18 December 1959, Volume 130, Number 3390 SCIENCE

Dentistry at Its Centennial Crossroads

Prevention is the only rational solution to dental health; basic science, the only hopeful approach.

Reidar F. Sognnaes

Dental disease is now practically everybody's disease, and a great many people have begun to wonder what dental health, and the dentist bills, are coming to. Currently, we are seeing the dentist to the tune of over $1600 million per year, about one-sixth of our nation's total expenditure for health. If this sounds high, consider that there are nearly 100,000 dentists in the United States, yet that only one-third of the damage to our teeth is being repaired. Many communities are without dentists. Many families are dentally indigent. There is an estimated backlog of 700 million unfilled cavities in our population. Seventy percent of those over 35 years of age are in need of bridges and dentures because of teeth already lost or damaged beyond repair. With our people's increasing life span, the dental needs of the aged are growing steadily. It would take 250,000 dentists working for 10 years merely to eliminate the present backlog of common dental defects.

Even if we had enough dentists to do the job (there are no such resources in sight), the out-of-pocket cost of dental repairs would be only a fraction of the real cost. What should we allow as the value of working-time lost, pain endured, productivity cut, merely because of going to the dentist?

Today's dental researcher, however, is trying to discover the basic biological factors in dental health and disease. He uses innumerable refined research techniques of modern biological laboratories, exploring the new vistas disclosed by the electron microscope and the secrets revealed by tooth-and-bone-seeking radioisotopes. He is trying to find out how teeth and bones develop; how saliva affects the teeth; how gums and teeth give clues to bodily health and biological aging; how certain rare food elements affect oral conditions.

Notwithstanding this broadening scope of dental science, we are still merely scratching the surface of the problem. Modern dental technology, developed over the past century, is so good that people who can command the best have come to reconcile themselves to fillings, bridges, and plates, to pain and discomfort endured, to time lost and money spent. For the rest of the population and for the new generation, conventional repair will not solve the problem. Prevention is the only rational solution, research the only hopeful approach.

Increasing Support of Research

The recent history of the health sciences gives excellent assurance of positive developments. We have seen as much progress as one could ask for in return for our limited investment in dental science. For example, in the mid-twenties only 12 American dental schools out of the 43 then in existence had any funds at all earmarked for scholarly pursuits—a total of $41,270 for the entire country, an average of less than $1000 per year per school. Today, most of our 47 dental schools are in a position to conduct research. In the whole nation there are currently at least 500 active dental-science workers who have initiated various research projects basic to dental health.

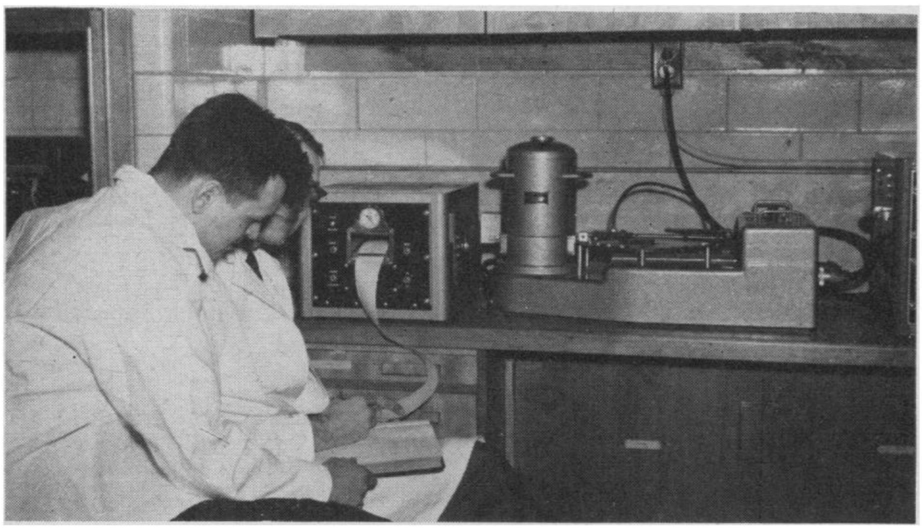
Behind much of this encouraging growth is the federal government. In Bethesda, Maryland, 50 of the 1000 doctors working in the National Institutes of Health are now engaged in work in dental science; 25 of them are dentists, the other half, Ph.D.'s working in the National Institute of Dental Research (NIDR).

This program began just ten years ago, when the newly created NIDR sponsored research fellows in six extramural dental institutions, at a cost of $33,000. Little by little, additional funds were provided for specific research projects in dental schools. By 1958, the NIDR made a total of nearly 300 extramural grants, amounting to about $2.5 million dollars for the nation's dental research effort. Dental schools themselves finance some additional research. But even today the funds for scholarly pursuits are relatively limited, by modern standards of health education and research. The total endowment of the 27 privately supported dental schools in the United States is less than $10 million. Student tuition and dental-clinic fees are the principal sources of support. And yet, in the long view, what is especially encouraging about all this is the fact that a certain amount of dental research now has become a normal day-to-day activity in nearly all of our dental schools. Furthermore, many other scientific institutions—state, private, and industrial—are beginning to concern themselves one way or another with some aspects of research related to dental health and disease.

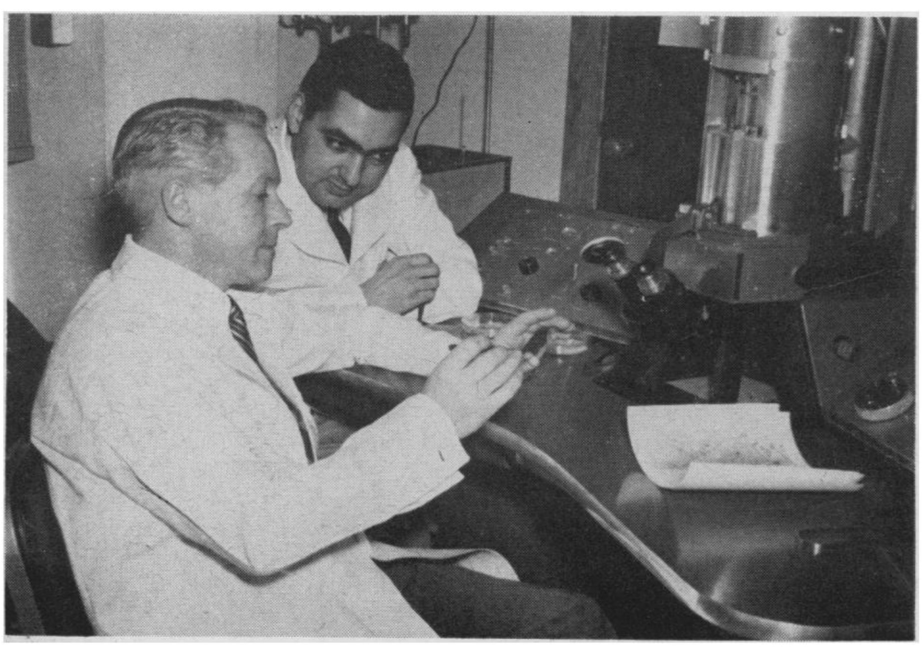
At the same time, today's technological developments for saving teeth are

The author is Charles A. Brackett Professor of Oral Pathology and acting dean of Harvard University's School of Dental Medicine.

being improved each year. The electric drill has been a boon to mankind in comparison with the treadle-operated drill of not too many years ago. Today, ideas for developing new "drills," more efficient and less painful, designed to operate on three completely different principles, are being explored. The air-brasive drill, in effect a miniature sand-blasting machine, was the first new approach (it proved to be not quite what the doctor ordered!). The ultra-sonic drill, next in line and still in limited use, cuts into a tooth by vibrating an abrasive slurry against it at a very high frequency. The "jet"-propulsion drill, now on the horizon and showing perhaps the greatest promise, does its work by means of compressed air, or by a rapid stream of water, which turns the drill mandrel at speeds exceeding 200,000 revolutions a minute. In fact, even the electric motors are being revolutionized to provide increased speed, effectiveness, and painlessness; and in place of drill points of simple steel we now have carbide and diamond-tipped burs, stones, and wheels.



New clues to biochemical interference with dental disease are now being sought through the use of tooth- and bone-seeking radioisotopes, here being traced with a Geiger counter in a wing of the radio-biology laboratory, initiated by the Atomic Energy Commission, at the Harvard School of Dental Medicine.



Sponsored by the new dental teacher-training program of the National Institutes of Health, a dental research fellow and staff sponsor at the Harvard School of Dental Medicine explore, with the aid of the electron microscope, the microstructural response of oral tissues to biological aging.

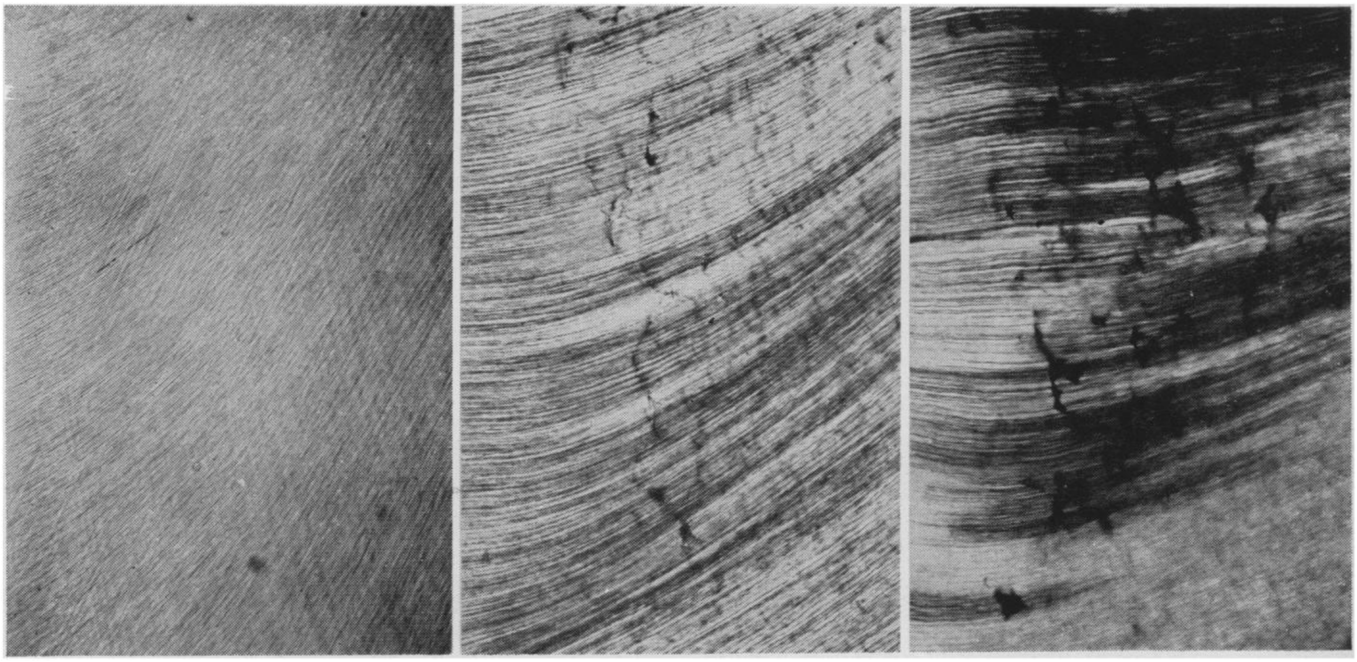
Together with this progress in the preparation of teeth for restoration have come techniques for making extremely fine-grained and accurate casting of inlays, crowns, and bridges; new and better dental alloys; new acrylic and other dental plastics; and countless other new appliances and materials. Last year the American Dental Trade Association was told that up to 80 percent of current sales of dental equipment and materials were products which only seven years before had been research curiosities.

But even in some of the technological areas of dentistry there are still gaping voids. For instance, we need a very much better material for the so-called silicate fillings which most dentists and patients prefer for conspicuous cavities in the front teeth. Such fillings are, to be sure, almost indistinguishable from the natural tooth. Unfortunately, that is their principal virtue. The silicate filling material is comparatively brittle and soluble in the mouth; it is not particularly friendly to the underlying tissue; it does not make a genuine physical or chemical bond with the living tooth; and considerable undercutting of the healthy part of the tooth is required in order to anchor the filling.

In today's world no scientist would say that this problem could not be solved. To solve it would be well worth while. It is estimated that our nation spends over $50 million per year on silicate fillings, and that in less than five years, on an average, these will require replacement. If one could do nothing more than double the life expectancy of such a filling material, the saving in money would be a handsome return on the investment in research. Still greater would be the value of time saved and discomfort avoided.

Much of the research in new materials and equipment is now being carried on by commercial organizations, although some schools still do work on the technological level. The National Bureau of Standards and the American Dental Association have to a large extent taken over from the dental schools the function of testing and certifying physical and chemical properties of products offered for use in restorative dentistry.

Nevertheless, the whole structure of standard restorative dentistry is still too much of a mechanical stopgap and not enough of a biological science. In prin-

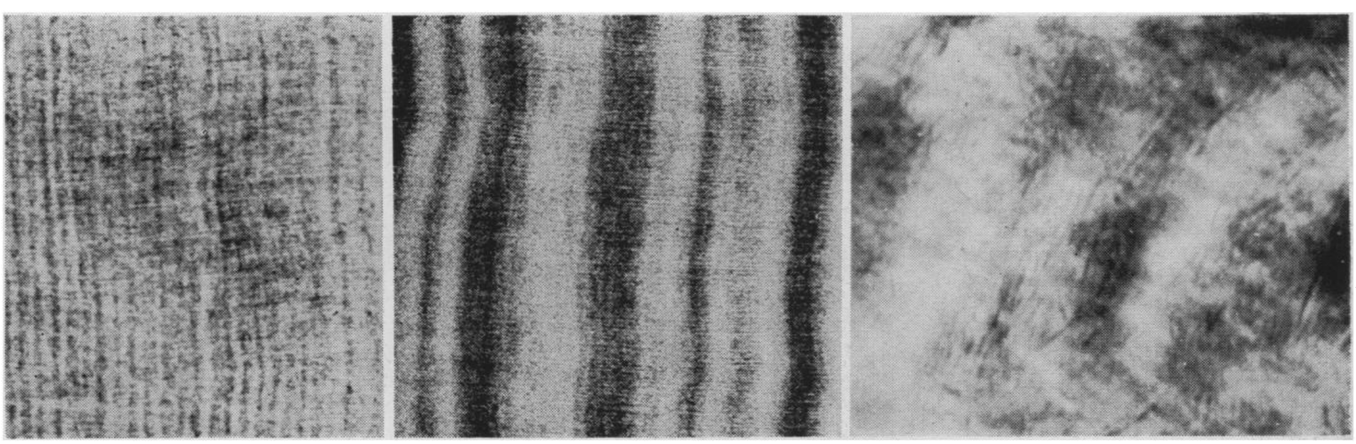


Comparison of the tooth structure of a monkey, an ape, and a man shows deterioration in the developmental quality of dentin, the ivory core of teeth. The rhesus monkey, from India, has beautifully calcified dentin (left). The wild chimpanzee of central Africa has dentin with faulty granular calcification (center). The dentin of *Homo sapiens*, even that in teeth from the prehistoric cave-dwellers of Mount Carmel, Palestine (right), exhibits completely uncalcified interglobular spaces, a widespread defect in modern man.

ciple, the filling of teeth is based on the admission that, within very narrow limits, cavities cannot be healed. A substantial number of cavities can be prevented by the fluoridation of public water supplies—an intelligent step in modern public health that unfortunately is vigorously opposed by a "militant minority." When cavities occur, they cannot be reversed. Treatment still must consist in removing healthy tooth substance far beyond the area of decay ("extension for prevention") in order to limit the inevitable recurrence of decay. But must we resign ourselves to endless retreat and rear-guard fighting? Can't we take the initiative and attack the enemy before he attacks our teeth?

Broadening Scope of Research

Largely as a result of recent federal research support, we have learned a good deal about the most common of the oral diseases—the most common of all diseases—tooth decay. Now cavities can be induced at will in laboratory rats for more precise study of cause and prevention. The old slogan that "a clean tooth never decays" has come under thorough study and has stood up to the most rigorous testing in experiments with germ-free and tube-fed rats. It is only too evident that the conventional oral cleaning approach to the tooth-decay problem has been wholly inadequate. Yet, there is obviously no gaping flaw in our theory. The trouble

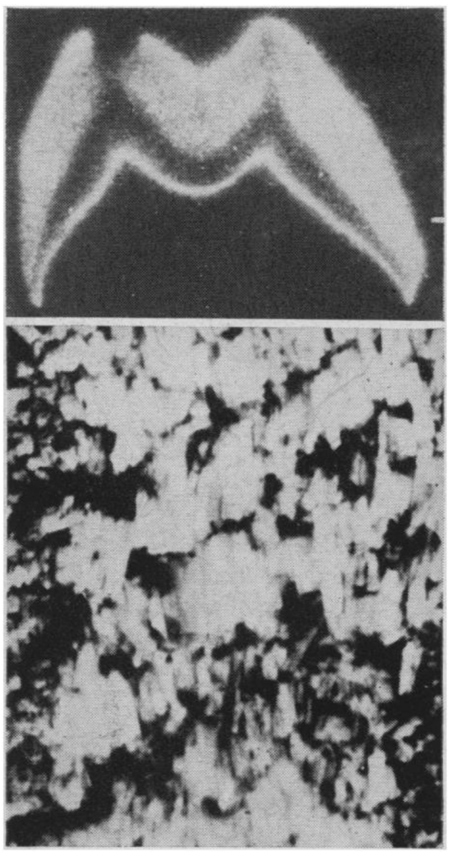


Ivory, big brother of the dentins and first cousin of bone, as seen by means of optical (left), x-ray (center), and electron (right) microscopy. Transmitted light reveals, at left, a regular rhythm of vertical growth lines, whereas the microradiograph in the center shows that ivory is, in fact, subdivided into broad layers of high and low (dark) microdensity, readily seen at a magnification of 100. When much thinner sections of ivory are studied with the electron microscope at a magnification of 200,000 (right), the ultimate inorganic apatite building blocks look like miniature cigars the size of exclamation points, similar to those in other dentin and bone.

seems to be that a clean tooth simply does not, in fact, exist—at least one that is clean from a microbial point of view, and that apparently is what counts. We now have to face up to the prospect of undertaking long-term exploration of other underlying influences on tooth decay—nutrition, genetic factors, ingredients of saliva, and so on.

From circumstantial evidence, we know that saliva is important to oral health. When the salivary glands are destroyed by radiation or removed by surgery, rampant tooth decay occurs very quickly and the gum tissue is more likely to become inflamed. It would seem to be a simple matter to determine the composition of saliva in a normal mouth and compare it with the saliva in a diseased mouth. But unhappily, unlike blood and other body fluids, which have a critical base-line composition readily established by standard methods, saliva fluctuates over a wide range as far as the common body chemicals are concerned. Yet, it is altogether probable that more intensive research may reveal that some unknown ingredient of saliva, possibly organic in nature, is of diagnostic significance and as important to the mouth as blood itself is to the rest of the body. Though we have done some searching, this area is still wide open for research.

We know far too little about the deeper secrets of etiology, pathology, and prevention. A case in point is the condition known as pyorrhea, characterized by inflamed and receding gums, rapid destruction of the jawbone, and the falling out of otherwise useful teeth —a widespread problem in our aging population. It is a curious fact that this disease can occur even in individuals who in other respects seem altogether well, showing no systemic illness even under the most searching diagnostic observation. The long bones of the patient's body may be quite normal, and nothing untoward shows in his organs or body fluids.



Modern biophysical research tools are now being brought to bear upon the hardest tissue of the human body, the dental enamel, which covers the visible crowns of the teeth. (Top) An autoradiograph of the calcifying molar of a monkey, after intravenous injection of radioactive phosphorus, shows distinctly different patterns of phosphate deposition in the enamel and in the dentin (bright inner contour line). (Bottom) Electronmicrograph (× 50,000) of calcified enamel, sectioned with a diamond knife, shows an orderly array of pencil-shaped apatite crystals, much larger in size than those seen in rapidly calcifying ivory, other dentin, and bone. [From joint studies with Dr. James Shaw (top) and Dr. Robert Frank (bottom)]

(Top) The dental clinic of the first university-affiliated dental school, two decades after its establishment at Harvard in 1867. (Bottom) Dental students in clinic at the Harvard School of Dental Medicine today.

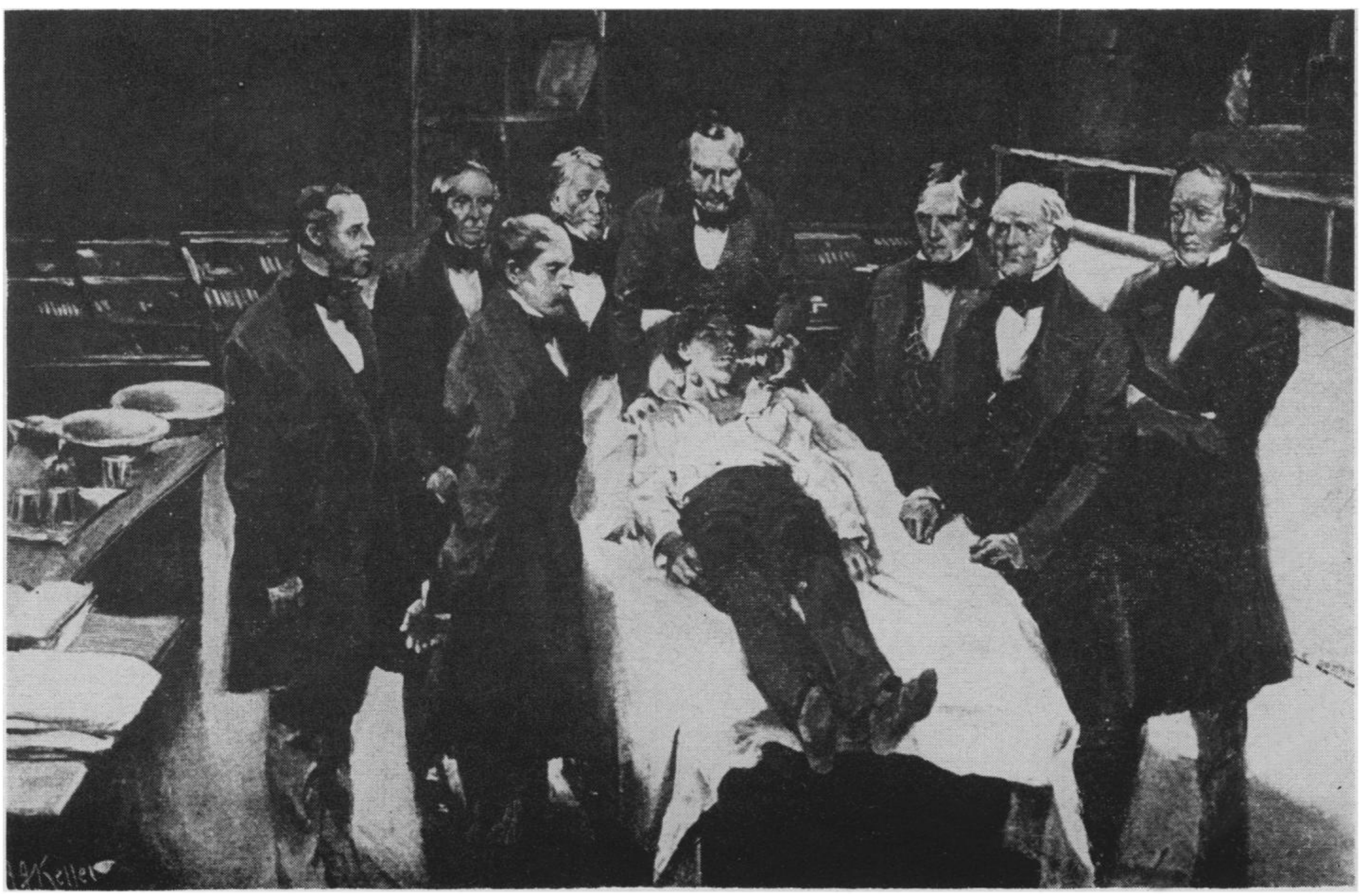
On the other hand, an occasional older person may show signs of skeletal disease, such as osteoporosis—the "Swiss cheese bone" condition that sometimes accompanies menopause—but the bones of the jaw will appear to be unaffected. Yet, sometimes it is in the mouth and the jawbone that the signs of a general bodily ailment, such as the hormonal disease known as hyperparathyroidism, may be first seen. These are but a few examples of the seemingly complex oral health problems that, so far, have defied our limited efforts at control and prevention.

Some aspects of dental research suggest that this is a more difficult field of science than we have thought. The primary site of decay, the dental enamel, "hard as a rock," is unique in the human frame because it is indeed a kind of rock. The enamel appears unbiological in that it is made up of mineral crystals instead of cells; it is so remarkably hard that only a diamond or hardened steel can scratch it. Enamel contains no blood vessels or nerves. It seems impervious to protective body fluids and antibodies from within and, unfortunately, equally unaffected by man-made "wonder drugs" and antibiotics that work directly through blood and cells. Nevertheless—or perhaps *because* of these peculiarities—most people do experience tooth decay, which begins with a pitting of this diamond-hard and impermeable enamel. Once the enamel is breached, a cavity inevitably forms in the dental ivory below. No known bodily process prevents the cavity from growing larger, ultimately infecting the underlying "nerve" or pulp of the tooth and causing abscesses and infections in the jawbone, which occasionally spread beyond the jaw, directly to the adjacent organs or to the valves of the heart. Attainable knowledge could change this course of events.

Steppingstones to Better Health

It is abundantly clear, from the history of the health sciences, that there can be a considerable time lag between the steps through which basic research exerts its full impact upon education and, in turn, upon practice.

The British Royal Society, officially recognized in 1662, was the first to establish opportunities for full-time devotion to scholarly pursuits in basic medical science, albeit with an eye fixed on specific disease problems, notably tropical diseases. The French Academy of Science, which in 1816 became a branch of the Institute of France, stimulated research both in biological and natural sciences. In 1885, Louis Pasteur's work, through the springboard of chemistry, became extended in scope and time by the productive medical research institute named after him, in Paris. The German Koch Institute,

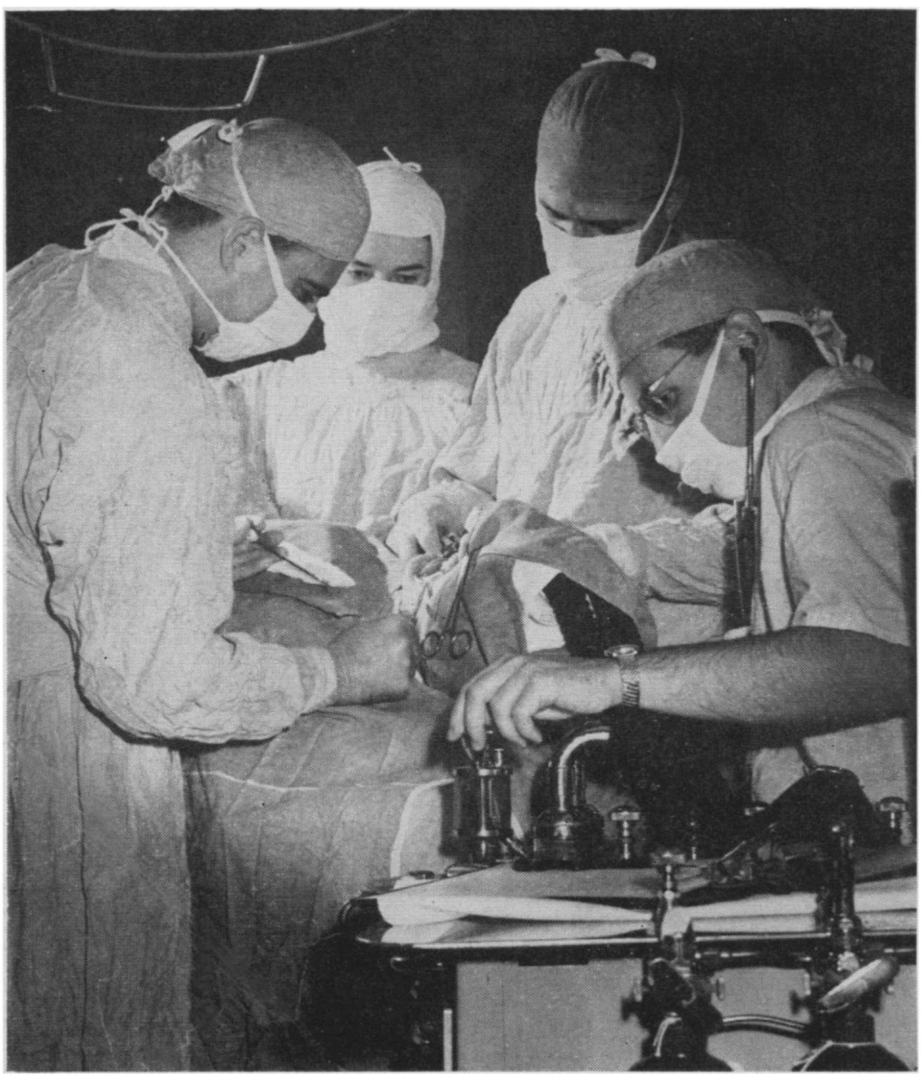


William T. G. Morton, a Boston dentist, giving the first public demonstration of ether inhalation for surgical anesthesia, on 16 October 1846, in the Bulfinch Building ("ether dome"), still a part of the Massachusetts General Hospital in Boston. In the room there now appears the following inscription: "On October 16, 1846 in this room, then the operating theatre of the Hospital, was given the first public demonstration of anaesthesia to the extent of producing insensibility to pain during a serious surgical operation. Sulphuric ether was administered by William Thomas Green Morton, a Boston dentist. The patient was Gilbert Abbott. The operation was the removal of a tumor under the jaw. The surgeon was John Collins Warren. The patient declared that he had felt no pain during the operation and was discharged well December 7. Knowledge of this discovery spread from this room throughout the civilized world, and a new era for surgery began."

in 1891, grew out of the Institute for Infectious Diseases, spurred by the discovery of the causative agents involved in tuberculosis and cholera. Many medical research centers created scholars in Germany (the Kaiser Wilhelm Society), in Sweden (Karolinska Institut), and elsewhere. And in England the Lister Institute (the British equivalent of the Pasteur Institute) concerned itself with basic research as well as with serum and vaccine preparation; the British Medical Research Council Laboratory at Hampstead, with experimental pathology, applied physiology, therapeutic drugs, and biometrics.

In this country the National Academy of Sciences was established during the Civil War to advise on national problems, including health and disease. But it was at the turn of the century that the boldest step toward scientific medicine was taken—the generous endowment of the Rockefeller Institute for Medical Research in New York, in 1901, "for the purpose of research in any field that gave promise of a return in medicine." From the Rockefeller Institute, vital and vitalizing information emerged, covering a wide range of basic medical sciences (biophysics, biochemistry, physiology, experimental and comparative pathology), as well as disease-oriented research (on metabolic disturbances, infectious diseases, experimental surgery, and heart disease).

Not only did these research institutes contribute to the understanding and prevention of disease; they were feeding knowledge worth teaching into medical schools the world over, introducing new concepts and principles that challenged the best intellects. "Over and above this immediate result," Abraham Flexner observed later, "it is something to possess in every country institutions in which earnest men of all races and nations cooperate for ends that obliterate national lines" (*1*).



Modern oral surgery under general anesthesia at the Massachusetts General Hospital, directed by the chief of dental service and attended by students from the Harvard School of Dental Medicine.

Notwithstanding these long and glorious traditions in medical research, Abraham Flexner found little impact upon medical education and practice when, in 1910, he reviewed the countrywide situations in the United States and Canada (*2*). But through his broad insight he could propose remedies for which there were already tested prescriptions.

The teacher-researcher, the physician-scientist, was a well-established entity in the centers of medical learning in Austria, Germany, France, and Britain. In the United States medicine had, in addition to the flourishing Rockefeller Institute for Medical Research, a pioneering university medical school, Johns Hopkins, molded according to the best traditions of medical research, teaching, and patient care known to 20th-century physicians. These were the steppingstones to scientific medicine.

When William Gies, 16 years later, surveyed the status of academic dentistry in the United States and Canada (*3*), he recognized that there had been great technical developments, but he found that for academic standards comparable to the best in medicine, there was no place to look but ahead. There were no research institutes for dental science (our National Institute for Dental Research was established in 1947, its building will be completed in 1961); there was no prototype (comparable to Johns Hopkins) for academic centers of learning in dentistry to show what an environment of scholarship and excellence could do for the educational standards of a dental school; there was not sufficient basic information about the oral cavity to bring biological science to bear upon the teaching of dental students and the care of dental patients.

Can dentistry be expected to progress as medicine has progressed if tested steppingstones are by-passed? Gies did not think so. Thirty years ago, after reviewing the status of academic dentistry in the United States and Canada, he made this recommendation (*3*, p. 237): "In order to strengthen dental education at the point of its greatest weakness, funds sufficient to enable the school to pay adequate salaries must be provided, and suitable means must be devised for the selection and training of the most competent prospective teachers and investigators. Fellowships and special funds are needed to encourage and support advanced study and research by the most promising candidates for whole time teaching positions."

Two significant steps in this direction were taken in 1929, when the Rockefeller Foundation provided equal grants to Yale University and the University of Rochester to enable a selected group of dentists to broaden their medical-science base and gain research experience. Men of leadership emerged.

But Gies looked to the root of dental education, the environment where the dentists themselves are educated in the first place (neither Rochester nor Yale have undergraduate dental schools), when he concluded (*3*, p. 240): "The dental schools in this country and in Canada, lacking endowments and in most cases being obliged to keep the quality of their work to the level of their income from fees, will be unable to proceed with the suggested improvements unless, individually, they receive large gifts of funds for the purpose."

The same can be said today. Only when the dental schools themselves become more adequately supported and staffed for scholarly pursuits can the spirit and method of science be more fully incorporated into the fabric of dental education and practice.

WHEREAS many Perſons are ſo unfortunate as to loſe their Fore-Teeth by Accident, and otherways, to their great Detriment, not only in Looks, but ſpeaking both in Public and Private :—This is to inform all ſuch, that they may have them re-placed with falſe Ones, that looks as well as the Natural, and anſwers the End of Speaking to all Intents, by *PAUL REVERE*, Goldſmith, near the Head of Dr. *Clarke's* Wharf, *Boſton*.

***** All Perſons who have had falſe Teeth fixt by Mr. *John Baker*, Surgeon-Dentiſt, and they have got looſe (as they will in Time) may have them faſtened by the above, who learnt the Method of fixing them from Mr. *Baker*.**

Paul Revere, in announcing his dental practice in the Boston papers in August 1768, credits as his preceptor an Englishman, John Baker, believed to be the first qualified dentist to practice in this country. [From B. W. Weinberger, *History of Dentistry in America* (Mosby, St. Louis, 1948)]

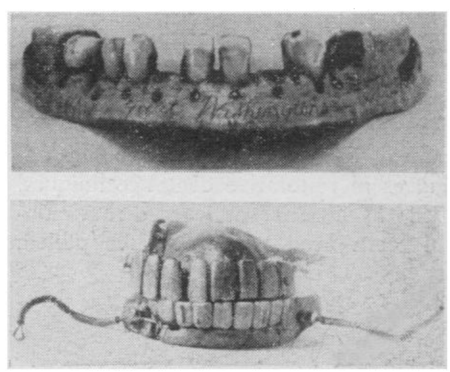
Education of Dental Researchers

On the basis of analogies to many other areas of disease, it is reasonable to assume that the answers to questions in dentistry will be interrelated, and related, as well, to problems in the other health sciences. One may suppose, therefore, that the thousands of medical researchers in hospitals and biological laboratories will eventually produce clues and even, perhaps, solutions. If and when they do, it may be by happy accident—fortunately accidents can occur in science—rather than by design. These health researchers, focusing on a host of dramatic disease problems, have their hands full, and we may have to wait for several generations for specific contributions to dental health.

Meanwhile, the busy practicing dentist is not likely to drop his practice and begin learning to be a biological research worker; nor can the chemist, physicist, or scientist in some other discipline be expected to desert his work and begin to study the problems of dentistry. A more realistic approach than that of simply waiting for miracles from researchers in other disciplines or from established dental practitioners would seem to be the fostering of a new strain of biological scientists with established interest and experience in dentistry. These new dental scientists could and should be trained from the ground up, within the university; but to attract some of the scientifically motivated young dental graduates into this unexplored field would require substantial support for postdoctoral research training. Through this approach the smallest investments are sure to pay significant dividends.

Such support has been enormously productive in medicine. During the past five years, $100 million was allocated to medicine by the National Institutes of Health for university and hospital training of medical researchers. The first similar step in dentistry was taken in 1957, with an appropriation through NIDR of half a million dollars, divided among 16 dental schools, for the training of teacher-researchers in the dental field. If extended through governmental as well as private support, such advanced training of scientists and academicians in dentistry could become an important first move toward ultimate achievement of dental health.

The ground has already been prepared. Today's students are receiving a good foundation in biology upon which to build. For example, at the Harvard School of Dental Medicine, the dental students have been afforded the opportunity, since 1943, of spending their first two years beside the medical students, taking exactly the same courses under the same professors and being exposed to the same high standards and climate of expectancy. The first two years of biological science are followed by two years of practical work in diagnosis and treatment in the clinics of the dental school and its academically associated institutions, Massachusetts General Hospital, Children's Hospital, and Forsyth Dental Infirmary. In addition, each dental student is granted the privilege of working with a faculty sponsor on a problem of research. With this foundation in biological science and patient care, the young doctor of dental

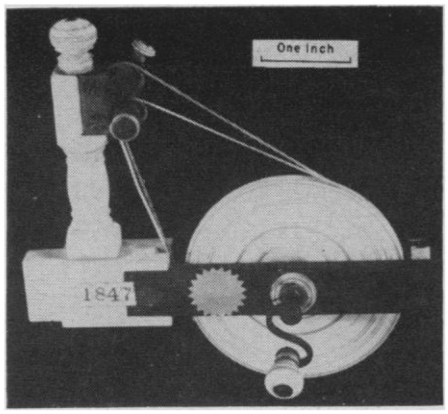


Two of George Washington's "bridges." (Top) Lower plate carved from hippopotamus ivory by the New England dentist John Greenwood in 1789. (About × 1.3) (Bottom) Ivory teeth inserted onto a full lower and upper set, believed to be the first known example of gold swaged plates. The spiral springs pressed the dentures against the gums and were altered by Greenwood according to specifications by Washington himself in 1798. [From B. W. Weinberger, *History of Dentistry in America* (Mosby, St. Louis, 1948)] medicine, in addition to acquiring clinical dental skills, is also on the road to becoming a biological scientist. Through further postdoctoral activity and growth, he may find that he is developing a special field of practice, or an area of special research interest which may lead toward an academic career in dentistry.

This new strain of dental scientist and specialist is being bred through various other programs. Some schools emphasize studies implementing the basic laboratory sciences, others concentrate on specialized clinical training. Such advanced postdoctoral education for dentists represents one of the United States' most important new contributions to modern dentistry. In increasing but still relatively small numbers, men with broad training are coming out of the dental schools, to join the faculties of other dental schools, here and abroad, and to work in research laboratories, in clinics, and in private dental offices.

A Change in Emphasis

It is a century now since organized dentistry became established in the United States, in 1859. A dozen years earlier a Boston dentist, William Morton, had already demonstrated to the satisfaction of doctors and patients everywhere the anesthetic effect of sulfuric ether, using it successfully for painless surgery at Massachusetts General Hospital. The fact that this blessing to humanity was established by a dentist is perhaps not especially significant, but dentists like to think that it was altogether appropriate, and even symbolic: the relief of pain and the painless removal of irreparably decayed, loose, and abscessed teeth had always been a prime concern of dentistry. Then came the long series of groping advances in restorative dental techniques. Little by little it was learned that painful teeth need not always be pulled,



A tusk for a tooth auger. Century-old hand-turned dental "engine" with a handle for drill chuck and a pulley wheel made of ivory.

that at least some could be saved. Through this realistic "first come, first served" approach, dentistry has arrived at a point where the modern dentist can all but improve upon nature, as sparkling smiles from Hollywood to Washington amply demonstrate.

In a paradoxical sense, dental art and technology may well have become too good, too soon, for the good of dental science and biology. The clumsy, uncomfortable "sea-horse" dentures of hand-carved hippopotamus ivory of an earlier day (neither President Washington nor the kings of Europe could command anything better) have long been replaced by light-weight dentures, bridges, and crowns hardly noticeable to the wearer, or to anyone else for that matter. In the realm of restorative materials and techniques, we still can expect further improvements. But there is now a new "first": The goals have been moved away from extraction and restoration to control and prevention. The pioneers of the new frontiers of dentistry are the dental research workers who seek to know "why" as well as "how."

The way to dental health is clear. Step number one is to implement the research training for dental scientists. This requires substantial long-term support. To get this under way the federal government must step in with support specifically earmarked for the training of teacher-researchers, until dental schools come to attract a greater share in endowments by private foundations. Among the 4000 philanthropic foundations listed in *American Foundations and Their Fields,* six are already specifically naming dentistry as within their field of interest, and four of these cite advances in dentistry as being among their major aims. The Kellogg Foundation, one of these, now supports a Commission for the Survey of Dentistry. Step number two is to enable properly trained dental scientists to pursue basic research on a long-term basis rather than be confined to narrow, short-term projects. Step number three is for this new breed of dental scholars and investigators to extend and deepen their collaboration with scientists and experts in other fields, in situations ranging from laboratory research to "chair-side" and bedside patient care.

Ultimately, this three-pronged approach will elevate the whole triad of teaching, research, and service for dental health. American dentistry, now at its centennial crossroads, has a challenging future. The Pasteur and the Salk of dental health could well be just around the corner. To support the growth and development of this new strain of oral biologists is our best investment in dental health—in the health of those who are expected to be on their feet and to do their jobs—practically everybody's health.

References

1. A. Flexner, "Institutes for medical research," in *Medical Education* (Macmillan, New York, 1925), p. 293.
2. ———, *Carnegie Foundation for the Advancement of Teaching, Bull. No. 4* (New York, 1910).
3. W. Gies, *Carnegie Foundation for the Advancement of Teaching, Bull. No. 19* (New York, 1926).