Discussion

Wide ranges of alpha$_1$-antitrypsin function and concentration were found in groups of serum samples of Pi MM, MS, and MZ persons. The ranges were wider in a group of serums from patients with obstructive pulmonary disease than in a control group, and demonstrated greater overlap of types MS and MZ with type MM. Although in the control group in this study Pi MZ samples were clearly separated from all MMs by immunochemical quantitation, this was not true in the patient group. In addition, in this laboratory recently other Pi types have been noted to have alpha$_1$-antitrypsin function and concentration in the MZ range; these include types FF, FS, FM, MV, SS and SZ. Finally four MM samples have been identified with alpha$_1$-antitrypsin concentrations of less than 1.5 mg per milliliter — well within the range of MZ samples.

Although screening tests based on quantitative methods have been proposed for detection of the MZ type, measurements of alpha$_1$-antitrypsin function or concentration cannot be expected to give a reliable indication of the MZ or MS Pi types. Any screening test employing quantitative methods must be accompanied by definitive Pi typing analysis.

References

1. Fagerhol MK, Laurell C-B: The Pi system-inherited variants of serum alpha$_1$-antitrypsin, Progress in Human Genetics. Edited by AG Steinberg, AG Bearn. New York, Grune and Stratton, 1970, pp 96-111
2. Eriksson S: Studies in α_1-antitrypsin deficiency. Acta Med Scand (Suppl) 432:1-85, 1965
3. Sharp HL, Bridges RA, Krivit W, et al: Cirrhosis associated with alpha-1-antitrypsin deficiency: a previously unrecognized inherited disorder. J Lab Clin Med 73:934-939, 1969
4. Glasgow JFT, Hercz A, Levison H, et al: Alpha$_1$-antitrypsin deficiency with both cirrhosis and chronic obstructive lung disease in two sibs. Am J Med (in press)
5. Janoff A: Inhibition of human granulocyte elastase by serum α_1-antitrypsin. Am Rev Resp Dis 105:121-122, 1972
6. Lieberman J: Heterozygous and homozygous alpha$_1$-antitrypsin deficiency in patients with pulmonary emphysema. N Engl J Med 281:279-284, 1969
7. Talamo RC, Allen JD, Kahan MG, et al: Hereditary alpha$_1$-antitrypsin deficiency. N Engl J Med 278:345-351, 1968
8. Falk GA, Siskind GW, Smith JP Jr: Chronic obstructive pulmonary disease: a subgroup of patients identified by serum alpha$_1$-antitrypsin and immunoglobulin concentrations. Am Rev Resp Dis 103:18-25, 1971
9. Kueppers F, Fallat R, Larson RK: Obstructive lung disease and α_1-antitrypsin deficiency gene heterozygosity. Science 165:899-901, 1969
10. Fagerhol MK, Hauge HE: Serum Pi types in patients with pulmonary diseases. Acta Allergol (Kbh) 24:107-114, 1969
11. Erlanger BF, Kokowsky N, Cohen W: The preparation and properties of two new chromogenic substrates of trypsin. Arch Biochem Biophys 95:271-278, 1961
12. Talamo RC, Langley CE, Hyslop NE Jr: Comparison of functional and immunochemical quantitative analysis of alpha$_1$-antitrypsin, Pulmonary Emphysema and Proteolysis. Edited by C Mittman. New York, Academic Press, 1972, pp 167-172
13. Laurell C-B: Antigen-antibody crossed electrophoresis. Anal Biochem 10:358-361, 1965
14. Fagerhol M, Laurell C-B: The polymorphism of "prealbumins" and α_1-antitrypsin in human sera. Clin Chim Acta 16:199-203, 1967
15. Kueppers F: Genetically determined differences in the response of alpha$_1$-antitrypsin levels in human serum to typhoid vaccine. Humangenetik 6:207-214, 1968

SPECIAL ARTICLE

ANNUAL DISCOURSE – ORGAN REPLACEMENT, FACIAL DEFORMITY, AND PLASTIC SURGERY

Joseph E. Murray, M.D.

PLASTIC surgery, second only to obstetrics as the oldest surgical specialty, is tested most rigorously in the treatment of facial deformities. Through the centuries the mutilated nose cut off as punishment for murder, theft, or infidelity,[1] the congenital cleft lip,[2] and the face eaten by cancer or torn by trauma have forced the reconstructive surgeon to seek imaginative ways to restore both function and an aesthetically acceptable appearance.

Whenever possible, surgical repair is performed by joining together adjacent areas; often, however, additional tissues such as grafts of skin, cartilage, fascia, or bone are needed to replace the missing or injured parts (Fig. 1). These grafts supply only the framework or bulk rather than replace missing cellular functions. The ultimate in reconstruction is total replacement of an old defective part by a new one. Although not yet possible for facial defects, organ replacement is an effective, accepted, and still developing treatment for renal failure.

In this discourse I will trace my involvement in organ transplantation to the current interest in craniofacial defects and then conclude with observations on the role of plastic surgeons in the delivery of health care for today's society.

Organ Replacement

People often ask how I, a plastic surgeon, became so involved in kidney transplantation. It started during World War II on our Plastic Surgical Service at Valley Forge General Hospital in Pennsylvania headed by Dr. J. B. Brown* and Dr. Bradford Cannon. There many burned patients were dying for lack of sufficient unburned skin to be used as grafts. The obvious answer was to use skin from other human beings, but the immunological barrier standing between all humans, except for monozygotic twins, prevents permanent sur-

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*Dr. Brown had written, in 1937, the first precise clinical study on the permanent survival of skin grafts between monozygotic twins.[3]

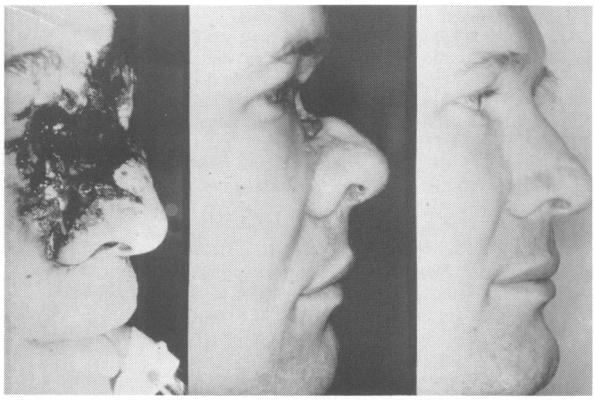

Figure 1. Variety of Autogenous Grafts Available to Restore Function and Appearance.

A shows destruction by bullet of skin, bone, cartilage, and mucosa. B shows the patient three months after debridement and wound closure by split-thickness skin grafts (note bone loss, nasocutaneous fistula, and upward tilt of nose secondary to wound contraction). C shows the patient one year after closure of the fistula by local tissue, pedicle flap from arm for surface closure and iliac-bone graft.

vival of skin allograft* and therefore limits their usefulness.

After World War II and completion of training, on my return to the Peter Bent Brigham Hospital I wanted to study the mechanism of rejection of skin allografts. At that time, in 1951, the Medical Service under Dr. G. W. Thorn had developed a strong interest in hypertension and renal disease. Dr. J. P. Merrill and Dr. C. W. Walter had devised a functioning artificial kidney, Dr. J. H. Harrison was Chief of Urology, Dr. D. M. Hume had begun a series of unmodified kidney transplants in man, and under Dr. F. D. Moore's guidance, I decided to use the kidney rather than skin as a laboratory test allograft.

In the early 1900's Carrel, having perfected the surgical technics for vascular anastomoses, had shown that kidney autografts in dogs survived for a long time, whereas allografts transplanted by the same technic functioned for only a few days and then were rejected with an intense, local, non-suppurative reaction.[4]

It was strange that even as late as 1951, there was a consensus that renal autografts would not function permanently even though no immunologic barrier existed between donor and host. Deterioration in renal autograft function was assumed to be due to absence of nerve supply, to abnormal lymphatic drainage, to ascending infection from the cutaneous ureterostomy, or to other, unknown circumstances. By 1954, I had studied in the Surgical Research Laboratory at Harvard Medical School a number of dogs with life-sustaining autografts[5] and demonstrated that a solitary autograft could function indefinitely with normal renal function if the autografted kidney were placed in a proper thermal environment intra-abdominally, with good ureteral drainage into the bladder, and with vascular anastomoses performed as described by Carrel.[4]

Therefore when the first identical twin dying of uremia was referred to the Peter Bent Brigham Hospital in the autumn of 1954, we had available a proved laboratory model for the human operation. The immediate and complete success of this first human twin transplant[6,7] served as a major stimulus for our endeavors to break the immunologic barrier and to bring the benefits of organ replacement to uremic patients, most of whom were young and otherwise healthy. One of our twin recipients receiving a transplant in May, 1956, completed a normal pregnancy 16 months later; today, she has normal renal function, has had two children, leads a normal life, and is the world's longest survivor of a renal transplant.[8]

Dr. F. D. Moore, in his book, Transplant, the Give and Take of Tissue Transplantation,[9] gives a lively account of the development of organ transplantation. He mentions the use of total-body x-irradiation tested in the late 1950's as an immunosuppressive agent in mice, rabbits, and dogs. This total-body x-ray protocol followed by bone-marrow infusion and then by the renal allograft proved difficult to adapt to man. From many attempts at the Peter Bent Brigham Hospital only one successful transplant resulted, a young man given a transplant in January, 1959, from his di-zygotic twin brother.[10] Today, he has obtained his Ph.D. in Philosophy, has married, has good renal function and leads a normal life — the longest surviving renal-allograft recipient in the world. During these years Hamburger[11] and Küss,[12] in Paris, working separately, also achieved isolated unpredictable successes with the use of related living donors.

The real impetus to worldwide kidney transplantation came from the use of immunosuppressive drugs, which were more efficient and less dangerous than total body irradiation, with an additional advantage that the dosage could be continuously adjusted. After Schwartz and Dameshek, in 1959,[13] produced in rabbits a specific drug-induced immunologic tolerance to human serum albumin after the use of 6-mercaptopurine (6-MP), Calne[14] and Zukoski[15] independently achieved considerable prolongation of renal allografts in dogs with the use of the same agent.

Azathioprine,† the imidazole derivative of 6-MP, was soon found by Calne and me[16] to be more effective and less toxic than 6-MP. In the previous nine years in our laboratory we had never achieved a single survival of a canine renal allograft beyond 15 days. During the year 1960, using azathioprine in varying doses and combinations, we could produce healthy, bilateral nephrectomized, renal allografted dogs of continually longer duration — 42 days, 78 days, and then over 100 days. Those were exciting times. We used azathioprine

*Grafts between two individuals of the same species (synonymous with the old term "homograft").

†Trade name, "Imuran" — formerly coded "BW 57-322" and appearing as such in our early publications.

first for a human recipient of a renal allograft in 1961. A patient given a transplant in April, 1962, became the first human being to survive beyond one year after receiving a kidney from a cadaver.[17]

Many other centers in Paris, Edinburgh, London, Richmond, Los Angeles, and Denver were extremely active at this time, and increasing numbers of long surviving recipients from parental, sibling, and cadaveric donors were being obtained. Groth, in his recently published Landmarks in Clinical Renal Transplantation,[18] mentions Goodwin, who added the use of steroids, Starzl and Hume, who produced for the first time good results in a majority of patients, Dausset and Terasaki, who first applied histocompatibility tests to select the most suitable donor-recipient combinations, Franksson, who used thoracic-duct drainage of lymphocytes as an immunosuppressive aid, and Woodruff, whose work led to the use of antilymphocyte globulin in clinical transplantation.

Today, about 75 per cent of living related donor transplants function at two years, with only slight loss thereafter; for cadaveric donor transplants about 50 per cent function for two years but with a greater loss over the following years.[19] Transplant failure does not mean death of the patient because most patients return to hemodialysis awaiting a second, third, or even a fourth transplant.

Better tissue typing and donor-recipient matching are required to achieve further improvement. Also needed are more specific and less toxic methods of immune suppression. Available drugs are far from ideal agents, although when effective they allow patients to live full lives, to have normal children, and to perform unlimited physical activity except as related to physical injury to the transplant. The marked improvement in organ preservation, especially by Belzer,[20] allows up to 48 to 72 hours of kidney storage — ample time for tissue typing, for shipping the organ anywhere in the world to the best matched recipient, and for optimal preparation for an elective operation.

Although the kidney remains by far the most frequently transplanted organ, over 10,000 having been recorded, liver and heart transplants have been successful. Starzl,[21] using Moore's technic,[22] has several liver-transplant survivors beyond two years, and Calne[23] one beyond three years. Shumway's group[24] has several recipients of cardiac transplants surviving for over three years with excellent quality of life. Their overall survival figures are actually better than those seven years ago for cadaveric renal grafts.

To conclude this phase of the discourse on organ replacement, it is ironic that skin, the first tissue to be studied extensively, has proved to be the most difficult to allograft successfully. Skin, together with lung, are the barriers between our internal milieu and the external environment, and hence, teleologically, the most highly developed to detect and react against foreign substances — witness hives and asthma as the most common hypersensitivity states. Although the treatment of burns has been improved by use of preserved skin allografts, they serve only as temporary, not permanent, biologic dressings.

Facial Deformity

How does all this relate to facial deformity? Currently, transplantation of an intact orbit, jaw, nose, palate, or esophagus does not apply; yet the seed has been planted, and investigations are under way in the field of craniofacial defects in a manner reminiscent of the early days of transplantation.

In 1957 a nine-year-old boy with rhabdomyosarcoma of the orbit, recurrent after x-ray therapy and two surgical resections, was referred to the late Dr. Donald Matson, of Harvard Medical School, Children's Hospital Medical Center and Peter Bent Brigham Hospital. Dr. Matson's prior experience with similar situations had been dismal, with patients dying piteously of local disease but with no distant metastases. Together, we developed and performed radical surgical resection of all bone, muscle, and sinus tissues between the frontal and temporal lobes of the brain, as far posteriorly as the anterior clinoid process, and inferiorly to the hard and soft palate. The immediate repair was by a split-thickness skin graft. Three years later a pedicle flap was substituted to give better protection. Today, this grown man has completed his education, leads a normal life and as a hobby water-skis and does underwater diving. This experience with combined cranio-orbito-facial resection and reconstruction has been adapted with success for other patients and other types of tumors[25]; in addition it has increased our interest in other varieties of craniofacial problems.

Around 1960 Dr. L. Swanson, currently chief of dental services at Children's Hospital Medical Center, and I started our collaborative treatment of children and young adults with mandibular prognathism (Fig. 2), secondary cleft lip and palate defects, first and second branchial-arch syndromes, and varieties of maxillary and mandibular hypogenesis. At first our therapy was more or less routine, but it soon became apparent that many observed deformities did not fit into standard patterns or syndromes. For example, in some patients, after early trauma, defects mimicking congenital syndromes developed; in others, after cranial-nerve resection for brain tumors, hypertrophic growth patterns developed in the distantly denervated orbital and malar bones. In still other patients with longitudinal growth studies, secondary and tertiary defects became apparent that could have been prevented by correction of the primary defect at an earlier age.

In the mid-1960's, the first generation of patients with craniosynostoses successfully treated by Drs. Ingraham and Matson were growing up with excellent brain function but with faciostenosis, failure of the mid-face to grow. Some patients showed exophthalmos secondary to hypoplasia of the bony orbit, recession of the cheeks and malar areas, marked maxillary underdevelopment, and malocclusion.

Here was a new problem demanding a fresh look. The existing routine treatment consisted of secondary

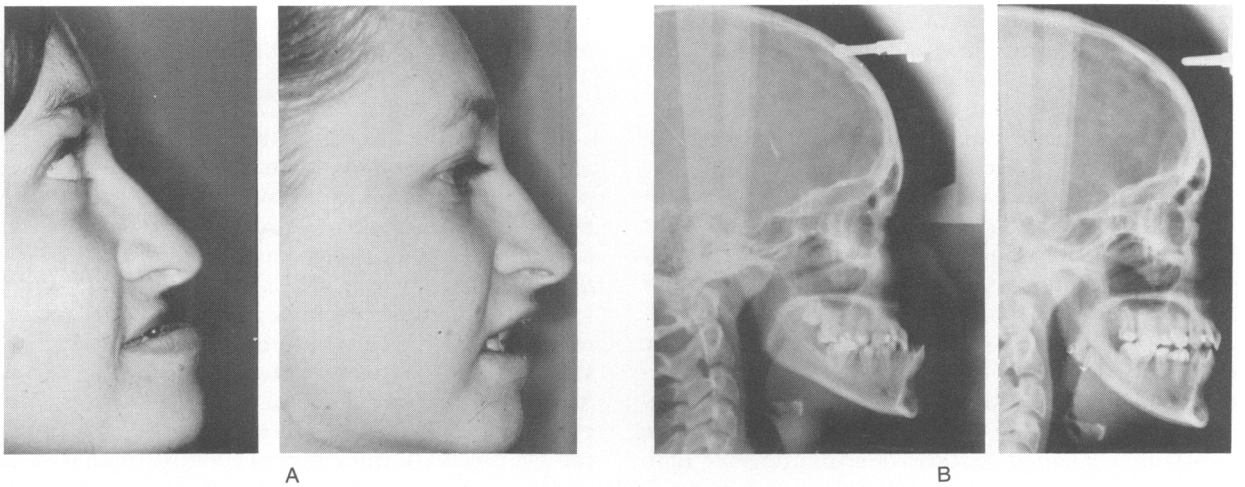

Figure 2. Preoperative (Left) and Postoperative (Right) Views of a 16-Year-Old Girl after Osteotomy and Setback of the Mandible for Prognathism (A).

This simultaneous improvement in function and appearance she considers a major turning point in her life. X-ray films of the same patient (B) demonstrate preoperative malocclusion (left) and correction (right) after bilateral oblique osteotomies at mandibular angles. Note wire sutures at the operative sites.

procedures unsatisfactory to both patient and surgeon. If our analyses were correct and the primary deficit was failure of growth centers at the base of the skull, the obvious correction would be to detach all facial structures from the skull and advance them as a single unit, thus enlarging the bony orbit to allow space for the eye, advancing the maxillary alveolus and teeth to obtain good occlusion and restoring symmetry of the cheeks and nose as well (Fig. 3).

We planned for the procedure for over a year, studying fresh anatomic specimens to determine sites for the osteotomies and to note the directional pull of the muscles and ligaments. In 1966 we performed the first such operation in the United States.[26] It proved successful and has been performed with increasing frequency since. One patient received an unexpected postoperative bonus with improvement in hearing so striking that she discarded her hearing aid.

One year later we learned that Dr. Tessier, plastic surgeon in Paris, had previously performed not only similar procedures but also more complex osteotomies to correct hypertelorism and nasal encephaloceles. In 1959 Tessier had begun his surgical analysis of faciostenosis, hypertelorism, facial encephaloceles, and other major defects. After trial operations he discontinued his attempts until 1964, when he performed a second but still unsuccessful series of test procedures. After more study finally in the mid-1960's he achieved success. His work, first published in 1967 and reprinted in English,[27] serves as a model for skill and scholarship throughout the world.

During the past four years Dr. Swanson and I have continued our analysis and treatment of these craniofacial problems, including hypertelorism. In addition we have developed a compound silicone-osseous prosthesis for mandibular reconstruction that com-

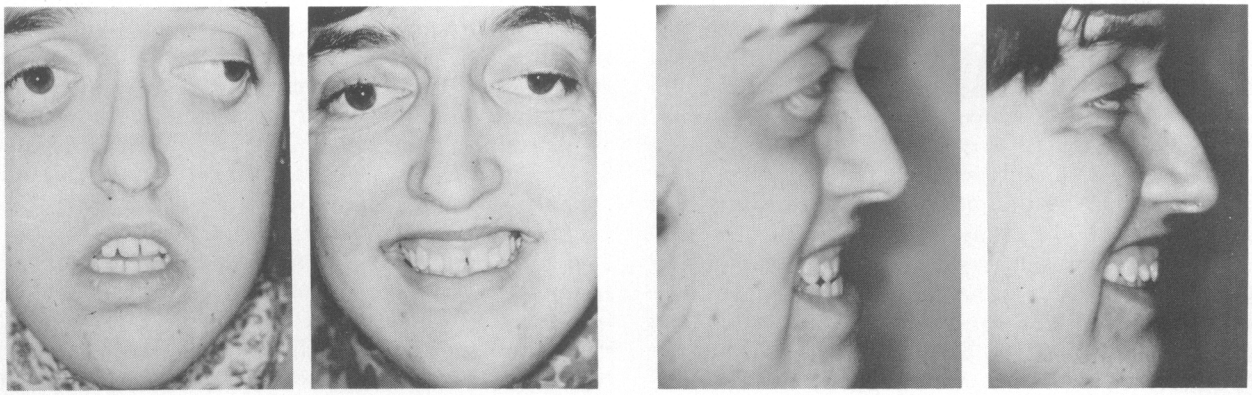

Figure 3. Teen-Age Girl with Residual Midfacial Stenosis (Preoperative Views on the Left) after Successful Craniectomies in Infancy for Craniosynostosis.

Note postoperative correction (right) of exophthalmos, maxillary underbite and flat cheeks after one-stage midfacial advancement after en bloc osteotomy of malar-orbital-maxillary-nasal bones.

bines the benefits of excellent contour and nonreactivity of the silicone with the permanent healing attributes of autogenous bone grafts.[28]

The first international conference on craniofacial defects in October, 1971, organized by Converse and Pruzansky, brought together geneticists, embryologists, cell biologists, dental disciplines, speech pathologists, neurosurgeons, ophthalmologists, and otologists, as well as plastic surgeons. Only a few groups in the world are currently involved in treating these types of patients. Over the next decade the field will grow, perhaps as rapidly as transplantation did during the 1960's. To obtain maximum benefit for the patient and to achieve optimal scientific output, clinical groups must maintain close associations with the related basic sciences.

Role of Plastic Surgery in Delivery of Health Care

The plastic surgeon has a twofold responsibility — to the individual patient under his care and for the delivery of services on a nationwide basis. Whether the defect is congenital, traumatic, neoplastic or esthetic, reconstructive surgery must be defined in its broadest sense, not just correction of a defect but rehabilitation of the patient for life's responsibilities. In some medical circles (probably more so in a university setting) there is a tendency to downgrade esthetic or cosmetic surgery. In my opinion, this is a serious error. We cannot deny the social or personal importance of disfigurement, real or subjective. There will always be public demand for esthetic surgery. It is imperative that it be performed by qualified surgeons who will not act with crass commercialism and dispense technics on demand. Rather, the plastic surgeon must act with experience and judgment to weed out the patients for whom surgery will bring only further mental turmoil. When Blair, in 1938, was establishing the American Board of Plastic Surgery, he wanted to maintain a close relation with general surgery so that surgeons primarily interested in reconstruction would remain in the mainstream and not be relegated to a "fringe practice around the corner."

What sort of patient seeks esthetic surgery, say, for a face lift? It may be a recently widowed or divorced woman seeking employment, an airline stewardess approaching the late 30's, a happily married man or woman 60 or 70 years old who just doesn't like sagging cheeks and neck and baggy eyelids. Once the patient has learned the facts about time involved, discomfort, expense, and possible complications and decides to go ahead with the operation, he or she deserves the same consideration and respect as any other hospitalized patient.

Much to my pleasure, my colleagues frequently call me to suture facial lacerations on themselves or their families; do not members of the general public likewise deserve the skills of plastic surgery when they go to the Emergency Ward of their community hospital? The effective delivery of complete reconstructive surgery must be available to all society, not to just a segment. One estimate by a prepaid group plan sets the need of one plastic surgeon for every ½-million population. This is certainly unrealistic. Such a ratio indicates either that many categories of plastic surgical care that the patient considers his right would be delayed or omitted or that the work would be performed by others in the absence of a trained reconstructive surgeon. More realistic figures presented by Dr. Jurkiewicz at the 1970 meeting of the American Society of Plastic and Reconstructive Surgery indicate that at least 1000 more trained plastic surgeons are needed in this country immediately, and that number might conceivably be quadrupled within the next few years.[29]

The present annual output of roughly 100 certified plastic surgeons is inadequate to cope with demand and will remain so while only ⅓ of this country's medical schools support training programs in the specialty. Currently, there are 101 residency programs in plastic surgery with 250 residents in training, with the lowest percentage of foreign medical graduates of any specialty, including the specialty of general surgery. The current ratio per million population is eight for plastic surgery, 24 for otolaryngology, 42 for orthopedics, and 133 for general surgery. It is obvious that more well trained plastic surgeons are needed. The massive study on surgical manpower, directed by Dr. F. D. Moore under the Study of Surgical Services of the United States (SOSSUS), sponsored jointly by the American College of Surgeons and the American Surgical Association, will shed more light on needs and probably bear out the estimates made in 1970, especially since tightening of surgical standards will lead to a further demand for qualified surgeons.

In my opinion, every hospital should have at least one and preferably two certified plastic surgeons on its active staff. Such a recommendation does not imply that these plastic surgeons should take exclusive care of all patients for each of the disease categories mentioned earlier. It does mean, however, that all patients in these hospitals will have the benefit of the reconstructive surgical skills needed for their specific conditions.

While the production of more trained plastic surgeons is awaited, proper utilization of currently available manpower demands attention. Within inner cities maldistribution is potentially correctable with proper and effective planning. The rural areas offer a different challenge. The American Board of Plastic Surgery lists no certified plastic surgeon in Idaho or Montana, and no more than two in each of the nine states of Arkansas, Delaware, Iowa, Maine, Nebraska, North Dakota, Vermont, West Virginia, and Wyoming. Thus, a sizable segment of the population lacks available plastic surgeons. The problem relates not only to this specialty, for in ⅓ of the nation's counties, the physician census is about 30 per cent of the general average.[29]

Conclusions

Specialization and even subspecialization such as surgery of deafness, retinal detachment, and hip re-

placement have developed in response to public demand. We doctors must remain in the mainstream of medicine and surgery in the broadest sense while pursuing areas of special interests. Progress in other disciplines often dictates which fields of research and study are ready for clinical exploitation. The work on craniofacial defects may follow the pattern of transplantation biology; transplantation gave a clinical stimulus and orientation to immunology, and perhaps craniofacial studies will in a similar way influence genetics and embryology.

The plastic surgeon with adequate background in basic surgery is in a good position to select and participate in new areas of clinical research. He not only derives immediate personal gratification in performing surgery to benefit a fellow human but also receives intellectual stimuli from fellow scientists in efforts to teach and expand knowledge. If he is really fortunate, he may even be invited to give the Annual Discourse before the Massachusetts Medical Society — an honor and privilege that I have appreciated and cherish.

References

1. Gnudi MT, Webster JP: The Life and Times of Gaspare Tagliacozzi, surgeon of Bologna 1545-1599. New York, Herbert Reichner, 1951, Chapters 7, p 106
2. Celsus AC: De Medicina. London, William Heinemann Ltd, 1935, Book 7, Vol 2, Chapter 9, pp 363-365
3. Brown JB: Homografting of skin: with report of success in identical twins. Surgery 1:558-563, 1937
4. Carrel A: Technique and remote results of vascular anastomoses. Surg Gynecol Obstet 14:246-254, 1912
5. Murray JE, Lang S, Miller BF, et al: Prolonged functional survival of renal autotransplants in the dog. Surg Gynecol Obstet 103:15-22, 1956
6. Murray JE, Merrill JP, Harrison JH: Renal homotransplantation in identical twins. Surg Forum 6:432-436, 1955
7. Merrill JP, Murray JE, Harrison JH, et al: Successful homotransplantation of the human kidney between identical twins. JAMA 160:277-282, 1956
8. Murray JE, Merrill JP, Harrison JH: Kidney transplantation between seven pairs of identical twins. Ann Surg 148:343-359, 1958
9. Moore FD: Transplant, The Give and Take of Tissue Transplantation. New York, Simon and Schuster, 1972
10. Murray JE, Merrill JP, Dammin GJ, et al: Study on transplantation immunity after total body irradiation: clinical and experimental investigation. Surgery 48:272-284, 1960
11. Hamburger J, Vaysse J, Crosnier J, et al: Transplantation d'un rein entre jumeaux non monozygotes après irradiation du receveur: bon fonctionnement au quatrième mois. Presse Med 67:1771-1775, 1959
12. Küss R, Legrain M, Camey M, et al: Homotransplantation rénale chez l'homme: à propos de 3 cas. Mem Acad Chir 87:183-199, 1961
13. Schwartz R, Dameshek W: Drug-induced immunological tolerance. Nature (Lond) 183:1682-1683, 1959
14. Calne RY: The rejection of renal homografts: inhibition in dogs by 6-mercaptopurine. Lancet 1:417-418, 1960
15. Zukoski CF, Lee HM, Hume DM: The effect of 6-mercaptopurine in renal homograft survival in the dog. Surg Gynecol Obstet 112:707-714, 1961
16. Calne RY, Murray JE: Inhibition of the rejection of renal homografts in dogs by Burroughs Wellcome 57-322. Surg Forum 12:118-120, 1961
17. Murray JE, Merrill JP, Harrison JH, et al: Prolonged survival of human-kidney homografts by immunosuppressive drug therapy. N Engl J Med 268:1315-1323, 1963
18. Groth C: Landmarks in clinical renal transplantation-collective review. Surg Gynecol Obstet 134:323-328, 1972
19. The Ninth Report of the Human Renal Transplant Registry. JAMA 220:253-260, 1972
20. Belzer FO, Kountz SL: Preservation and transplantation of human cadaver kidneys: a two-year experience. Ann Surg 172:394-404, 1970
21. Starzl TE, Giles G, Lilly J, et al: Indications for orthotopic liver transplantation: with particular reference to hepatomas, biliary atresia, cirrhosis, Wilson's disease and serum hepatitis. Transplant Proc 3:308, 1971
22. Moore FD, Smith LL, Burnap TK, et al: One-stage homo-transplantation of the liver following total hepatectomy in dogs. Transplant Bull 6:103-107, 1959
23. Calne RY: Transplantation of the Liver. Transplant Proc (in press)
24. Dong E, Stinson EB, Shumway N: Clinical transplantation of the heart. Ann Surg (in press)
25. Murray JE, Matson DD, Habal MB, et al: Regional cranio-orbital resection for recurrent tumors with delayed reconstruction. Surg Gynecol Obst 134:437-447, 1972
26. Murray JE, Swanson LT: Mid-face osteotomy and advancement for craniosynostosis. Plast Reconstr Surg 41:299-306, 1968
27. Tessier P: The definitive plastic surgical treatment of the severe facial deformities of craniofacial dysostosis: Crouzon's and Alpert's diseases. Plast Reconstr Surg 48:419-442, 1971
28. Swanson LT, Habal MB, Murray JE, et al: Silastic-osseous prosthesis for mandibular reconstruction: development and application. Plast Reconstr Surg (in press)
29. Tanzer R: Presidential address, before American Association of Plastic Surgeons, Salt Lake City, Utah, May 14-17, 1972. Plast Reconstr Surg (in press)

MEDICAL PROGRESS

MEDICAL MANAGEMENT OF PRIMARY HYPERTENSION (Third of Three Parts)

Lot B. Page, M.D., and James J. Sidd, M.D.

Guanethidine

Actions

Guanethidine, like reserpine and methyldopa, exerts its antihypertensive action by interfering with neurotransmission at the adrenergic postganglionic nerve terminals, and thereby decreasing arteriolar vasoconstriction. Guanethidine acts both by preventing the release of norepinephrine from the postganglionic nerve terminals and by depleting norepinephrine stores at these terminals.[180-184] Guanethidine also partially depletes the myocardium of its catecholamine stores.[185] Unlike methyldopa, guanethidine does not interfere with the synthesis of norepinephrine or result in the synthesis of a false neurotransmitter.

Guanethidine decreases heart rate, stroke volume and cardiac output, probably owing to its sympatholytic action on the heart.[145,185,186] The decrease in cardiac output contributes to the antihypertensive action of this drug. Although blood pressure is reduced somewhat in the supine position, the effect of guanethidine

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