Historical Events on Development of Experimental Microsurgical Organ Transplantation

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The successful clinical organ transplantation certainly depended upon technical accomplishment and immunological unlocking in many key points in consequences of allografting. While these events have made history, serving domestic animals to investigate in allied vital organ transplantation had very rocky ways to be paved for years. Since we foresaw obstacles of growing public sentiments and mounting expenditures for employing domestic animals for organ transplantation research, we chose rats for possible replacement of domestic animals. While canine kidney transplantation studies were in progress, this idea of replacing domestic animals to rats was suggested by Fisher and I during rat blood vessel surgery. Fisher secured a monoscope for optical aids and the author, young at the time, was placed with Zeiss Loupe, 7-0 silk suture, laboratory made miniature Satinsky clamp and end-side portacaval shunt was attempted in the 400 gram rats from latter part of 1957. I was able to suture portal vein to inferior vena cava (IVC) and also side-side anastomosis of these vessels (Fig. 1). The most of rats' IVC and aorta at certain level below the left renal vein entrance are fused and inseparable. A simple technique of arteriovenous fistula (AVF) was created by making small opening in the IVC on the opposite side from this fused vessel. The common wall was opened by needle or scissors and IVC opening was closed. This way the heart valves forming mild vegetation, mimicking those of rheumatic mitral and aortic valvulitis. The bacterial clearance study was done injecting streptococcus Salivarius and those animals with AVF markedly delayed clearing bacteria from the systemic blood stream. The prolonged persistence (i.e. after 48 to 72 hours) of bacteremia in animals with fistulas may be due not only to a delay in clearing of bacteria but also to seeding of organisms into the circulation from the cardiac lesions. While the latter is a distinct possibility and has not been totally eliminated by these studies, the facts that there was a greater number of animals with positive blood cultures than with cardiac lesions, and that many of the latter were of the rheumatic type from which bacterial emboli would not be expected, minimizing this possibility. We were also able to observe the effect of arterialized liver by combined AVF and side-side portacaval shunt after ligation of IVC above the portacaval shunt point, promoting aortic blood to traverse through AVF and portacaval shunt, then reach to the liver.

While portacaval shunt paper was in the hands of Dr. Wangensteen, chief editor of Surgery journal in 1959, I was able to complete the procedure of rat kidney transplantation by 1960. We then began to prepare a moderate size of an exhibit panel, consisting 4 faces of illustration of portacaval shunt, arteriovenous fistula, liver arteriolization and kidney transplantation. Our exhibit was...
next to Dr. Wangensteen's Cooling treatment of bleeding gastric ulcer and drew many visitors. It occurred to me to transplant rat stomach to see if those completely denervated stomach would

secrets HCl and pepsin. Vast investigations on secretory capabilities for heterotopic pancreaticoduodenum (PD), liver (partial and whole) as well as stomach transplants were completed. Thus, we

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were hoping to replace domestic animals so that public will be free from their concerns and hoped to reduce burdens of larger animal surgery. After the publication of end-side portacaval shunt in the rat, we had two visitors from New York. As seen in Fig. 2, Jacobson and Tomita7 acquired rat blood vessel anastomosis in end-side manner.

As I explored the possibilities on rat organ transplantation,89 Dr. Frank Dixon of immunopathology at University of Pittsburgh was employing rabbits for Masugi nephritis study and was about to abandon larger animals. His group of researchers was ready to investigate in the rat model since availability of inbred strains, such as B.N.; D.A.; Fisher; Buffalo; Lewis; etc., and also they were getting ready to move to California. The late Dr. Feldman of Dr. Dixon’s group informed me, “Sun, as soon as we establish a sizable laboratory, we will call you to come to California and do kidney transplantation for our group. I’m sure it will be beneficial to both of us and for all are interested in organ transplantation in experimental and clinical settings as well.” At that time (1963-1964) we were engaged in newborn puppy kidney transplant study as well as clinical kidney transplantation. After 8 clinical kidney transplants, I joined Dixon group at the Scripps Clinic. At the clinic, Dixon group, assisted by Dr. Unanue, started massive study on rat kidney transplant as to Masugi nephritis as to transference of antibody from/to nephritic animals following kidney transplantation of normal rat to diseased rat and vice versa.

Shortly after the publication of rat kidney transplantation in nephritic rat, Dr. John Merrill from the Harvard University invited me twice to instruct his staffs and fellows. His problem was clinical twin kidney transplants among which one received a kidney from sibling whom developed similar nephritic ailment later on. Other problems were added to further investigations and employing inbred rat would be very beneficial to clinical applications. After the first course of instruction only one surgeon, Dr. Rowinski, was able to transplant the rat kidney and he returned to Poland. At the 2nd instruction course very enthusiastic internist Ronald Guttmann was called in almost everyday after my return from Boston and reported back of his transplantation progress. Thus, in the hands of technically refined skill, he was converted to microvascular organ transplant surgeon. His publication awakened many clinical organ transplant surgeons and well accepted as staff at McGill University.

Since employing inbred strain Lewis rats, organ rejection sequences were eliminated from the study. Heyman’s nephritis study was also done using the model of adjuvant substance injection to footpad of the rats and transplanted likewise. While these project kept research fellows busy, Edgington and others10 could be able to transplant partial rat liver to examine growth pattern of the partial liver as to source of blood input: hepatic arterial alone, combined with portal blood, or portal vein blood input alone. I was encouraged by not only by Dr. Dixon, but also late Prof. Hasting who told me that if I can transplant rat liver, the Scripps Clinic will be further known to the world. From partial liver transplantation to total liver transplantation and partial liver with splanchnic organ transplantation study also became worthwhile. At late hours, I was permitted to transplant stomach,
pancreas at the lab with help of industrious assistant, Dr. Koopmans, a graduate student at University of California, San Diego (UCSD) who was interested in "hunger" problems in parabiotic rats. After transplanting rat’s liver, pancreas and stomach tubes were placed to collect the bile, pancreatic and gastric juices in the Bollman restraining cages. All above transplant techniques were performed in so-called heterotopic organ transplantation manner and then total liver transplantation technique was described. We concluded from these studies that partial heterotopic liver transplant in clinical settings could be very well accepted model if the host ailing liver could be cirrhotic or malformed, which does not jeopardize the life of the host by its presence since the removal of these diseased organs shed hazardous effect.

While I was at the Scripps Clinic, techniques for rat’s heart-lung, spleen, testicle, pancreatoduodenum and stomach transplantation were developed. In fact my full time dual appointment with the Scripps Clinic and UCSD have kept me very busy. I believe that some unpublicized events are worthwhile to mention. In 1966, Dr. Oldstone (Fig. 3) asked me to try transplanting a head of one rat to another for testing if high molecular substance could be travel cross the cerebral hemi-

sphere. Under ether anesthesia one rats head was transected at the neck and left carotid artery and jugular vein were ligated. The right carotid artery and jugular vein were end-side anastomosed to the left side of the host rats corresponding vessels. While the host rat was at the anesthetic stage, these heads were shown to Dr. Dixon. He examined the 2 headed rat and told Dr. Oldstone, “Tell Sun, he can publish anything but this two headed model should not be publicized because it can create negative image of the Scripps by public.” The two-headed rat died next day. Looking back the history, Carrel and Guthrie were the first to transplant dog’s head in the beginning of the last century, then the Russian surgeons reported of such event around 1960’s also using dogs.

From Italy, Doctor Fox and Doctor Montors reported one artery anastomosis on rat heart-lung, performing heterotopic transplant by aorto-aortic reunion sufficed the isolated heart and lung to beat adequately, but his model yielded high incidence of lung abscesses. In order to minimize this incidence, all lung lobes were removed except one small lobe, which could function as blood reservoir. After I joined Dr. Orloff’s group, partial and orthotopic liver transplant models were put to various physiological studies. The model of pancreatoduodenal transplant was employed in alloxan diabetic rat and further this study was extended to investigate allografted pancreaticoduodenal transplant with Dr. Scott from the Great Britain using Cyclosporine A as sole immunosuppressant. As these transplantation models developed or refined from our laboratories, “public sentiments free”, or lesser sentiments, organ transplant studies were made available to support or deny preexisting models on adapting larger animals for research or clinical models of their validity.

After my retirement from UCSD, Dr. Gittes and I had many ideas to explore the possibility to transplant allied vital organs in consecutive manner to see if certain vital organ(s) may survive longer than the host’s biological life span. Also these studies shall aid to solve vital organ shortage since there will be many transplanted patrons carrying prolonged lives. These vital organs should be available when they encounter fatal disaster, thus the transplanted organs should
CONCLUSION

A short rat blood vessel and organ transplant history is presented portraying works by the author. Other historical events on initial rat heart by Abbott and associates and small intestinal transplant by Monchick and associates were meritorious rat organ transplants and shall be on the list of historical events. The Phase of immunological studies on rat organ transplants were carried out with Dixon Group at the Scripps Clinic and the physiological phase of rat organ transplants including pancreasoduodenum and other organs were carried out at University of California, San Diego (UCSD) surgical research laboratories. After my retirement in 1985, we concentrated upon so-called "Consecutive organ transplant" studies in which pancreas, duodenum, liver, kidney survived much longer than the host's life span (Lewis rat's life span is around 24 months). From this consecutive organ transplant study, we were able to observe intrasplicenic gonads' fate which no other reports were comparable as ours since we were transplanting spleens bearing gonads frequently to different hosts to see the gonads' transformation into malignant ones.

During my long years of laboratory works, I have had many able scholars studied with me. They were learned not only from me, but also left with many impossible tasks, questions and opportunities to go on further steps. Thus, my dear colleagues and I achieved to replace the use of domestic animals to rodents for the organ transplant research. However, with some exceptions, larger animals are needed to certain laboratory investigations.

REFERENCES

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