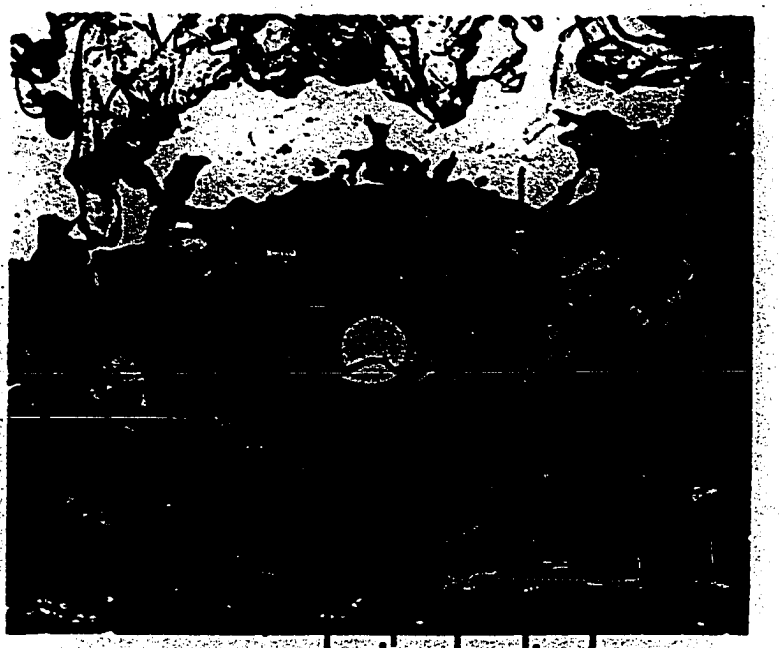


Figure 30. Section from dog 24 of ivalon epicardial plaque and myocardium after 64 days fixed in buffered neutral formalin and stained with hematoxylin and eosin 36X

a. Cardiac muscle
b. Zone of hyperplastic epicardium
c. Zone of lymphocytes
d. Fibrous connective tissue
e. Ivalon sponge

Figure 31. Section of tissue reaction after 40 days around silatube implanted in the lateral thoracic wall subcutaneous tissue of dog 2, fixed in buffered neutral formalin and stained with hematoxylin and eosin 240X



a b c d e

Figure 32. Section of tissue reaction after 8 days around RTV-502 implanted in the lateral thoracic wall subcutaneous tissue of dog 37, fixed in buffered neutral formalin and stained with hematoxylin and eosin 95X

Figure 33. Section of tissue reaction after 14 days surrounding RTV-502 coated epivascular micrometer implanted around the left carotid artery of dog 42, fixed in buffered neutral formalin and stained with hematoxylin and eosin 95X

a. Undifferentiated mesenchymal cells
b. Zone of loosely arranged fibroblasts, neutrophils and macrophages
c. Zone of densely packed fibroblasts and collagenous fibers

Figure 34. Section of tissue reaction after 50 days around medical grade silastic implanted in the lateral thoracic wall subcutaneous tissue of dog 18, fixed in buffered neutral formalin and stained with hematoxylin and eosin 240X

Figure 35. Section of tissue reaction after 15 days around an implant coated with Dow 980 varnish in the lateral thoracic wall subcutaneous tissue of dog 31, fixed in buffered neutral formalin and stained with hematoxylin and eosin 95X

Figure 36. Section of right jugular vein of dog 28, 2 days following implantation of an implant coated with Dow 980 silicone varnish, fixed in buffered neutral formalin and stained with hematoxylin and eosin 95X

Figure 37. Section of tissue reaction after 40 days around teflon insulated lead wire implanted in the lateral thoracic wall subcutaneous tissue of dog 2, fixed in buffered neutral formalin and stained with hematoxylin and eosin 95X

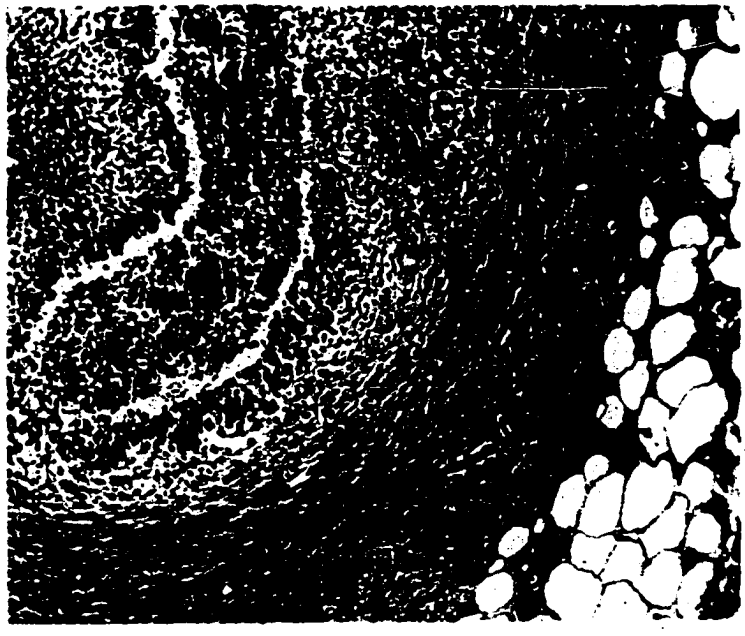


Figure 38. Section of tissue reaction after 33 days around a teflon grommet implanted in the dorsal thoracic wall skin of dog 51, fixed in buffered neutral formalin and stained with hematoxylin and eosin 240X

Figure 39. Section of tissue reaction after 656 days around a teflon grommet implanted in the dorsal thoracic wall skin of dog 6, fixed in buffered neutral formalin and stained with hematoxylin and eosin 95X

Figure 40. Recording of EKG and PKG from dog 45 after 25 days showing aberrations due to electrical shorting of receptacle terminals by tissue fluid

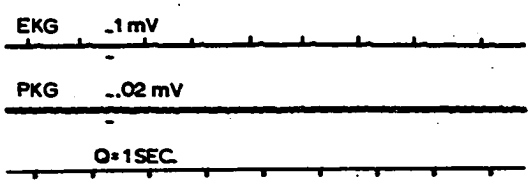
Figure 41. Recording of EKG and PKG from dog 39 showing configurations of waveforms during normal operation of a multiple transducer implanted system

Figure 42. Recording of EKG, PKG and pneumogram from implanted transducers in dog 56 (pneumographic information processed by portable Wheatstone bridge-transistor preamplifier)

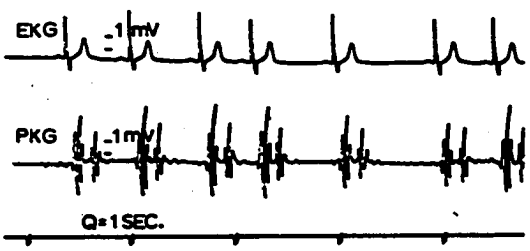
Figure 43. Recording of EKG and PKG from implanted transducers in dog 45 immediately after surgery

Figures 44 - 48. Recordings of EKG and PKG post-operatively, at 7, 11, 14 and 35 days, from implanted transducers in dog 51 showing the progressive decline in the output of the piezo-electric heart sound transducer due to fluid penetration into the system

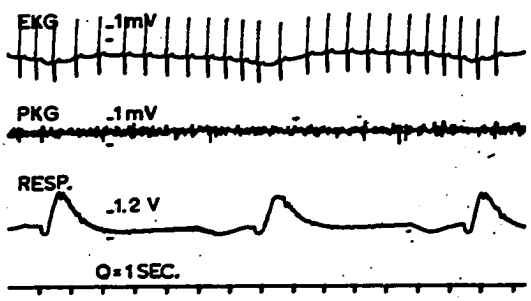
DOG 45 (25 DAYS)



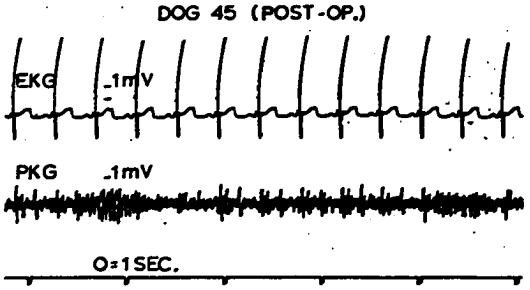
DOG 39 (2 DAYS)



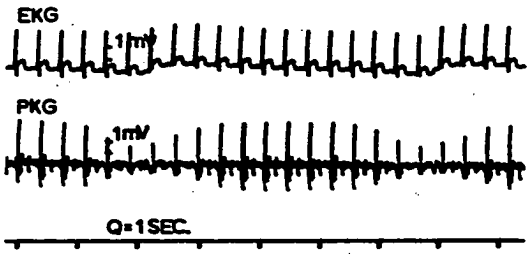
DOG 56 (7 DAYS)



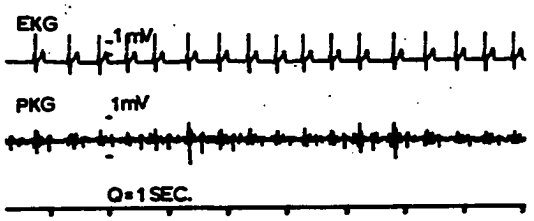
DOG 45 (POST-OP.)



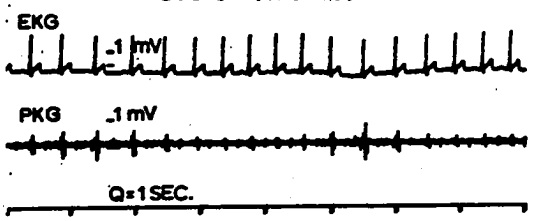
DOG 51 (POST-OP.)



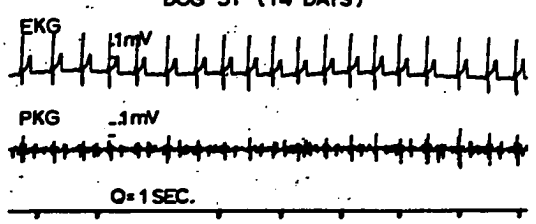
DOG 51 (7 DAYS)



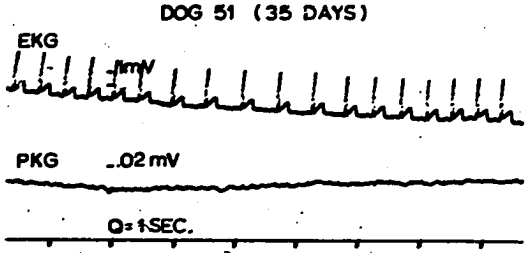
DOG 51 (11 DAYS)

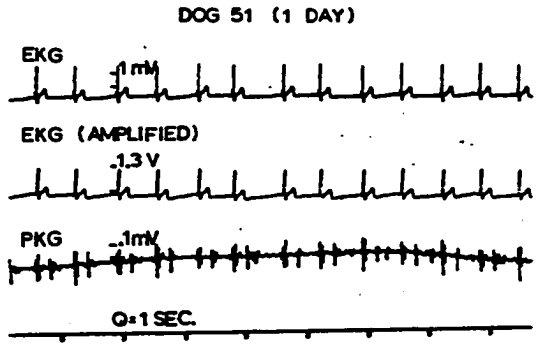


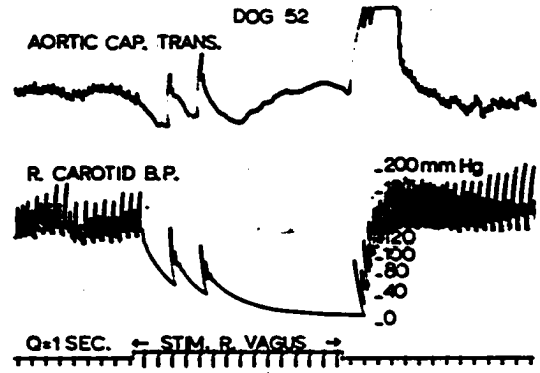
DOG 51 (14 DAYS)

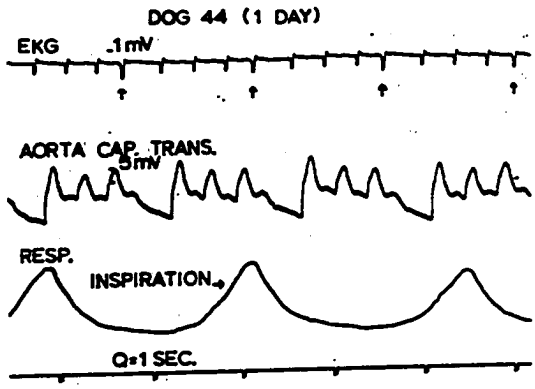


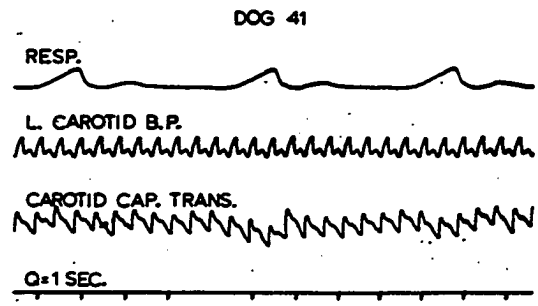
DOG 51 (35 DAYS)

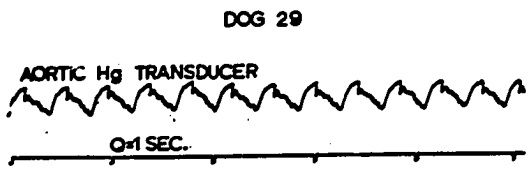


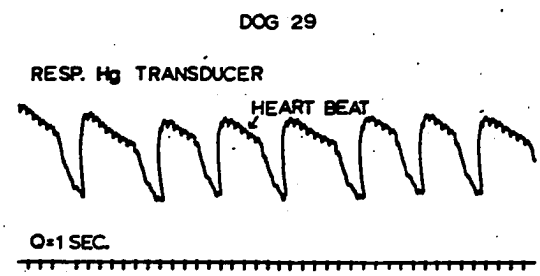

DOG 51 (1 DAY)
EKG
.1mV
EKG (AMPLIFIED)
1.3 V
PKG
.1mV
Q=1 SEC.

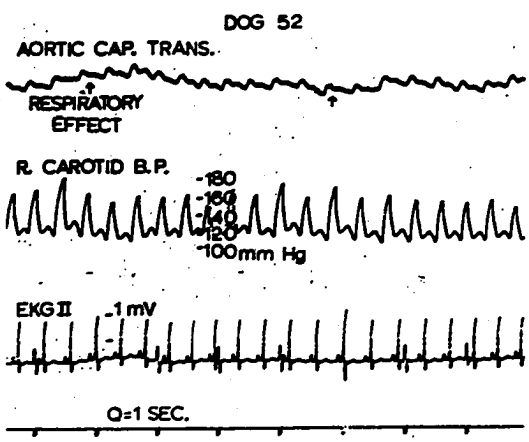

DOG 52
AORTIC CAP. TRANS.
R. CAROTID B.P.
200mm Hg
120
100
80
40
0
Q=1 SEC. ← STIM. R. VAGUS →


DOG 44 (1 DAY)
EKG
.1mV
AORTA CAP. TRANS.
5mV
RESP.
INSPIRATION
Q=1 SEC.


DOG 41
RESP.
L. CAROTID B.P.
CAROTID CAP. TRANS.
Q=1 SEC.


DOG 29
AORTIC Hg TRANSDUCER
Q=1 SEC.


DOG 29
RESP. Hg TRANSDUCER
HEART BEAT
Q=1 SEC.


DOG 52
AORTIC CAP. TRANS.
RESPIRATORY EFFECT
R. CAROTID B.P.
180
160
140
120
100mm Hg
EKG II
.1mV
Q=1 SEC.

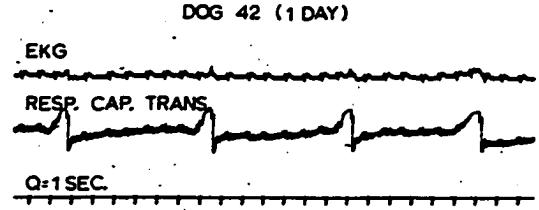
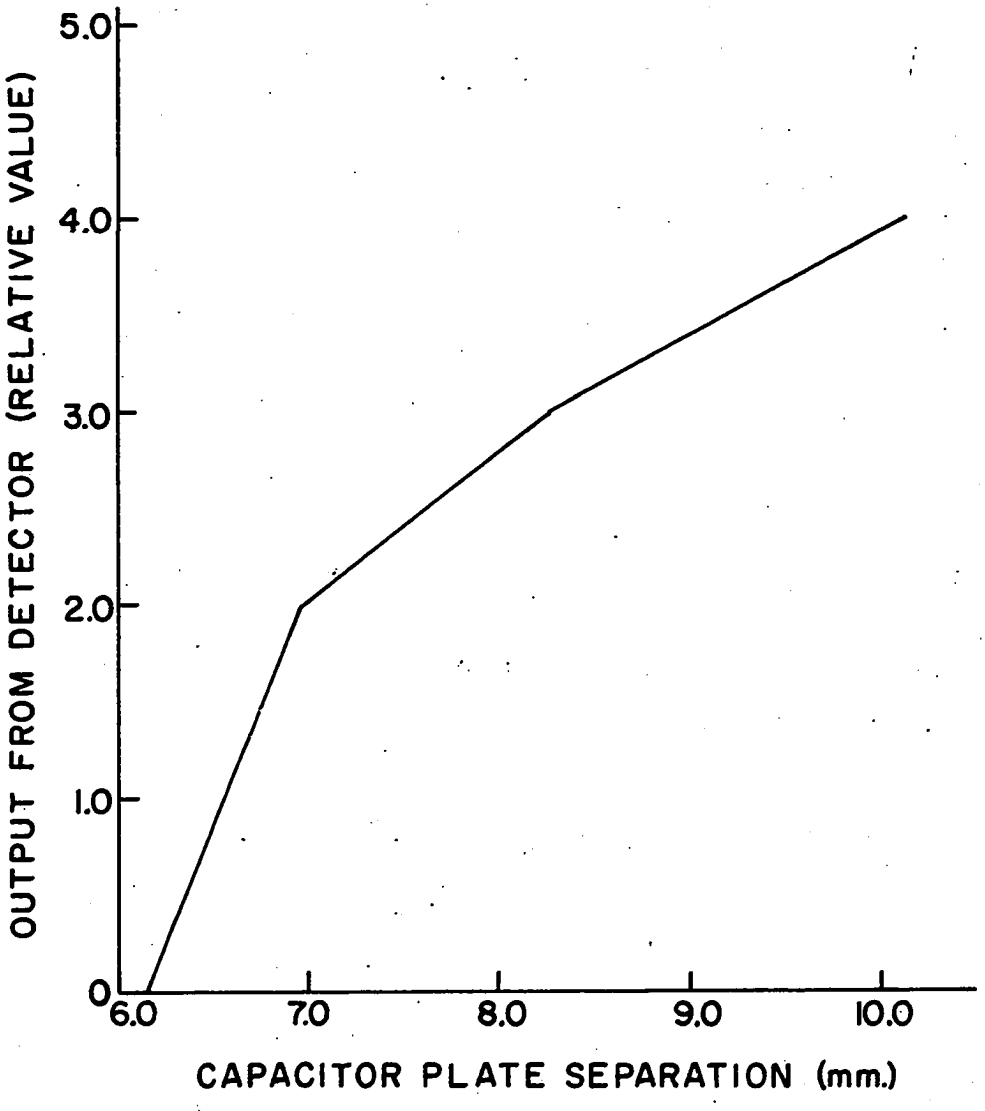

DOG 42 (1 DAY)
EKG
RESP. CAP. TRANS.
Q=1 SEC.

Figure 57. Plot of calibration data for a capacitive epivascular micrometer


OUTPUT FROM DETECTOR (RELATIVE VALUE)
5.0
4.0
3.0
2.0
1.0
0
6.0
7.0
8.0
9.0
10.0
CAPACITOR PLATE SEPARATION (mm.)