Autonomic Reinnervation of Cardiac Transplants: Further Observations in Dogs and Rhesus Monkeys

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CONSISTENT autonomic reinnervation of cardiac autotransplants in dogs has been well documented.[2,6,7] Kontos and colleagues [6] observed evidence of reinnervation in some dogs which had received cardiac allografts. In contrast, no sign of reinnervation was reported in primate autotransplants.[13] Accumulated information in long-term survivors of clinical heart transplantation [1,8,9] also revealed no evidence of reinnervation. Literature explaining this apparent paradox is not presently available. This report is primarily concerned with the factors influencing reinnervation of the cardiac transplants, utilizing different species and both auto- and allotransplantation.

Materials and Methods

Animals. Four groups of animals were prepared as follows: Monkey autotransplant group: 17 adult rhesus monkeys, weighing 5.0 to 8.0 Kg., underwent cardiac autotransplantation. Dog autotransplant group: 30 mongrel puppies, weighing 3.5 to 6.5 Kg., underwent cadiac transplantation. Dog allotransplant group: eight mongrel puppies (4.0 to 8.0 Kg.) with cardiac allografts, maintained by immunosuppressive treatment, were chosen from a series of experiments described in detail elsewhere.[5] Control group: five normal puppies and five normal rhesus monkeys were used as controls.

Technic of Heart Transplantation. The preparation and surgical procedure were basically the same as in allotransplantation of the heart under profound hypothermia reported previously,[4] except for a few modifications. As premedication, triflupromazine* (1.5 mg./Kg.) instead of chlorpromazine was used with atropine (0.1 mg./Kg.) and meperidine (6.0 mg./Kg.) in the puppy, and with atropine (0.05 mg./Kg.), meperidine (4.0 mg./Kg.), and phencyclidine (1.0 mg./Kg.) in the monkey. Surface cooling of the recipient by ice-water immersion was discontinued when the rectal temperature declined to 22°–23° C. Excision and implantation of the heart were performed using a modification of the Lower-Shumway technic under total circulatory arrest for 35 to 50 minutes. Care was taken to include the crista terminalis and a part of the superior vena cava in the graft, thus avoiding mechanical injuries of the sinus node. The coronary arteries of the excised heart were flushed with heparinized Ringer's lactate solution (10° C), and kept in this solution for 5 minutes. Continuous silk sutures were used to anastomose the right atrium, atrial septum, left atrium, aorta and pulmonary artery in that order. Circulation was restored by manual massage, blood transfusion and artificial respiration. To rewarm, the animal was immersed in a 42° C. water bath, and the chest cavities were flushed with warm saline (42° C.). The heartbeat was restored spontaneously in 12 of 17 monkeys and in a few puppies. In the remaining cases, electrical shocks converted the ventricular fibrillation to regular beating with no difficulty.

Testing Procedure. A series of studies was carried out in the long-term survivors of each group to compare the circulatory response to electrical and reflex activation of the autonomic nervous system. The time of studies and the interval of repetition were altered as increasing experience indicated so as to discern promptly the initiation and completion of autonomic reinnervation.

The dogs were anesthetized with 50 mg./Kg. of intra-

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* Vesprine, Squibb, triflupromazine hydrochloride.

venous urethane and 15–20 mg./Kg. of intravenous sodium pentobarbital. Some dogs were first studied in an unanesthetized state to observe respiratory arrhythmia and reflex activation of the autonomic nerve responses. The monkeys were anesthetized with phencyclidine, 1.0 mg./Kg. intramuscularly, followed by 10 mg./Kg. of intravenous sodium pentobarbital. The animals were allowed to breathe spontaneously except for studies involving stimulation of the stellate ganglion; the Bird respirator was required in these experiments.

The arterial pressure curve was measured through a cannula inserted into the femoral or carotid artery and connected to a Statham P23AA pressure transducer and a Grass Polygraph. The respiratory curve represented by the chest wall movement and the electrocardiogram were recorded simultaneously.

Electrical stimulation of the cervical vagus nerve and the stellate ganglion was carried out with a bipolar electrode placed around the exposed nerve and connected to a stimulator.* Square wave electrical stimuli of 30 cps., 1 msec. duration, 3–7 volts, were applied for 3–5 seconds, and the changes in heart rate, arterial pressure, respiratory curve, and electrocardiogram on the recorder were observed.

Responses to the following pharmacologic agents were tested; norepinephrine 0.2 μg./Kg. intravenously, atropine 0.03–0.3 mg./Kg. intravenously, tyramine 0.05 mg./Kg. intravenously after atropinization, and amyl nitrite ** inhaled through an endotracheal tube for 20 seconds.

Criteria used to assess cardiac reinnervation were as follows:

Parasympathetic reinnervation:

1. Cervical vagus nerve stimulation: Immediate slowing or cessation of the pulse with initiation of electrical stimulation of the right and/or left vagus nerve was considered as a definite sign of parasympathetic reinnervation.

2. Sinus arrhythmia: Recurrence of respiratory arrhythmia and reflex bradycardia due to eyeball pressure indicated unequivocal parasympathetic reinnervation.

3. Intravenous norepinephrine: Increase in blood pressure without significant increase (more than 10% of original rate) in heart rate after injection of norepinephrine indicated positive parasympathetic reinnervation and possible sympathetic reinnervation.

Sympathetic reinnervation:

1. Stellate ganglion stimulation: Cardiac acceleration occurring within 3–4 seconds of initiation of electrical stimulation of the stellate ganglion was considered a definite sign of sympathetic reinnervation.

2. Amyl nitrite inhalation: Cardiac acceleration (increase of more than 10% of the control value) and hypotension (decrease of more than 25% of the control value) after inhalation of amyl nitrite was considered as a positive finding of sympathetic reinnervation.

3. Intravenous tyramine: Cardiac acceleration (increase of more than 5% of control value) and elevation of blood pressure after injection of tyramine in completely atropinized animals were considered as positive indications of sympathetic reinnervation.

* Laboratory Stimulator Model No. 104A, American Electronic Laboratories, Inc.

** Aspirol No. 2, amyl nitrite 0.18 ml., Eli Lilly and Co., Indianapolis.

Results

Survival Data and Postoperative Progress. Monkey autotransplant group: Nine of 17 monkeys completely regained consciousness and survived more than 24 hours. Two of the nine died subsequently of acute cardiac failure caused by A-V dissociation. Seven have survived with normal activity for 3–16 months and were used for the reinnervation studies. The electrocardiogram of these animals showed regular sinus rhythm with heart rate ranging from 110 to 175 per minute. Transient idioventricular rhythm was observed during the reinnervation studies in two of the animals, but converted to sinus rhythm at the end of the studies.

Dog autotransplant Group. Two series of cardiac transplantation were carried out in a total of 30 puppies; in the first series, five of 17 survived long enough to permit study. Three are alive and well 4 to 5 years after operation. The transplanted heart enlarged proportionally as the body grew to adult size, and one female dog delivered normal puppies three times. Despite their satisfactory general condition, they frequently demonstrated arrhythmia such as nodal rhythm, idioventricular rhythm and nonrespiratory sinus arrhythmia. Only one dog showed consistent sinus rhythm.

In the second series, seven of 13 which survived for 1 to 15 months were used for the reinnervation studies. Responses to pharmacologic agents were tested mainly in this group. Probably because of technical improvement, six of seven showed regular sinus rhythm.

Dog allotransplant Group. Table 1 shows results obtained in eight puppies with cardiac allografts maintained by various combinations of immunosuppressive regimens, with special reference to survival time, cause of death, clinical manifestation of rejection crises which were successfully treated, and presence or absence of autonomic reinnervation. The criteria for diagnosis of rejection crisis were electrocardiographic low voltage, appearance of arrhythmia, loss of appetite, fever, and leucocytosis.

Electrical Stimulation of the Vagus Nerve. In eight experiments in the monkey autotransplant group studied

TABLE 1. *Summary of Reinnervation Studies in Allotransplant Dogs*

Animal No.	Immunosuppression*	Survival Time (days)	Cause of Death	Rejection Crisis#	Reinnervation (Days)	
					Sympathetic	Parasympathetic
HH-11	Az. + Pr.	91	Chronic rejection	+	70 (−)	70 (−)
HH-19	Az. + Pr. + Di.	175	Bone marrow depression	−	73 (+)	73 (+)
						42 (−)
HH-24	Az. + Pr. + Di. + Th.	151	Chronic rejection	+	144 (−)	144 (−)
HH-49	Az. + Pr.	49	Acute rejection	+		40 (−)
HH-59	Az. + Pr.	78	Acute rejection	+	68 (−)	68 (−)
HH-67	Az. + Pr. + Di.	107	Chronic rejection	−	68 (+)	68 (+)
HH-74	Az. + Pr. + Di.	50	Distemper	+	42 (−)	42 (−)
HH-84	Az. + Pr. + Di. + Th.	36	Acute rejection	+		36 (−)

* Az.: azathioprine, Pr.: prednisolone, Di.: dipyridamole, Th.: thymectomy.
\# Clinical manifestation of rejection crisis observed before the date of reinnervation studies.

prior to the 70th postoperative day, seven animals responded negatively and one had a positive response at 60 days, whereas 14 experiments conducted after 72 days consistently exhibited a positive response. Thus far, reinnervation of the parasympathetic nerve has been confirmed between 60 and 126 days (Fig. 1).

In the dog autotransplant group, the earliest positive response was obtained at 30 days, and seven dogs showed reinnervation of the parasympathetic nerve between 30 and 62 days. In four dogs, in which stimulation experiments were initiated in the late postoperative period (>4 months) there were eventual positive responses, and another dog responded negatively on the 32nd day and died the following day of A-V dissociation (Fig. 2).

In the dog allotransplant group, two animals had positive repsonses at 68 and 73 days. These dogs showed no clinical sign of impending rejection until that time. In contrast, the remaining six dogs had at least one episode of rejection crisis, which was suppressed successfully, and failed to have positive responses to vagal stimulation between 36 and 144 days after transplantation (Table 1).

All control animals showed immediate slowing or cessation of the heartbeat with severe hypotension in response to stimulation, and responded uniformly in a

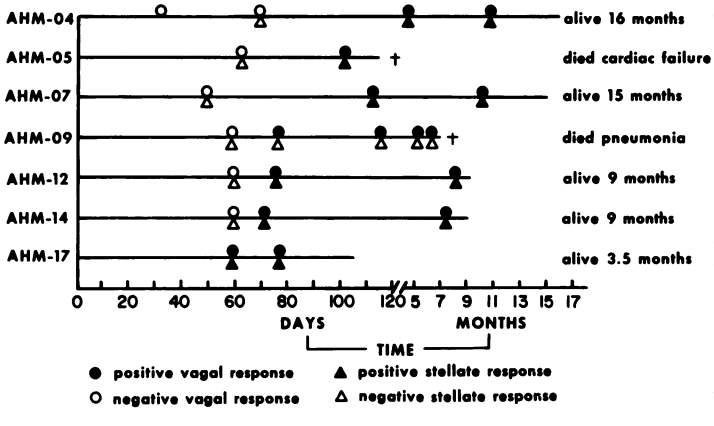

FIG. 1. Results of electrical stimulation of the vagus nerve and stellate ganglion in autotransplant monkeys.

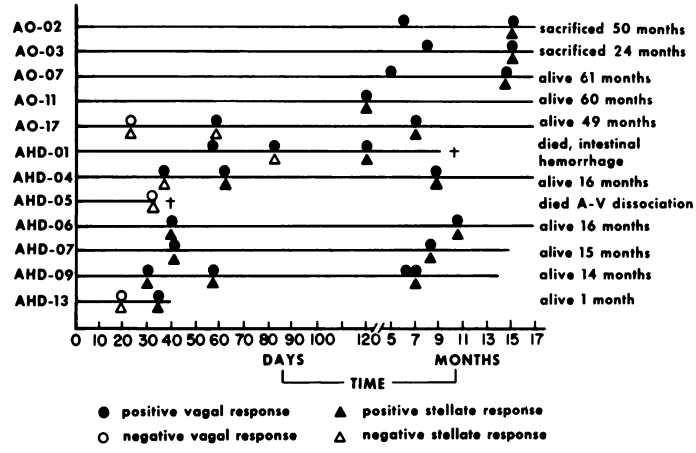

FIG. 2. Results of electrical stimulation of the vagus nerve and stellate ganglion in autotransplant dogs.

series of stimulation repeated at intervals of a few minutes. Response to stimulation was sometimes so minor in animals with cardiac transplants that we observed immediate decreases in heart rate of 10–30% without significant changes in blood pressure. Subsequent tachycardia and hypertension were observed occasionally. Such response, obtained more frequently in the early postoperative days than the later, suggests the initial stage of partial reinnervation (Fig. 3).

Electrical Stimulation of the Stellate Ganglion. To exclude any humoral factors, cardiac acceleration observed within 4 seconds from the initiation of stimulation was considered a positive response. Stimulations of the vagus nerve and stellate ganglion were usually carried out on the same day and converted to a positive response simultaneously between 60 and 126 days in the monkey except for one animal which repeatedly exhibited a negative sympathetic response at 59, 77, 116, 155, and 187 days after operation (Fig. 1). Response to stimulation in the dog autotransplant group was somewhat different from that in the monkey group. Of eight dogs, stimulated early enough to detect the initiation of reinnervation, five responded positively to sympathetic

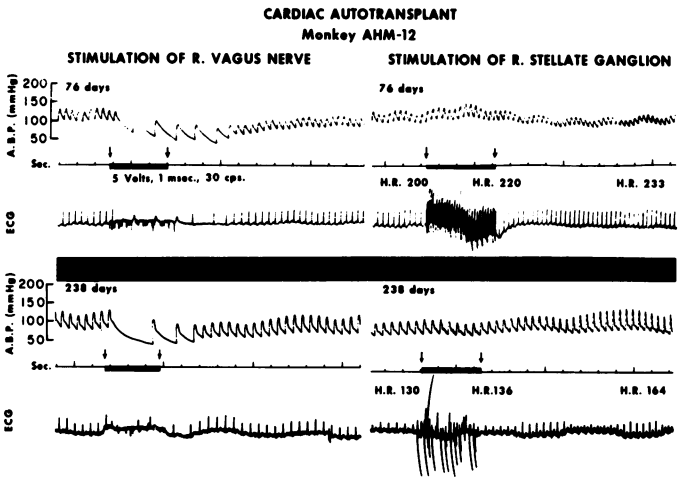

FIG. 3. Responses to electrical stimulation of the vagus nerve and stellate ganglion in an autotransplant monkey at 76 and 238 days after operation. Note the minor responses at 76 days (top) suggesting the initial stage of partial reinnervation. Responses at 238 days (bottom) show a marked change in heart rate and arterial pressure (A.B.P.).

and parasympathetic stimulation between 30 and 62 days; but in the remaining three dogs, sympathetic reinnervation was delayed in relation to parasympathetic reinnervation. A positive response was confirmed up to 15 months in all dogs with one exception; one animal died on the 32nd postoperative day (Fig. 2).

Two dogs of the allotransplant group, which showed positive parasympathetic reinnervation at 68 and 73 days after operation, had positive responses to stellate ganglion stimulation on the same day (Table 1).

Respiratory Arrhythmia and Reflex Bradycardia Due to Eyeball Pressure. Respiratory arrhythmia observed consistently in the control animals was resumed in three autotransplant monkeys, two autotransplant dogs and two allotransplant dogs. All animals responded positively to parasympathetic reinnervation after vaginal stimulation. In the remaining animals with positive vagal response, the change observed was so small as to render a definite conclusion almost impossible. Reflex bradycardia caused by eyeball pressure was clearly exhibited in two autotransplant monkeys at 60 and 187 days after operation (Fig. 4), and in one autotransplant dog at 199 days after operation.

Response to Intravenous Norepinephrine. Intravenous injection of 0.2 μg./Kg. of norepinephrine induced hypertension with a slight alteration of heart rate in the control animals. Heart rate increased significantly in the cardiac autotransplants without proven sympathetic and parasympathetic reinnervation. After accomplishment of parasympathetic reinnervation, only one of 13 monkeys and one of eight dogs showed significant tachycardia (Tables 2, 3).

Response to Amyl Nitrite Inhalation. Control animals showed positive evidence of reflex tachycardia in response to amyl nitrite-induced hypotension at all times studied. The results of stellate ganglion stimulation and amyl nitrite inhalation were compared in 14 studies on seven monkeys, in nine studies on five autotransplant dogs and on all control animals. Complete correlation between these two tests was achieved in the autotransplant monkeys (Table 2). Correlation was less complete in the autotransplant dogs; three animals with positive stellate response revealed insignificant tachycardia after amyl nitrite inhalation (Table 3).

Response to Intravenous Atropine. The dosage of atropine required to block parasympathetic innervation completely (as tested by vagal stimulation) was 0.14 mg. ± 0.02 mg. (mean ± standard error) in control monkeys, 0.08 mg. ± 0.02 mg. in autotransplant monkeys, 0.25 mg. ± 0.04 mg. in control dogs, and 0.22 mg. ± 0.02 mg. in autotransplant dogs. Apparently monkeys are more sensitive to atropine than are dogs. In both species, the amount of atropine required to block parasympathetic reinnervation tended to increase when the study was performed in the later postoperative period, although these studies did not permit statistical validation for this observation.

Response to Intravenous Tyramine after Atropinization. All control monkeys and dogs responded to intravenous tyramine with an increase in heart rate (>5%). Following heart transplantation, the response became obscure in the monkeys even with proven sympathetic reinnervation by stellate stimulation. Only one of six monkeys tested showed a clear response (Table 2), whereas all five autotransplant dogs treated with tyramine had increased heart rates (Table 3).

Discussion

The function of cardiac transplants has been largely clarified by recent intensive study of clinical cases and laboratory animals. Although the capability of a de-

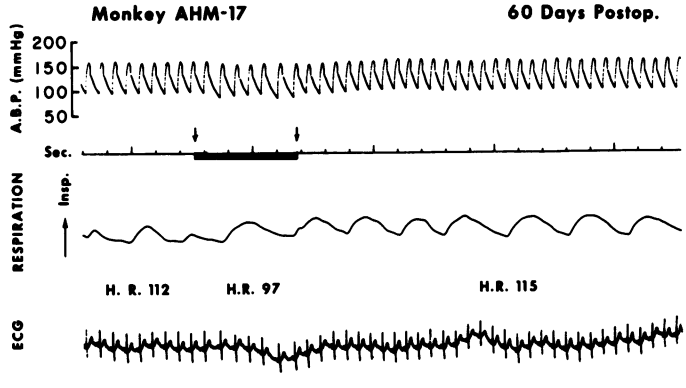

FIG. 4. Reflex bradycardia due to eyeball pressure observed in an autotransplant monkey at 60 days after operation.

TABLE 2. *Response to Pharmacologic Agents in Autotransplant Monkeys and Control Monkeys*

Animal No.	Days after Transplantation	Parasympathetic Reinnervation	Sympathetic Reinnervation	Heart Rate/Min.					
				Norepinephrine		Amyl nitrite		Tyramine	
				Before	After	Before	After	Before	After
AHM-04	69	−	−	160	184	158	160		
	126	+	+						
	315	+	+	152	156	150	180	152	154
AHM-05	102	+	+	138	140	140	155	144	150
AHM-07	113	+	+	144	146	162	178		
	299	+	+	165	165	144	178	114	130
AHM-09	77	+	−	146	140	138	145		
	116	+	−	153	152	135	147		
	155	+	−	170	174	168	180		
AHM-12	76	+	+	175	190	150	175	170	180
	238	+	+	138	140	140	155	144	150
AHM-14	72	+	+	151	167	140	168	172	176
	218	+	+	157	158	160	178	163	166
AHM-17	60	+	+	167	163	160	222	140	140
	78	+	+	155	155	153	170	131	135
Control-1		+	+	132	128	130	154	142	174
Control-2		+	+	165	171	154	175	162	180
Control-3		+	+	178	175	160	200	147	162
Control-4		+	+	147	158	170	210	148	162
Control-5		+	+	113	124	132	160	172	184

Parasymphathetic reinnervation was confirmed by response to vagus nerve stimulation.
Sympathetic reinnervation was confirmed by response to stellate ganglion stimulation.

nervated heart does not preclude full rehabilitation or long-term survival, there undoubtedly exist certain alterations in performance and the adaptation mechanism. Whether these alterations persist permanently or are modified gradually by effective reinnervation is an important issue in proper postoperative management.

Studies in adult dogs after cardiac autotransplantation consistently revealed evidence of autonomic reinnervatio of the transplant within 3 to 6 months [6] and sometimes as early as 26 days after transplantation.[7] Similar evidence was reported by Kontos *et al.*[6] in some (but not all) dogs living with allotransplanted hearts. However, no such evidence has been reported in the baboon [13] nor in man.[1,8,9]

There are several factors which possibly influence the establishment of reinnervation, such as species difference, age, size, technic of transplantation, and donor-recipient relationship. Testing procedures and direct and/or indirect effects of immunosuppressive drugs also must be considered.

The present study confirmed evidence of sympathetic and parasympathetic reinnervation not only in puppies but also in rhesus monkeys almost uniformly within 2 to 4 months after autotransplantation. The time required in monkeys was longer than that observed in puppies, but was somewhat shorter than that reported in adult dog autotransplants. This finding suggests that reinnervation of the cardiac transplant is not a species specific phenomenon, and might even be expected in humans as well under favorable conditions. Since the puppies and monkeys studied were of similar size and the technic for transplantation was the same in both, species difference may account for the minor disparity in time between these two groups of animals.

In the process of regeneration of the severed nerve undergoing Wallerian degeneration, a sprout of growing axon in the proximal stump of severed nerve advances into a remaining tube of Schwann sheath. The velocity of this process is not constant. The initial delay occupying several days in the scar of sectioning is followed by rapid growth into the Schwann sheath with a gradual deceleration, and by a final delay prior to the onset of function. The average velocity of the entire process in the somatic nerves is calculated as 1.0–2.0 mm./day, and the rate of the autonomic nerve regeneration appears to be on the same order as for the somatic nerves.[3] This value properly substantiates the interval required in our study of puppies and the data reported by other investigators [6,7] in adult dogs, although the possible effect of age also cannot be excluded.

Our observations on allotransplantation revealed good correlation between the laboratory manifestation of the rejection phenomenon and the absence of reinnervation. To achieve a successful regeneration of the severed nerve, a hollow tube of Schwann sheath must be left intact to provide a passage for the regenerating axon. If the rejection phenomenon takes place during this process, occlusion or destruction of Schwann sheath by cell infiltration or tissue degeneration will disturb the advance of axon growth tips. Such findings have been well-

TABLE 3. *Response to Phamacologic Agents in Autotransplant Dogs and Control Dogs*

Animal No.	Days after Transplantation	Parasympathetic Reinnervation	Sympathetic Reinnervation	Heart Rate/Min.					
				Norepinephrine		Amyl nitrite		Tyramine	
				Before	After	Before	After	Before	After
AHD-04	62	+	+						
	264	+	+	210	210	214	218	205	215
AHD-05	32	−	−						
AHD-06	40	+	+	172	176	174	198	175	184
	313	+	+	214	214	220	238	210	222
AHD-07	41	+	+	130	132	134	160	130	152
	246	+	+	108	112	110	142	100	162
AHD-09	30	+	+	158	162	141	163	144	166
	208	+	+	152	120	150	176	175	194
AHD-13	20	−	−	112	184	124	119	120	178
	35	+	+	176	230	180	208	172	180
Control 1		+	+	117	97	117	137	125	154
Control 2		+	+	174	176	202	212	156	190
Control 3		+	+	176	184	174	204	176	208
Control 4		+	+	210	212	195	232	178	202
Control 5		+	+	148	154	142	186	145	178

Parasympathetic reinnervation was confirmed by response to vagus nerve stimulation.
Sympathetic reinnervation was confirmed by response to stellate ganglion stimulation.

documented in allotransplantation of the peripheral nerve.[11,14]

Detrimental effects of azathioprine or corticosteroid on the progression of nerve regeneration have been postulated, but may not be a serious problem. Two allotransplant puppies, treated continuously with the conventional dosage of these drugs, demonstrated positive responses of reinnervation at 68 and 73 days after transplantation.

Evaluation of various testing procedures for autonomic innervation of the heart has been described precisely by Willman,[12] Kontos,[6] and Thames [10] and coworkers. The present studies confirmed the applicability of similar criteria to monkeys as well as puppies. Although a positive response to electrical stimulation of the nerves shows unequivocal evidence of reinnervation, the testing procedures are impractical for clinical use. Noninvasive tests, such as recurrence of respiratory arrhythmia or reflex bradycardia due to eyeball pressure, proved to be useful in identifying parasympathetic reinnervation in some cases of the present series. Response to intravenous norepinephrine revealed a marked difference before and after parasympathetic reinnervation. Likewise, amyl nitrite-induced tachycardia correlated well with sympathetic reinnervation, especially in monkeys.

As would be expected from the nature of nerve regeneration, the animals' responses were of varying magnitude when the identical tests were repeated on different days. A weak response in the early postoperative days became stronger with passage of time, probably due to an increase in number and maturation of each regenerated axon. Furthermore, there are many reasons to believe that reinnervation will not recover to a quantitatively complete level. A smaller amount of atropine is required to block parasympathetic activity in the transplanted heart than in the normal heart. The small chronotropic response to intravenous tyramine in the transplanted heart indicates less storage of myocardial norepinephrine in the transplant. Peiss,[7] Ebert [2] and their co-workers reported a marked decrease in myocardial catecholamine content up to 18 months after transplantation.

Summary

Seven rhesus monkeys and 12 puppies with cardiac autotransplants and eight puppies with cardiac allografts maintained by immunosuppressants were repeatedly studied for evidence of autonomic reinnervation in the transplants. The evidence was confirmed by circulatory responses to electrical stimulation of the vagus nerve or stellate ganglion. Extent of reinnervation was further assessed by the reappearance of respiratory arrhythmia and by chronotropic response to various pharmacologic agents. Reinnervation of sympathetic and parasympathetic nerves in the monkeys' autografts was almost consistently confirmed as well as in the puppies' autografts, but the interval required in the monkey was longer. In the allograft series, two puppies which had no signs of impending rejection showed evidence of reinnervation on the 68th and 73rd postoperative days, whereas the other six puppies had episodes of rejection crisis and failed to reveal positive findings up to 5 months.

Although no evidence of reinnervation has been reported in clinical heart transplantation, these results in primates and dogs indicate the possibility of reinnervation provided immune reaction is properly suppressed.

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