answers to all questions we are already able to pose. Studies of RNA synthesis are valuable because they provide a direct measurement of transcriptional activity. But these studies remain incomplete until we succeed in unraveling the metabolic roles of the molecules whose synthesis we study. In this respect, the study of enzyme synthesis represents a better defined assay system, although the interpretation of observed fluctuations in synthetic rates is made difficult by the many steps that intervene between the genes and their finished protein products. We propose that a combination of protein biosynthetic and cytogenetic analysis is a promising assay system for further investigation.

References and Notes

1. J. Lederberg, in *Current Topics in Developmental Biology*, A. A. Moscona and A. Monroy, Eds. (Academic Press, New York, 1966), vol. 1, p. x.
2. Th. Boveri, *Sitzungsber. Phys. Med. Ges. Würtzburg* (1904).
3. E. Hay, in *The Stability of the Differentiated State*, H. Ursprung, Ed. (Springer Verlag, New York, in press); A. Burnett, *ibid.*
4. J. B. Gurdon, *Quart. Rev. Biol.* **38**, 54 (1963).
5. D. D. Brown, in *Current Topics in Developmental Biology*, A. A. Moscona and A. Monroy, Eds. (Academic Press, New York, 1967), vol. 2, pp. 48–75.
6. D. T. Sullivan, *Proc. Nat. Acad. Sci. U.S.*, **59**, 846 (1968).
7. ———, thesis, Johns Hopkins University (1967).
8. D. Gillespie and S. Spiegelman, *J. Mol. Biol.* **12**, 829 (1965).
9. K. Scherrer and J. E. Darnell, *Biochem. Biophys. Res. Commun.* **7**, 486 (1962).
10. R. J. Britten and D. E. Kohne, in *Carnegie Inst. Wash. Year Book* **65** (1965–1966), pp. 78–106.
11. K. D. Smith, R. B. Church, B. J. McCarthy, *Proc. Nat. Acad. Sci. U.S.*, in press.
12. B. J. McCarthy and B. J. Hoyer, *ibid.* **52**, 915 (1964).
13. J. Paul and R. J. Gilmour, *Nature* **210**, 992 (1966).
14. G. W. Beadle, *Chem. Rev.* **37**, 15 (1945).
15. W. Beermann, *Chromosoma* **12**, 1 (1960).
16. E. H. Grell, K. B. Jacobson, J. B. Murphy, *Science* **149**, 80 (1965); H. Ursprung and J. Leone, *J. Exp. Zool.* **160**, 147 (1965).
17. J. B. Courtright, R. B. Imberski, H. Ursprung, *Genetics* **54**, 1251 (1966).
18. J. B. Courtright, *ibid.* **57**, 25 (1967).
19. A. M. Seligman, H. Ueno, Y. Morizono, H. L. Wasserkrug, L. Katzoff, J. L. Hanker. *J. Histochem. Cytochem.* **15**, 1 (1967).
20. H. Ursprung and E. Schabtach, *Archiv. Entw.-Mech. Org.*, **160**, 243 (1968).
21. B. Ephrussi and M. C. Weiss, *Proc. Nat. Acad. Sci. U.S.* **53**, 1040 (1965), H. Harris, J. F. Watkins, C. E. Ford, G. E. Schoefl, *J. Cell Sci.* **1**, 1 (1966).
22. 1 × SSC ≡ 0.15*M* NaCl, 0.015*M* sodium citrate.

23. Supported by NSF grants GB-4451 (H.U.), GB-5629 (K.D.S.), PHS grants 1-F2-GM-24, 115 (W.H.S.) and 1 TI HO-139 (D.T.S.).

Dental Research: The Past Two Decades

National Institute of Dental Research interdisciplinary programs have broadened the base of dental science.

Alvin L. Morris and Richard C. Greulich

Twenty years ago an act of Congress created the National Institute of Dental Research (NIDR) in recognition of the fact that dental disease is a threat to the nation's health, well-being, and productivity. In the intervening period there has evolved a generation of dental practitioners and researchers whose concepts of dental disease, dental practice, and related research are so modified as to add an entirely new dimension to their functional role as health specialists. In earlier efforts of the profession to establish a separate identity in the field of health, the mouth was considered, mistakenly, a biologic entity. Largely through the influence of NIDR, dental science has moved from a mechanical to a biological orientation, and the oral cavity is again looked upon as an integral component of the body. In the process, by shedding a narrow identification and aligning itself with a broad front of basic sciences, dental science has made exciting progress toward an understanding of oral disorders. At the same time, it has increasingly provided information of fundamental importance to other fields of scientific endeavor. The occasion of the 20th anniversary of the creation of NIDR, the major source of support for oral health research and research training in the United States, affords an opportunity to assess where the dental sciences stand today in a broad spectrum of research whose full import is yet to be realized.

The Scope of Dental Sciences

It is not possible to accurately define the boundaries of dental research. While there are those who, in the past, have related it only to investigations whose titles include the words *tooth* or *mouth*, such a restricted viewpoint is totally inappropriate today. The biochemist studying the cross-linkage of collagen, the microbiologist studying the polysaccharide coating of streptococci, the metallurgist investigating the phenomenon of corrosion, the crystallographer examining the structure of the apatite crystal are all engaged in work of vital interest to dentistry. This statement can be expanded to include the research of scientists from 30 discrete disciplines.

That research involving the oral cavity must inevitably implicate a wide range of science disciplines is obvious when the total oral environment is considered. Anatomically the mouth includes all basic tissue elements. The penetration of the teeth through the oral mucosa is the only example of the loss of continuity of the protective layer of skin or mucosa which lines all body surfaces or cavities. The nature of the union between the soft tissue of the oral cavity and the tooth structure in an erupted tooth is anatomically unique, as is the suspensory ligament by which the tooth is anchored in bone. The salivary glands, functioning under neural and endocrine control, excrete each day approximately 1500 milliliters of fluid containing minerals, glycoprotein, and enzymes. There is evidence in animals which suggests an endocrine function for these glands. The oral cavity has a rich microflora which includes bacteria with a full range of oxygen dependency. Commonly present in the oral cavity are various dental-restorative

Dr. Morris is assistant vice president for the Medical Center, University of Kentucky, Lexington: Dr. Greulich is director of intramural research, National Institute of Dental Research, Bethesda, Maryland.

materials, such as gold, silver amalgam and other alloys, silicate cements, and acrylic polymers. Often there is a measurable galvanic potential between dissimilar metals in the electrolyte-containing saliva. Further complicating this environment are the drying and other effects of frequent exposure to outside air, and the ingestion of foodstuffs and other materials representing a limitless range in terms of chemical structure and physical consistency. Temperature changes of from 0° to 60°C, occurring within seconds, are commonly associated with the eating habits of Americans.

A brief review of NIDR grants and training programs may provide some insight as to the manner in which the base of the dental sciences has been broadening. The first direct appropriations for dental research grants were included in the 1948 budget of the National Institutes of Health. In 1950, the then newly established Institute of Dental Research first obtained its own appropriation, amounting to $1.78 million. That figure has now, in 1968, reached $30.3 million. In a 20-year period, NIDR support for research grants has gone from $111,000 to $15.9 million, and the expenditure for fellowships has risen from $20,000 to $1.97 million. The Institute did not begin to support training grants until 1957, when $0.5 million was allocated for that purpose. It is expected that this figure will reach $5.5 million in 1968.

While the training of clinical investigators remains a major program interest of NIDR, priority has consistently been given to education in the basic sciences. Of the 237 individuals who completed their training in the past 2 years under training programs or fellowships supported by NIDR, the ratio of basic-science trainees to clinical-science trainees was about three to one. Institute funds are currently supporting 445 graduate students, 183 of whom are in predoctoral programs. Of the remaining students at the postdoctoral level, 245 are dentists, two are physicians, one is a veterinarian, and 14 are Ph.D.'s engaged in advanced study.

As interest in expanding dental research increased, it was logical to encourage more dentists to become trained in research techniques. Prior to 1940 there were only 20 dentists in the country who had received the Ph.D. as well as the D.D.S. or D.M.D.; that figure had reached only 47 by 1950. Today approximately 142 dentists hold both degrees. Of the 245 dentists now receiving training support, 114 are seeking a Ph.D. The NIDR recognizes, however, that it is also both appropriate and necessary to support the training of individuals who are not primarily identified with the dental profession. In recent years there has been a steady increase in the number of NIDR training grants awarded to institutions that have no affiliated dental school. Table 1 summarizes the basic-science disciplines in which training is currently being supported by NIDR.

Table 1. Distribution of active NIDR fellows and trainees in basic science disciplines as of November 1967.

Basic science discipline	Number of trainees	Number of fellows
Anatomy	44	4
Anthropology	11	1
Biochemistry	21	
Biology and oral biology	18	4
Biophysics	17	2
Biostatistics	1	
Chemistry	7	1
Computer science	3	
Crystallography	11	2
Dental materials	21	4
Developmental biology	1	
Embryology	2	1
Endocrinology	2	1
Epidemiology		1
Genetics	7	1
Growth and development	1	
Histology and histochemistry	6	2
Microbiology	16	2
Nutrition	12	1
Pathology	20	14
Pharmacology	8	5
Physics	1	1
Physiology	18	5
Psychology	12	3
Radiation biology	3	2
Speech pathology	32	
Zoology	1	1
Total	296	58

The present character of dental research is well illustrated by the intramural activities of NIDR. There, some 100 professional investigators, more than half of whom are trained at the doctoral level in fields other than, or in addition to, clinical dentistry, carry out full-time research leading to better control of oral disorders and to their prevention. While much of this research is clinically oriented, a substantial part seeks to provide a necessary underpinning of basic knowledge and takes off from the vantage points of pure biochemistry or microbiology, experimental morphology, genetics, and other disciplines. This multidisciplinary approach has resulted in an improved capacity to deal with dental ills, giving rise in the process to a large body of information relevant to other health areas. Such "cross-fertilization" is evident in the fact that, of the 93 research projects currently being conducted by NIDR staff, 78 percent are being carried out in collaboration with researchers in other institutes. Also, in a recent 10-month period NIDR scientists contributed papers on original research to 50 scientific journals.

A brief survey of current dental research is given in the following sections. The samples are drawn in large part from ongoing intramural programs at NIDR. Both parallel and disparate studies are being carried on in academic and nonacademic centers of research in many areas of the country.

Microbiological Studies

Oral pathoses exemplify particularly well the principle that infectious disease develops only when there is optimum conjunction of microbial, host, and environmental factors. This concept is now being emphasized in a continuing systematic examination of dental caries—a bacterially mediated acid decalcification of dental hard tissues.

A substantial body of laboratory data developed during the past two decades strongly supports the definition of caries as an infectious and transmissible disease. Although no clear-cut evidence of infection and transmission has yet been obtained in man, the present evidence does not rule out this possibility. Consequently, current microbiological research stresses determinants of host susceptibility and resistance in caries in much the same fashion that it stresses such determinants for lesions of the oral region definitely known to be infectious.

Although various bacteria have been shown to be cariogenic in gnotobiotic animals, the weight of findings focuses attention on a group of anaerobic streptococci (Fig. 1) found in the human and animal oral cavity which are characterized by the ability (i) to form extracellular polysaccharide (dextran) specifically from sucrose, (ii) to form intracellular polysaccharide (amylopectin) from various carbohydrates, and (iii) to ferment sorbitol and mannitol. The extracellular polysaccharide is not utilized by the bacteria but seems to be responsible for their adherence to the tooth surface as dental plaque. The intracellular polysaccharide accumulates during periods of intake of dietary

sugar by the host, but otherwise it is fermented to lactic acid, and thereby the period when acid decalcification can occur is prolonged. The ability to ferment mannitol and sorbitol serves as an indicator characteristic and is not known to contribute to the development of caries.

Even these streptococci, however, vary widely in cariogenicity; the variation is due in part to differences in the diet and in the strain of test animal. An important factor is variation in the ability of the microorganisms to implant themselves in the particular host on a particular diet. It appears that some streptococci have little ability to synthesize extracellular polysaccharide from sucrose and are consequently unable to adhere to smooth surfaces of teeth. They can nevertheless initiate caries if they are trapped mechanically in pits and fissures of teeth.

Two studies were made in which germ-free rats were infected with streptococci isolated from rampant caries of human patients. Both of the streptococcal strains used in the studies are frequently present in large numbers in the dental plaque of patients having rampant caries. One of the strains did not possess the physiologic characteristics thought to lead to the formation of caries (the ability to ferment mannitol and sorbitol and to produce dextran and amylopectin), but it adapted to the rat mouths, changing antigenically as it did so, and produced caries, of increasing severity, with increasing frequency in three successive generations of rats. The other strain possessed the characteristics thought to lead to the formation of caries but produced only minimal carious lesions in one generation of rats after 11 months.

As for other oral pathoses, viral infection of cultured cells in vitro has made it possible to study the mechanisms of persistent cyclic infection with herpes simplex virus, which, in man, produces symptoms similar to those of herpes labialis (fever blister, cold sore). Cumulative evidence now shows that, in the in vitro studies, infection of cells with herpes simplex virus remains inapparent or becomes manifest according to fluctuations of an equilibrium wherein the cells first become resistant to the cytopathic effect of the original virus and then induce an increased pathogenicity of the virus. This cycle is accompanied by a subtle change in the antigenic specificity of the virus, and can be repeated. It seems possible that the viral changes result from incorporation of a portion of the host cell's genome into the virion.

Parallel studies of recurrent aphthous ulcerations (canker sores), a common debilitating and painful oral disease of unknown etiology, also have progressed, with encouraging results. A recent finding of significance is the presence of a transitional L-form of an alpha streptococcus not only in the oral tissues of several patients having the disease but in the blood stream as well. This organism was consistently recovered from lesions in numerous patients repeatedly examined over a 12-month period. Both human and animal studies have indicated that hypersensitivity to the antigens of this organism is an important factor in the development of the lesions. Currently, attempts are being made to develop a specific antiserum.

Studies in Mineralized Systems

The mineral components of enamel, dentin, and bone, as well as the processes of mineralization and demineralization in normal and abnormal states, have long been a central concern of dental research. Current activity in these areas is widespread and exploits a wide variety of technical approaches.

Without question, the presence or absence of fluoride in the apatite crystallites of enamel is the most important of the environmental factors so far identified as influencing the caries-forming process. In recent years research has focused on the still obscure mechanism by which the fluoride ion renders the crystalline structure of enamel less susceptible to attack. It has recently been established that the lat-

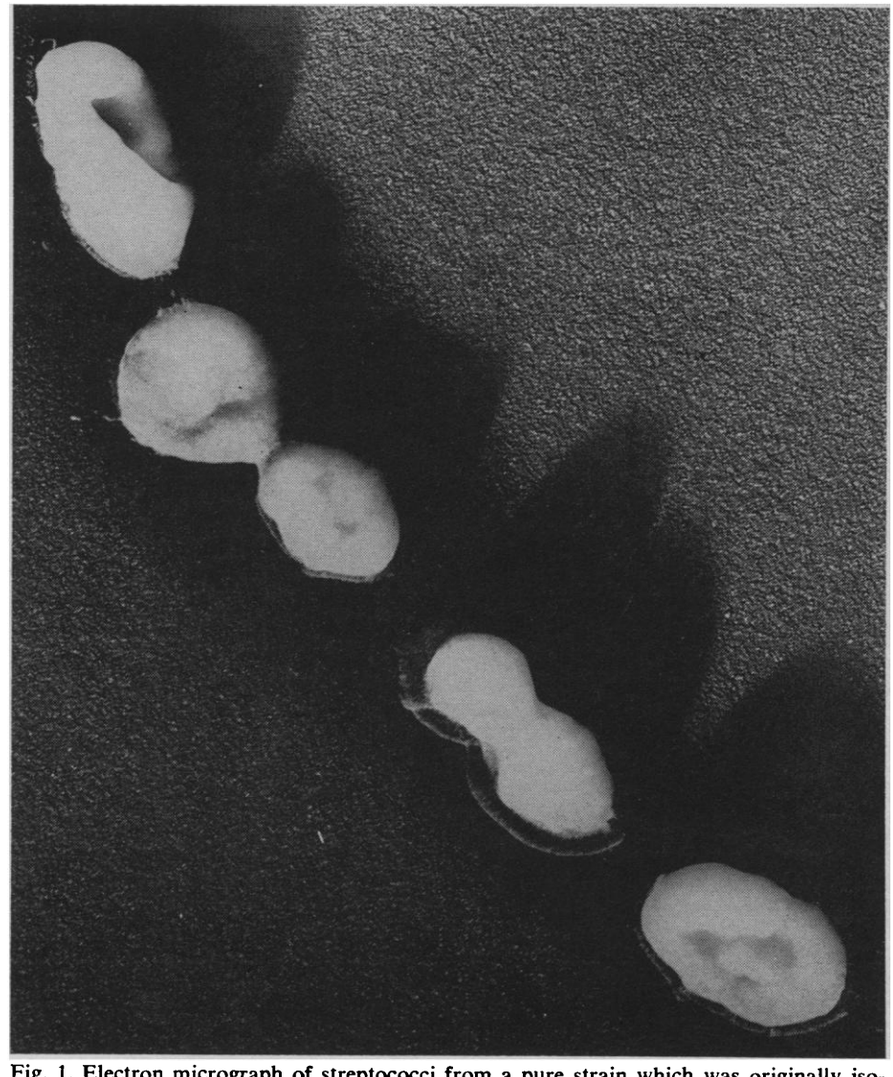

Fig. 1. Electron micrograph of streptococci from a pure strain which was originally isolated from carious tooth structure in the conventionally maintained laboratory rat. The bacteria shown here were grown in a culture tube, centrifuged out of suspension, washed, placed on specimen grids for electron miscroscopy, and shadowed with palladium to accentuate their structural detail (about × 37,000.) These are the organisms with which germ-free rats were inoculated, and which gave rise to dental caries.

tice perfection (crystallinity) of enamel improves with increase in fluoride content, and that it is this more perfect structure that renders the enamel less soluble in acid. Also, the increased perfection achieved in enamel is not solely a function of lattice *a*-axis direction, as is the case in bone, but may be related more importantly to the *c*-axis.

Examination of synthetic fluoride-containing calcium phosphates by x-ray diffraction and infrared spectrophotometry has shown that hydrogen bonding takes place between hydroxyl protons and fluoride anions during the transition. These observations suggest that the hydroxylfluorapatite may be slightly more stable chemically than the hydroxylapatite, as well as more resistant to acid.

Morphological studies of human enamel have provided valuable new data, contributing to a fuller understanding of its prismatic structure and the spread of the carious process. While earlier studies dealt with subsurface enamel, recent efforts have focused on the surface layer because of its apparent greater resistance to decalcification. In early carious lesions a seemingly intact surface layer frequently covers an area of extensive subsurface demineralization. In addition to such chemical differences as a higher fluoride content in the surface layer, morphological differences have been demonstrated in both deciduous and permanent teeth. A major distinguishing characteristic is the extension in permanent teeth of striae, which terminate at the surface of the enamel. These striae have been implicated in the spread of caries. Further study is needed, however, to determine whether the surface layer affords any real protection in permanent teeth.

Collagen in bone and teeth is normally calcified, and elastin in aortas may become pathologically calcified. The mechanisms by which these proteins initiate calcification are being studied. The addition of fluoride to an in vitro system has been shown to inhibit mineralization of the elastin. This is consistent with the suggestion that fluoride regulates the delicately balanced mineralization system by inhibiting deposition of the rapidly forming, initial mineral phase and becoming incorporated in the more slowly forming, stable mineral of bone.

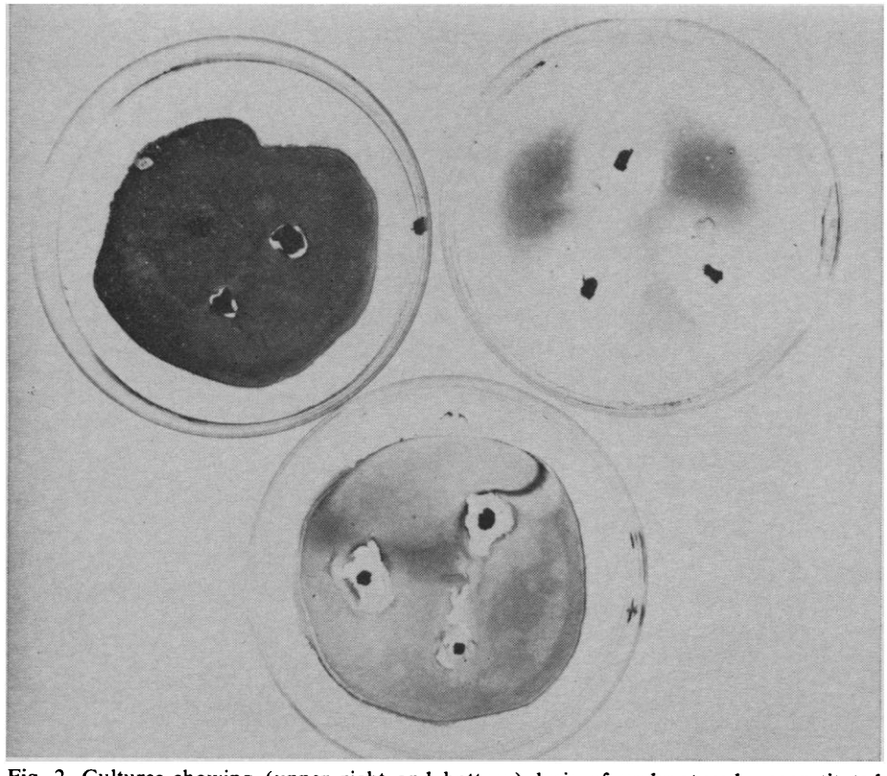

Fig. 2. Cultures showing (upper right and bottom) lysis of undenatured, reconstituted collagen gels by endogenous collagenase from skin-biopsy material from patients with amyotrophic lateral sclerosis, compared to (upper left) activity in normal skin. The specimens were incubated for 7 days at 37°C in a mixture of carbon dioxide and air (5 parts to 95 parts). The clear areas surrounding the biopsy skin samples indicate local dissolution of the collagen gel consequent to collagenase activity. In normal skin the activity is minimal. [Courtesy H. M. Fullmer]

Research on Connective Tissue

Periodontal disease (pyorrhea), which progressively destroys the periodontal ligament and alveolar bone surrounding the roots of the teeth, is the chief cause of tooth loss among adults. In studies of the formation and destruction of connective tissue, a recent clue now implicates the enzyme collagenase in the destructive process. Impressive degrees of endogenous collagenase activity have been found in gingival tissue under normal conditions, and strikingly increased concentrations of the enzyme have been found in biopsy samples from patients with periodontal disease. The collagenase detected appears to be that involved in the normal metabolic turnover of collagen. Work is progressing on the further purification of this enzyme, derived in quantity from cultures of human gingiva and, more recently, from human granular leukocytes.

Concurrent studies have revealed a low but significant level of collagenase in normal human skin, again with striking elevations associated with certain systemic disorders, such as amyotrophic lateral sclerosis (Fig. 2). Recently, collagenase and hyaluronidase activity has also been demonstrated in diseased human gingival tissues and in synovia from patients with rheumatoid arthritis.

Another aspect of this research focuses on the structure of the collagen molecule. Most studies of collagen have been confined to soft tissues, particularly skin, from which collagen in natural form can be readily extracted. Insoluble collagen, however, is of unique interest, since it comprises the predominant organic substrate of bone and dentin. Denatured collagen in bone has been shown to be generally similar to collagen in soft tissues, but it is highly cross-linked, a fact which accounts for its insolubility. Bone collagen from animals fed one of the lathyrogens, such as β-aminopropionitrile, does not cross-link normally and is much more readily extractable than collagen from normal animals. Studies to date indicate that collagen isolated from the bones of lathyritic chicks is similar to skin collagen in amino acid composition, denaturation temperature, and chromatographic properties.

Standard techniques have been applied to determine amino acid sequence in peptides derived from cleavage of α-1-chains. The sequence in one peptide containing 36 amino acids has recently been completely determined. Of particular interest is the finding that, al-

though hydroxyproline, which is formed from proline after assembly of the α-chains, occurs only in certain positions, hydroxylation at a given position is not necessarily complete. Furthermore, the extent of hydroxylation of a given prolyl residue is not always the same in the peptide from collagen of rat tail tendon as in the peptide from collagen of rat skin, although the amino acid sequence is otherwise identical. This difference may account in part for the specific properties and functions of collagens in different tissues of the same animal.

Studies in Growth and Development

In the United States, one of every 750 children is born with a cleft lip or cleft palate. Research has focused primarily upon rehabilitation of these children by means of better surgical and dental management, improved speech therapy, and other measures. Only recently has an effort been made to understand the causes of clefting as a step toward prevention.

One approach to this problem is through experimental teratology. In studies of etiologic mechanism in congenital defects of the oral region, attention has been directed to the oral manifestation of drug-induced malformations, particularly to cleft palate.

Recent emphasis has been focused on the teratogenic action of the ataractic agent chlorcyclizine. Studies have shown that norchlorcyclizine, a demethylated metabolite, is the form of the drug that is active in the production of malformations. Preliminary administration of homochlorcyclizine, a nonteratogenic analog of chlorcyclizine, sharply reduces both the tissue concentration of norchlorcyclizine and the incidence of cleft palate in rats. Simultaneous administration of an inhibitor of demethylation reaction and a teratogenic dose of chlorcyclizine reduces both the tissue concentration of norchlorcyclizine and the incidence of cleft palate. These studies clearly demonstrate the possibility of modifying an undesirable action of a drug while retaining its desired pharmacological activity.

Evidence that cleft palate can arise as a secondary response to disparate primary defects has been provided by a histological comparison of the aberrances produced in the developing rat palate by chlorcyclizine (Fig. 3) and by excessive doses of vitamin A. Chlorcyclizine inhibits the rotation of the palatal processes to the horizontal position, while excessive amounts of vitamin A inhibit their development. In both cases, abnormal form and function result.

There is no evidence that any outside factor causes clefting in man. Twenty to 30 percent of children born with the defect have a family history of clefts. However, some factor other than inheritance must be involved, since, when a cleft appears in an identical twin, there is only a 40-percent chance that both children will be affected. Epidemiology and genetics continue to be of primary importance in the search for a better understanding of this vexing problem. Complicating the picture is evidence that oral defects are not inherited as separate entities. It has been shown, for example, that a hereditary form of abnormal tooth calcification (dentinogenesis imperfecta) is associ-

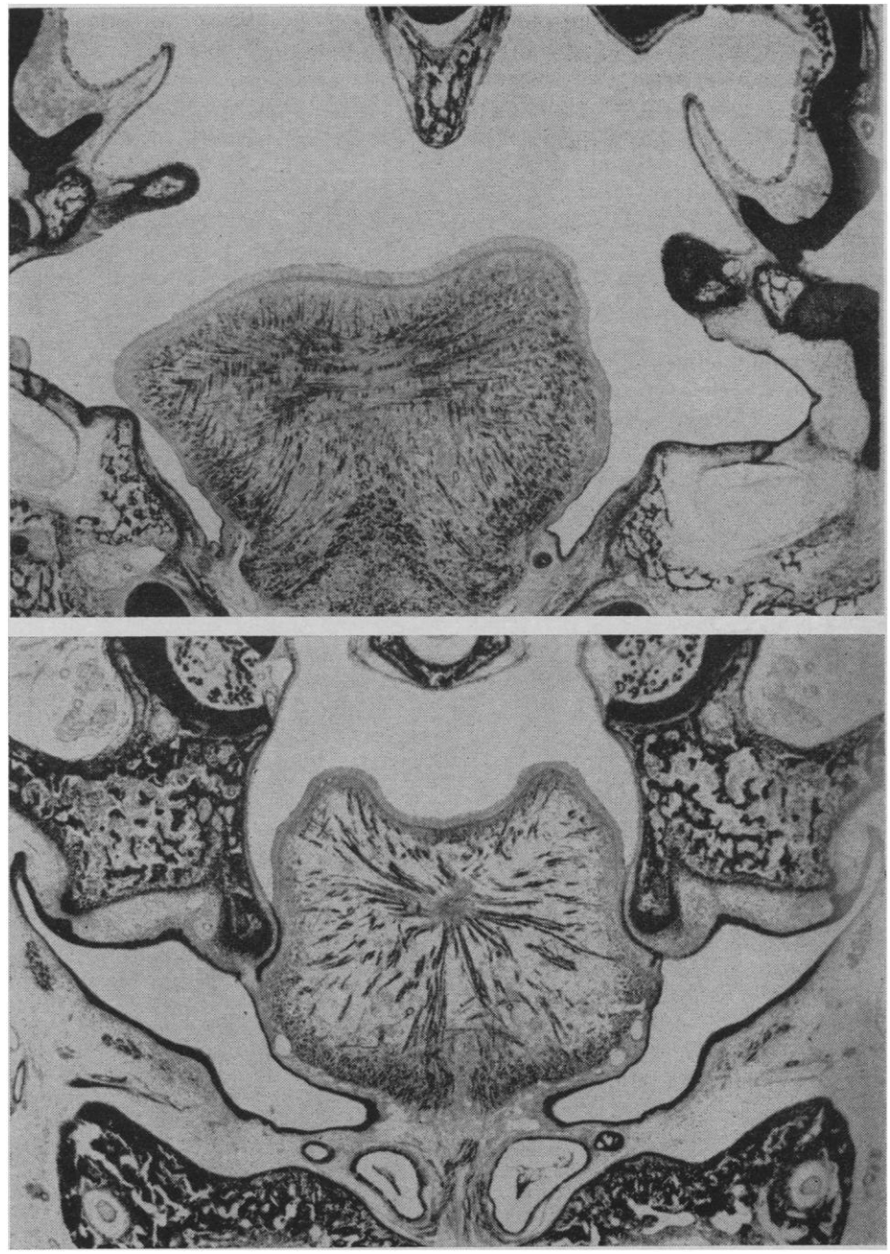

Fig. 3. (Top) Frontal section of the palatal area of a 20-day fetus from a pregnant rat previously given large doses of vitamin A, showing the persistence of ectopic chondrogenesis and the inhibition of palatal development, factors which resulted in a cleft palate. (Bottom) Frontal section of the palatal area of a 20-day fetus from a chlorcyclizine-treated rat, showing (i) well-developed intramembranous osteogenesis in the maxillae and (ii) vertically oriented palatal processes, factors which resulted in a cleft palate. [Alcian blue–PAS (periodic acid-Schiff-hematoxylin) stain; about × 32; courtesy A. J. Steffek]

ated with other defects of a systemic nature, such as deformities of the ears, sickle-cell anemia, cataracts, and circulatory disturbances.

Recent investigations indicate that a derangement in vitamin D_2 metabolism during pregnancy may be responsible for the cardiovascular anomalies of the supravalvular aortic stenosis syndrome, especially when this is associated with idiopathic infantile hypercalcemia. Peculiar "elfin" facies and dental anomalies, especially malocclusion, are reported to be common features of this syndrome. Various developmental defects of the craniofacial complex have now been observed in 77 percent of the offspring of rabbits given, during pregnancy, large doses of vitamin D_2. These anomalies included high palatal vault, dysgnathism, dental cross-bite, and hypoplastic incisor teeth.

Bioengineering Research

As used here, the term *bioengineering* is defined broadly to mean the interface which exists between dental research and the work of a wide range of engineers, physicists, and chemists. While the greatest emphasis remains in the area of materials science, there are many varied and important applications of telemetry to studies of oral health and dysfunction.

The primary functions of the mouth are mastication and speech. Both involve motion of the oral structure in very intricate and purposeful patterns. Dysfunctions of the neuromuscular system of the mouth not only impair chewing and speaking but also contribute to deterioration of oral and general health. Today, telemetry is providing a better understanding of oral neuromuscular function in health and disease. Intraoral and extraoral electromyographic techniques are being used to demonstrate the contributions of individual muscles and muscle groups to jaw movements. There is a further need for instrumentation which will record three-dimensional motions and will reproduce their direction, magnitude, velocity, and force. Also needed is an array of microprobes which can be placed in the mouth over a long period to register various changes in the oral environment. Similarly, smaller and more refined intraoral monitors must be developed for more effective studies of normal and pathologic speech.

Since tooth enamel cannot repair itself once it is destroyed through dental caries or trauma, a substitute material must be used for replacement. The requirements for such a material are demanding. It must be capable of withstanding wide and rapid temperature changes and heavy loading pressures, be resistant to corrosive action of food and bacteria and their degradation products, be nonsoluble in saliva, and be esthetically acceptable. Moreover, its use in dental work should not require unreasonable time and skills, and its cost must not be prohibitive. Although significant progress has been made toward meeting these requirements, dental treatment continues to be less than ideal, because of the limitations of available materials.

The primary need today is for an esthetically acceptable adhesive restorative material which is plastic but hardens quickly at mouth temperature and bonds tightly to enamel and dentin in the presence of moisture. Such a substance would require minimum preparation of the tooth, and its availability would substantially reduce the cost of dental care. Hope that some such ideal material will be developed may appear unrealistic until one considers the natural cements produced by some marine plants and by marine animals such as the barnacle. The natural cements form as a liquid, harden under water, endure wide temperature changes and heavy stresses, last for years, and attract minerals from sea water so that the attachment area increases with time. If such cements can be analyzed and the mechanism by which they harden under water can be explained, it should be possible to make similar substances suitable for permanent restoration of teeth. Some assistance in seeking the ideal material can be anticipated from the field of space technology. Great emphasis has been placed on materials science in preparation for orbital flights, long-range space travel, and lunar landings. Consequently, workers in the dental physical sciences are closely monitoring the progress of the space program.

The loss of even a single tooth disrupts the continuity of form and function of the total masticatory apparatus and leads to a sequence of inflammatory and degenerative changes that threaten the remaining teeth. At present the replacement of missing teeth through fixed restorations is expensive and time-consuming. The immediate insertion of a plastic replica directly into the socket following extraction of a tooth would be a relatively simple and economical procedure. Research on implantation is now receiving greater attention, following promising results in experiments in which plastic teeth implanted in baboons have served for as long as 6 years.

Until research leads to more effective control of dental disease, a large segment of the population will continue to require intraoral prosthetic appliances. Currently, over 20 million Americans, including half of all citizens over the age of 55, have lost all their natural teeth. The acrylic resins upon which they depend for their comfort, health, and social well-being leave much to be desired. More emphasis must be placed upon increasing the soft-tissue tolerance of prosthetic materials now in use. Extensive resorption of bony tissue underlying dentures is common in patients who have been edentulous for several years. Investigators are trying to develop improved materials and surgical techniques for placing implants in the jaws, thereby providing stable abutments upon which dentures may be seated.

Relation of Oral and Other Biological Systems

In the foregoing description of some of the current research in oral biology, many biologists will recognize relationships to their own investigations. The observations that follow emphasize these relationships still farther.

Nutritional deficiencies commonly affect oral tissues and are frequently manifested early in the mouth. In one study, for example, 36 percent of 914 patients hospitalized because of nutritional problems had pain of the oral soft tissues or a loss of tongue coating, or both, as the primary symptom. The lengths of the filiform papillae which comprise most of the covering of the tongue depend upon the constant and rapid proliferation of epithelial cells. An interruption of a systemic metabolic process affecting cell replication may, then, be first manifested clinically as a loss of tongue coating. It is reasonable to speculate that, with the advent of increasingly sophisticated microanalytical techniques, scrutiny of small but readily available biopsy specimens from the mouth will prove useful in diagnosis and therapeutic assessment in a variety of abnormal systemic conditions.

Already applicable in an analogous fashion are studies in oral exfoliative

cytology—the microscopic observation of cells from the surface of the oral epithelium which are scraped free with an instrument or are sloughed into the saliva. Such cells provide a ready source of material for chromosomal studies of all types. This approach was the basis for sex determination of the female athletes at the recent Olympic games in France. An evaluation of the nuclear dimensions of oral epithelial cells has provided an accurate measure of systemic response to treatment of pernicious anemia.

Diabetes mellitus is a complex disease of great interest to the dentist. The clinical management of periodontal disease cannot be achieved in a patient with uncontrolled diabetes. It has also been shown that the average dosage of insulin required to control blood glucose levels in patients suffering from both diabetes and periodontal disease is significantly decreased following periodontal therapy.

The hormonal changes associated with pregnancy result in an exaggerated response of the periodontal tissues to even minor sources of irritation. Thus, gingivitis (gum inflammation) and benign overgrowth of the gingivae complicate the pregnancy of many women. Paradoxically, women with dermatologic conditions involving the mouth or with chronic ulcerative disease of the oral mucosa frequently experience a marked improvement in these conditions when they become pregnant.

In studying systemic responses to the many agents which enter the body through the mouth, little attention has been directed toward absorption through the oral mucosa as a primary portal to the systemic circulation. That such absorption is recognized to occur, however, is evidenced by the fact that standard emergency treatment of the cardiac patient with anginal pain is the placing of a nitroglycerin tablet beneath the tongue. To what extent is such absorption involved in the short- and long-range response to tobacco? How are agents altered in the process of absorption? It has been established that one of the most effective ways to elicit a systemic allergic response to a drug is through topical application on oral tissues.

Within minutes following each tooth extraction or other surgical procedure in the mouth, oral bacteria can be isolated from peripheral blood. The bacteremia usually involves nonpathogens and is transient. At present this common phenomenon is believed not to have great significance except in patients with heart-valve damage resulting from previous rheumatic fever or in those who have had open-heart surgery. In such patients the bacteria tend to lodge and multiply on the damaged valves or altered endocardium, an event with such serious sequelae that medication with antibiotics is an absolute necessity.

It appears likely that there are other, less obvious but more complex, implications of this bacteremia, which is currently viewed as a routine event in daily practice. Evidence already exists linking the treatment of dental disease to subsequent kidney disease.

Dilantin sodium is the drug most commonly used for the control of epilepsy and other disorders of the central nervous system which result in convulsive seizures. The most significant side reaction to such treatment is an overgrowth of the connective tissue of the gingiva, which occurs in a large percentage of patients. It has been shown that a very substantial increase in collagenase activity of the involved connective tissue occurs. This connective tissue appears not to differ from that of many areas of the body except in its response to dilantin.

Malignancies of the oral cavity constitute approximately 5 percent of all cancer. The vast majority of these malignancies are epidermoid carcinomas which are characterized by a lack of pain and a tendency toward early metastasis. Probably as a result of the rich vascularity of oral tissues and their high mobility, spreading to regional lymph nodes may occur while the initial lesion is very small, measurable in millimeters. Death usually occurs before metastases spread below the clavicles. Treatment of oral cancer commonly results in disfigurement and interference with speech and swallowing. The primary hope for the patient with oral cancer lies in early diagnosis. Readily accessible tissues of the mouth offer an excellent opportunity for the oncologist to study precancerous lesions and malignant transformation. A large percentage of oral cancer develops in or from whitish, raised, hyperkeratinized areas of the mucosa. Clinical experience suggests that up to 30 percent of these rather common lesions, which develop in response to chronic irritation, may undergo malignant transformation in a 5-year period. Much effort has been directed toward study of the development of oral cancer in the cheek pouch of the hamster, where experimental cancer can be induced chemically by means of well-standardized and carefully controlled techniques.

For many years, dental researchers have been interested in the techniques and immunology of tooth transplantation in anticipation of the day when tooth storage banks may exist in many cities. Autogenous transplants—the transplantation of teeth within the same jaw—can now be accomplished with a high degree of success. Homologous and heterologous transplants, however, are rejected in most cases, as a result of the immune reaction. Teeth retain their antigenic properties even after being rendered nonvital by removal of the pulp and treatment with root-canal-filling materials.

There is good evidence that, if the components of saliva from healthy patients were known and the normal ranges of each component were established, saliva, like blood, could be a useful indicator of some aspects of systemic health. It has been shown that the chemistry of saliva from submaxillary glands in animals and humans can be altered by treatment with guanethidine but not by treatment with other drugs known to block the fibers of the sympathetic nervous system. This drug temporarily improves the chemical balance of organic components of submaxillary-gland saliva in children with cystic fibrosis without changing the concentrations of calcium, sodium, and potassium.

Challenges of the Future

Within the scope of this article it has not been possible to adequately cover the entire field or fields of research related to dentistry. By highlighting selected areas, we have made an effort to show that the base of the dental sciences is broadening. All who have participated in the progress of the past 20 years look to the future with optimism and excitement. Clearly, however, the potential for success and accomplishment is directly related to the potential for adding to the pool of scientific manpower in dental research and related fields. A serious manpower problem undeniably exists, and a high priority must be placed on seeking a solution.

One evidence of the escalation of manpower needs is the fact that approximately 23 dental schools are being expanded and seven new schools are in

various stages of development. The total capacity of the training programs currently supported by NIDR falls far short of meeting the immediate needs of even these expanding and new schools. The problem is not merely one of inadequate numbers, since in these training programs there is also maldistribution of students among the various science disciplines. Of the 316 individuals in these programs who are currently being trained in the basic sciences, only two to six are in each of such shortage areas as embryology, endocrinology, pharmacology, radiation biology, epidemiology, genetics, and biophysics. A correspondingly serious deficit exists in the very important discipline of biostatistics.

Further stimulation of dental-science-related research depends on the assembling of a critical mass of scientifically trained individuals who can stimulate and enrich one another and attract others to work with them. Toward this end, NIDR has begun to develop interdisciplinary, university-based dental research centers in several sections of the country. While these centers will serve as critical foci, parallel efforts are needed in order to provide a stronger scientific base in every dental school. The unqualified acceptance of research as part of the responsibilities of the dental academician must be encouraged.

Scientists from all disciplines basic to oral health must be challenged and, made aware of the needs and opportunities in the field of oral research, and thereby enlisted in the effort to meet these needs and opportunities. Indeed, such enlistment is one of the primary aims of the dental research centers program. All scientists must be made increasingly aware of the implications of their work for dental research. It is only through such combined efforts that appropriate depth can be added to the breadth that has been achieved in the dental sciences during the past 20 years.

NEWS AND COMMENT

The Draft: Grad Schools, Students Feel Impact of New Regulations

The curtailing of draft deferments for graduate students has caused considerable alarm among graduate school administrators. There are plenty of rumors about how University X will lose substantial numbers of graduate students, including teaching and research assistants, while University Y has supposedly devised an ingenious, if questionable, way to protect its teaching and research assistants from the draft. The true impact of the new draft regulations will not be assessable until the graduate schools reopen next fall, or perhaps even later. But a telephone survey by *Science* has turned up evidence that the new regulations have already had an adverse impact on scattered departments and graduate schools, as well as a pronounced influence on the volume of student job interviews. And while no graduate dean volunteered the information that he has devised an ingenious draft dodge for his teaching assistants, the survey did turn up a heated controversy about the propriety of a letter pertaining to the draft sent out by the physics department at Cornell University.

The alarm in graduate school circles stems from two recent draft decrees. The first ended deferments for graduate students except those in medical specialties and those who entered their second or subsequent year of graduate study in the fall of 1967. The second continued the policy of drafting the oldest eligible men first. The combined result of these two rulings is that men who are currently in their first year of graduate study and men who will graduate from college this June and will be entering the first year of graduate school next year are prime candidates for the draft. One survey of 122 graduate schools predicts that first-year graduate enrollments next year will decline by 50 percent or more, while the number of full-time second-year graduate students may drop by one-third. Indeed, some graduate deans are predicting nothing short of "disaster." They say the expected drop in graduate enrollments will hurt both the graduate schools, which will be faced with fewer students and a sharp drop in income, and the undergraduate colleges, which often depend heavily on graduate students to serve as teaching assistants in undergraduate courses. Professors who depend on graduate research assistants may also be adversely affected.

At this point it's difficult to find hard evidence indicating whether the graduate schools are "crying wolf" or whether disaster is, indeed, just around the corner. Gustave O. Arlt, president of The Council of Graduate Schools of the United States (CGS), reports that a recent sampling of various kinds of institutions throughout the nation revealed that applications and acceptances for graduate school next year are running about 10 percent ahead of last year, which is in line with the annual increases experienced over the past 5 or 6 years. Arlt notes that "on the surface everything looks perfectly serene and all right," but he wonders how many of those who have accepted graduate school positions will actually show up and how many of those who do show up will be drafted by the end of the school year. The great bulk of college seniors and first-year graduate students will not become vulnerable to the draft until the end of the current academic year, so many who had planned to attend graduate school next year may find they are drafted this summer.

The new draft rules have clearly affected graduate acceptances at some institutions and in some departments, particularly the sciences and engineering. At Iowa State University, the physics department thought it had 25 firm acceptances of fellowships or teaching assistantships, as of 15 April, but 10 of the 25 subsequently changed their minds and said they intended to get jobs or pursue other activities that might make them less vulnerable to the draft. At Indiana University, applications to graduate school dropped about 30 percent below last year's level, presumably at least partly because of student uncertainty over the draft. At