Retrospectroscope

Missed Opportunities

President Johnson once suggested that many important scientific discoveries were locked up in scientific laboratories and that the time had come to unlock these. I don't believe for a minute that LBJ was right. Scientists might try to publish *prematurely* (and sometimes succeed) but it's rare to find one who locks up his discoveries and keeps them hidden from the scientific public. Normal behavior of scientists is to make sure their observations and measurements are correct and then try to get them published as soon as humanly possible in the most widely read and prestigious journal in the field.

It is true, however, that researchers occasionally make important observations but don't know they've made them, or have all the information needed for a major discovery but don't make it. There's no way of telling how often it's happened and to whom but my guess is that it's an occurrence that few confess to; maybe more would after a few drinks, but rarely in writing. I call them "missed opportunities."

Sulfanilamide

Probably the most important miss here was the two-time synthesis of sulfanilamide before it was discovered a third time and finally put to clinical use. Sulfanilamide was first prepared in Vienna in 1908 by Paul Gelmo, then working for his doctoral thesis. At about the same time, Heinrich Horlein (later to become director of the medical division of the great I. G. Farbenindustrie) went to work with the Bayer Works and centered his research work on dyes. Because sulfanilamide was an easy starting point on which to construct dyes that were particularly color-fast (presumably because of the tight combination of the sulfanilamide element with the proteins of wool and silk), he began with several dyes formed with sulfanilamide as the base. Horlein never tested sulfanilamide for antibacterial properties, although Paul Ehrlich, a fellow German, had discovered arsphenamine, the "magic bullet" against syphilis, in 1909.

The second synthesis of sulfanilamide was in 1915, by Jacobs and Heidelberger at the Rockefeller Institute for Medical Research in New York. They decided to synthesize and test a number of chemical agents in the hope of finding one that was more bactericidal or less toxic against pneumococcal and streptococcal infections than optochin (an early but now-forgotten bactericidal drug). In their systematic search they prepared para-aminobenzene sulfonamide (sulfanilamide), much as Gelmo had in 1908. In line with then-current dogma, they thought that in order to fight infection *in vivo,* a substance had to be directly lethal to bacteria, and they didn't think that a substance as chemically simple as sulfanilamide could kill bacteria directly.

Heidelberger wrote in 1972 (1):

> Like everyone else at the time, Walter Jacobs and I thought that a substance had to be directly bactericidal in order to be useful in combatting bacterial infections. We had been successful with trypanosomiasis by applying Jacobs' idea of changing the -OH of -COOH to NH_2, as $-CONH_2$, in order to get an organic arsenical past tissue barriers. Accordingly, when we tried to get something better than optochin against pneumococcal and streptococcal infections, we started first with amides and then, by analogy, went on to $-SO_2NH_2$. *The possibility that any substance as simple as sulfanilamide could cure bacterial infections never entered our heads, nor did our microbiologist even ask to test it* [italics added]. We even improved Gelmo's method of preparation and went on to convert sulfanilamide into highly bactericidal substances which killed infected mice faster than the infections alone!
>
> As slaves to an idea, we missed the boat in 1915, losing the chance to save many thousands of lives, and the development of the sulfonamides was delayed twenty years.

The third discovery of sulfanilamide came in 1932 when Klarer and Mietzsch, chemists at I. G. Farbenindustrie, synthesized a red dye, "Prontosil," which three years later, Domagk, a German who won the 1939 Nobel Prize, showed to be a remarkable antibacterial agent in man. However, Fourneau's group at the Pasteur Institute in Paris quickly discovered that the active component of the red dye was none other than sulianilamide, first used by Horlein at I. G. Farbenindustrie in 1909, and that the rest of the compound was totally unnecessary.

No one will ever know whether chemists and pharmacologists at I. G. Farbenindustrie in the 1930s synthesized and tested *sulfanilamide* first or whether they tested only Prontosil and not sulfanilamide. The facts are (*1*) that Horlein used and patented sulfanilamide in 1909 (*2a*) and that by the 1930s it was no longer repatentable, and (*2*) that although Klarer and Mietzsch prepared what in 1932 proved to be a powerful antibacterial agent in mice, Domagk did not publish his clinical data until 1935. The suspicion will always linger that I. G. Farbenindustrie re-discovered and tested sulfanilamide first and spent the next few years in the early 1930s camouflaging ordinary sulfa into a new, complex, and above all, patentable compound—the red dye, Prontosil. Horlein, who was connected with the story from beginning to end, never told any more than he wrote in 1935 (2b):

> Further work on the azo-compounds by our chemists Mietzsch and Klarer led to the discovery of bodies with an incomparably greater action on bacteria than that possessed by any of the azo-compounds mentioned. But even these new compounds had no effect on mice infected with bacteria. In the course of our investigations, however, Domagk observed a certain activity on the part of azo-compounds containing sulphonamide in the streptococcal sepsis of mice, thus furnishing an important starting point for the preparation of new experimental series.
>
> Azo-dyes with sulphonamide and substituted sulphonamide groups were first prepared by me in collaboration with Dressel and Kothe, twenty-five years ago. At that time we were engaged in elaborating dyes for textile purposes which, in the direct dyeing of wools, would possess a greater degree of fastness to washing and fulling than dyes free from sulphonamide, while possessing the same degree of fastness to light as the latter dyes; i.e., dyes which would enter into a more intimate combination with the protein-cells of the wool than the dyes free from sulphonamide.
>
> The observation of Domagk on the action of one of these dyes on streptococci directed our subsequent work into a new channel. Numerous new azo-dye-containing sulphonamides were prepared, but the test object was no longer the wool fiber but the mouse infected with streptococci.

Artificial Kidney

This is a special case of interrelated "missed opportunities." Abel, Rowntree, and Turner in 1914 (3) published their experiments on vividiffusion in living animals but neither they nor anyone else seriously and successfully applied it to man until 1943 when Kolff did it in German-occupied Holland (4). You will say that no one could even try it in man until nontoxic anticoagulants and chemotherapeutic agents were available. But Abel and associates in 1913-14 used hirudin (that they themselves prepared from leeches), McLean published his discovery of heparin in 1916, and Best (5) noted that Schmidt had prepared a material similar to heparin in 1892 (6) and Doyon again in 1912 (7).

The point with respect to anticoagulants is that either no one saw a necessity for purifying heparin or hirudin to permit the artificial kidney to be used in man or, if clinicians saw a critical need, they lacked chemical expertise to do it themselves and had no chemical colleagues or pharmaceutical research laboratories to turn to. Charles Best, in retrospect, had no explanation of the failure to purify heparin for use in vividiffusion but did note that "after heparin became available many people stated that they had been thinking for many years of its use in cardiac and vascular surgery" (8).

The antibacterial agents needed could have been available in 1910 or 1917 had it not been for missed opportunities in this field (see above); and antibiotics could have been available in 1930 if Fleming had taken his observations a step further (from agar plates to experimentally infected mice) —another missed opportunity.

The Carotid Sinus and Reflex Control of the Circulation

Of all experiments in the physiology student laboratory, the one most certain to produce dramatic effects is the demonstration of the carotid sinus reflex. One can clamp both common arteries *below* their bifurcation and see an immediate rise in blood pressure (which does not occur if the branches are clamped *above* the bifurcation) or one can increase pressure in the

extracranial carotid arteries and note immediate slowing of the heart and fall in blood pressure.

These observations date back at least to 1836 when Astley Cooper noted that occlusion of the common carotid arteries led to an increase in blood pressure; he attributed it to the effects of intracranial ischemia (9). At least five physiologists between 1838 and 1885 confirmed his observations and agreed with his explanation.

Now it is important to note that in 1893 Bayliss (10) showed that these cardiovascular changes could not be due to cerebral ischemia because occlusion of both common carotid arteries did not markedly change blood flow to the medulla oblongata; the vertebral arteries still provided adequate blood flow to this region. Leonard Hill also presented strong evidence against the cerebral ischemia explanation when, in 1896, he was able to ligate successively both common carotids and both vertebral arteries in dogs without causing any abnormal behavior in the animal on recovery from these operations (11); this was because blood still flowed through the fifth artery to the brain, the anterior spinal artery. Nevertheless, Porter and Pratt still reported in 1908 (12) that raising blood pressure in the carotid arteries caused slowing of the heart by affecting blood pressure in the medullary centers. And in the same year, Eyster and Hooker (13) artificially raised blood pressure in the carotid arteries to 200 mm Hg and recorded a marked bradycardia and hypotension (see figure la); this they attributed to "a direct effect of the increased blood pressure upon the cardioinhibitory centre" in the medulla. Note the strong resemblance to figure lb taken from a paper by Hering, who in 1923 at last discovered the carotid sinus, its nerve, and the effect of stimulating the nerve endings electrically or mechanically (14).

It has been said: "We see what we look for and we look for only what we know." Eyster and Hooker had all the information needed to find the carotid sinus in 1908. All they had to do was to look an inch higher in the neck of a living dog and see the bulging, pulsating origin of the internal carotids, literally enmeshed in nerve fibers. Anrep and Starling still wrote in 1925 "a mechanical rise in blood pressure in the brain inhibits the vasomotor centre and stimulates the cardioinhibitory centre" (15).

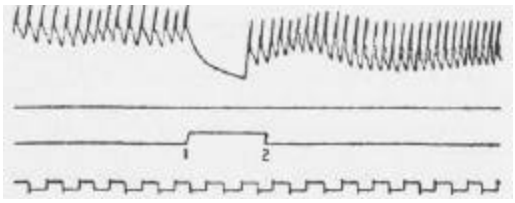


Fig. 1A. Between 1 and 2, Eyster and Hooker raised blood pressure to 200 mm Hg in the common carotid arteries of a dog while they recorded a decrease in blood pressure and heart

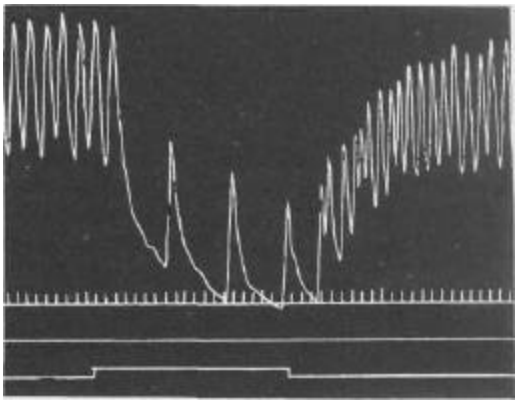


Fig. IB. During the period indicated by the signal marker (bottom line), Hering stimulated the right carotid sinus nerve of a dog; the tracing shows an immediate fall in systemic arterial blood pressure and bradycardia.

Nitrous Oxide, Ether, Local Anesthesia

Laughing gas parties were common in the early 1800s and Humphry Davy, who repeatedly inhaled nitrous oxide in his experiments of 1799, even suggested its use as a general anesthetic agent. But no one deliberately gave it to prevent pain until 1844—42 years of missed opportunities for how many physicians (and benefits to their patients).

Michael Faraday suggested in 1818 that ether be used to prevent surgical pain, and ether jags were a common form of social entertainment in the 1830s and 1840s; but no one gave it deliberately to prevent surgical pain until 1842.

Carl Koller, a young intern with his heart set on being an ophthalmologist, discovered in 1884 that cocaine was a superb local anesthetic for the eye. Yet since 1860, two years after the chemist Niemann had isolated cocaine from Peruvian coca leaves, it was well known that cocaine taken by mouth numbed the tongue. Koller's biographer, his daughter Hortense Koller Becker, wrote (16):

In 1862 Professor Schroff, in a paper read before

the Viennese Medical Society, pointed out that cocaine numbed the tongue, narrowed the peripheral arteries, and widened the pupils by its action via the bloodstream or when applied locally. Nor was he the only one to have experimented upon the eye. These facts were commented upon by Mantegazza in 1859, De Marles in 1862, the Spaniard Moréno y Maiz in 1868, and by many others. In 1879 von Anrep, at the Pharmacological Institute at Wurzburg, wrote a comprehensive experimental paper in which he also described the locally numbing effects of cocaine and even the dilation of the pupil upon local application, and he suggested that this drug might some day become of medical importance. "Strangely enough," commented G. F. Schrady in an editorial in the Medical Record of November 8, 1884, "Anrep did not note that the conjunctiva was insensible, or if so did not appreciate the significance of this fact."

In the textbook on pharmacology which my father studied at the University, he had underlined the following passage which appears in the article dealing with the coca plant:
"Local effects: Injection under the skin as well as painting the mucous membrane, for example, the tongue—brings about the loss of feeling and pain. 15 minutes after painting it Anrep was incapable of distinguishing sugar, salt and sour at the treated spot. Even the needle pricks could no longer be felt there, whereas the other unpainted side reacted normally. The loss of sensibility lasted between 25 and 100 minutes.

"[The article concludes with] Therapeutic Uses: Up to now cocaine has not found any medical use. But on account of its powerfully stimulating effects on the psyche, respiration, and the heart, and also on account of its anesthetizing effect upon the mucous membrane, it might deserve experimental trial in quite a number of diseases. [Relative to the therapeutic use of the coca leaves:] There have been some experiments but no trustworthy ones over an extended period. They are, however, sold commercially and highly recommended for all possible needs."

Sigmund Freud had carried out what is still regarded as the classic pharmacological study of cocaine and the young Koller was closely associated with Freud in some of his work. Koller's daughter gives this account of why it was Koller, and not previous workers, who discovered that cocaine had great potential as a local anesthetic:

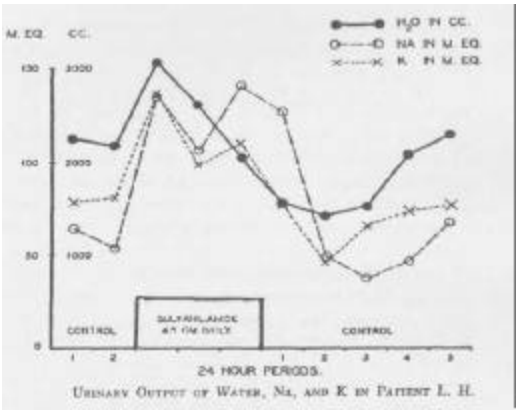
This is the chain of events which actually placed cocaine in my father's hand and focused his attention on it: Freud's interest in the drug, awakened primarily by the American literature on substituteing it for morphine, by which method he hoped to help his suffering friend, Fleischl; the actual purchase of the scarce, expensive product [by Freud] and the request he made of my father to engage in experiments during the course of which my father was required to take it by mouth. These were the circumstances that prepared the way for his particular discovery, yet cocaine had been handled, taken by mouth, and its effect even upon the eye, observed for twenty-five years without its usefulness in surgery occurring to anyone. "Upon one occasion," my father said, "another colleague of mine, Dr. Engel, partook of some [cocaine] with me from the point of his penknife and remarked, 'How that numbs the tongue.' I said, 'Yes, that has been noticed by everyone that has eaten it.' And in the moment it flashed upon me that I was carrying in my pocket the local anesthetic for which I had searched some years earlier. I went straight to the laboratory, asked the assistant for a guinea pig for the experiment, made a solution of cocaine from the powder which I carried in my pocketbook, and instilled this into the eye of the animal." The young assistant in Strieker's laboratory, Dr. Gaertner, was the sole witness to my father's discovery ... he retold it in a 1919 newspaper of which he was medical editor:
"Now it was necessary to go one step further and to repeat the experiment upon a human being. We trickled the solution under the upraised lids of each other's eyes. Then we put a mirror before us, took a pin in hand, and tried to touch the cornea with its head. Almost simultaneously we could joyously assure ourselves, "I can't feel a thing." We could make a dent in the cornea without the slightest awareness of the touch, let alone any unpleasant sensation or reaction. With that the discovery of local anesthesia was completed. I rejoice that I was the first to congratulate Dr. Koller as a benefactor of mankind."

Koller's daughter continued:

My father was, of course, aware that local anesthesia had more general implications and was not by any means limited to operations on the eye. "I had started from the fact that the drug made the *lips* and *tongue* numb, but I limited myself to the eye, wishing to make a contribution to ophthalmology and also wishing to establish a claim to the much-coveted position of an assistant at one of the large eye clinics. I did, however, directly suggest to my friend, Jellinek [assistant to Schrötter in the laryngological clinic], that he make experiments on the nose, pharynx, and larynx. He reported the results at the same meeting of the *Gesellschaft der Ärzte* (October 17) at which I read my [second] paper."

It was Roller's intense desire to obtain this position in Vienna and his conviction that an important contribution to ophthalmology would

almost guarantee an offer that led him to solve the most serious problem in that specialty—how to operate painlessly and safely on the eye. General anesthesia was unsatisfactory because the patient often retched and vomited in the recovery period and because his conscious cooperation was frequently necessary during the operation. Ironically, because of strong anti-Semitism in Vienna, he never received the assistantship and, in 1888, he emigrated to America, where he became one of New York's most eminent ophthalmologists, showered with many honors.



URINARY OUTPUT OF WATER, Na, AND K IN PATIENT L. H.

Fig. 2. After a control period of 2 days, Strauss and Southworth gave a subject 4.5 g sulfanilamide daily. Note diuresis and increased excretion of sodium and potassium.

Oral Diuretics

Oral diuretics as a class are one of the two most important new groups of drugs in the last 35 years—the other being chemotherapeutic and antibiotic drugs. Not many remember that sulfanilamide led to the discovery of chlorothiazide, the first of the oral diuretics.

In 1937, Hamilton Southworth at the Johns Hopkins Hospital noted that two of 50 patients treated with sulfanilamide began to breathe deeply. As a result, he studied 15 consecutive patients treated with sulfanilamide; the blood of each showed evidence of acidosis though none had *clinical* symptoms of acidosis (17). Pharmacologists at Hopkins then showed that a large single dose of sulfanilamide administered to dogs produced acidosis, and Strauss and Southworth demonstrated that in three normal human subjects, sulfanilamide led to acidosis, diuresis and increase in the renal excretion of sodium and potassium (18) (see figure 2).

Diuretics had long been an important part of treatment of congestive heart failure and edema but the only really effective diuretics in 1937 were mercurial diuretics and these required intravenous injection. Was sulfanilamide an effective oral diuretic that could at last replace intravenous injections of the organic mercurial compounds? And how did it produce diuresis?

In 1933, Roughton had isolated a new enzyme, carbonic anhydrase, from red blood cells and showed its property of greatly accelerating the reaction:

$$H_2O + CO_2 \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + H^-CO_3.$$

In 1940, Mann and Keilin found that some sulfonamides inhibit carbonic anhydrase; in 1941, Davenport and Wilhelmi found that carbonic anhydrase was present in the kidney, and, in 1945, Pitts and Alexander demonstrated the role of carbonic anhydrase in the exchange of hydrogen and sodium ions in the renal tubules and in the acidification of urine. Circumstantial evidence (though later shown not to be trusted) pointed to inhibition of carbonic anhydrase as the key to diuretic agents. Novello, Sprague, Beyer, and associates in the Renal Program at Merck, Sharp and Dohme synthesized a number of compounds in the sulfanilamide-carbonic anhydrase series and tested them for diuretic activity. They hit the jackpot with chlorothiazide (a compound resulting from ring closure of chlorodisulfamylaniline); it *is* a sulfonamide derivative, it *is* a carbonic anhydrase inhibitor, but its powerful diuretic action is *not* due to its ability to inhibit carbonic anhydrase (19).

Did the Hopkins group in 1937-1938 anticipate the train of events set into motion by Southworth's careful clinical observations? Dr. Robert Dripps asked this question of Southworth in 1972 and Southworth replied in part (20):

> I have been back over the original papers and have tried to think back over those days. Working with Perrin Long at Johns Hopkins, I was in on the first excitement of sulfa drugs and was lucky enough one day to pick up the first case of acidosis associated with the use of sulfanilamide. [see (17)]. The subsequent work done with Margaret Strauss of the Biochemical Department was an attempt to work out why the acidosis developed and incidentally showed that large doses did increase the urine volume and the renal excretion of sodium and potassium [see (18)]. It also showed,

> interestingly enough, that some hemoconcentration was produced but Bob Loeb, who went over the paper with me at Presbyterian where I had moved at the end of '37, was suspicious of the figures on blood sodiums and would not let me publish them. No one knew then about carbonic acid anhydrase and we therefore couldn't ex- plain the acidosis. By the time this paper came out, I was in the practice of medicine and was just winding up what I had done as a resident.
>
> It is hard to remember just how much we did think of the diuretic possibilities of what we had found. I don't think it was very much and yet the paper went through the hands of Warfield Longcope and Robert F. Loeb so I was not the only one who failed to see the potential future significance. It is my vague recollection that we didn't take it too seriously because we were giving big doses (up to 6 to 8 gms) of a drug the toxic and allergic effects of which were just being described all around us, and which we only considered using in people who had quite serious infections. I don't, however, remember any of us considering that an analogue of the drug might be developed which would have this effect in smaller doses and with less toxicity. Also those were the days when diuresis was not considered as important as it was subsequently. We had Salyrgan and we thought it was quite good for the waterlogged cardiac.

Southworth missed the opportunity to develop or participate directly in the development of oral diuretics; "It was hard," he said in retrospect, "to realize that I was on the brink of something important [in 1937-38] and didn't really appreciate it." However, his astute clinical observations showed Beyer and his associates where to look. And that must be satisfying in itself.

Other Missed Opportunities

Karl Landsteiner won the Nobel Prize for discovering human blood groups and could have won it twice over for discovering the viral cause of poliomyelitis and his work on the Rh factor. But he never connected his finding of blood groups in man with the cause of human transfusion reactions.

Werner Forssmann catheterized his own heart but missed the opportunity to follow up and use his new tool for diagnostic purposes. He tried (21) but got crushed by the German geheimrat system.

Marie Krogh devised a single breath test of diffusing capacity of the lungs but never used it for clinical diagnosis of disorders of the lungs or pulmonary capillary bed (22). However, she designed her test only to decide whether oxygen crossed the alveolar-to-capillary barrier by diffusion alone or in part by secretion. She had no need for it thereafter and in any case simple and rapid methods of gas analysis had to be invented before the test lent itself to use on large numbers of subjects and patients.

Waksman had a number of opportunities to discover streptomycin before 1944. The first was early in his scientific career; his main interest was then in soil (how it decomposed organic material added to it) and not in microbes, even though he did do studies on *Streptomyces griseus* between 1916 and 1919. Again, in 1932 he missed an opportunity when his pathologist friend, Beaudette, brought him a culture of tubercle bacilli apparently killed by a fungus growing on it; Waksman failed to study it. Then in the early 1940s his son Byron, now a prominent scientist in his own right but then a medical student, wrote to his father (23):

> In reading the reprints you sent me, I was struck again with the urge to do some work in the direction of finding an effective *in vivo* antagonist to the tubercle bacillus. I was particularly impressed with the relative simplicity of the method you have used in isolating fungi-producing antibiotic substances, and I wondered if exactly the same method could not be used with equal ease to isolate a number of strains of fungi or actinomycetes which would act against *M. tuberculosis.* They could be tested after isolation against some more rapidly growing organism such as *M. phlei in vitro,* and finally against the tubercle bacillus itself *in vivo.* .... From the little reading I have done, it is my impression that no one as yet has published any work of this nature. There is no question that it has a great deal of practical value or would have if successfully concluded.

His father answered: "The time has not come yet. We are not quite prepared to undertake the problem." I wonder if this was a misunderstanding: the *son* was prepared to tackle the research while still a medical student; the *father* was not. In 1944, the father was prepared and isolated streptomycin (24).

Gross was the first to successfully ligate a patent ductus arteriosus in a child but when Taussig offered him the first crack at the now famous "blue-baby operation" he had no interest in it, and turned her down. Learning that she was thinking of moving to Boston, he advised her not to come where she would not be tolerated. "Stay where you are wanted," he said (25). She did, and so Gross left the field wide open

for Alfred Blalock at Hopkins who eagerly collaborated with Taussig.

Hunt and Taveau in 1906 published a classic paper on the extraordinary physiologic activity of acetylcholine (26). In it they studied a number of other choline derivatives including succinylcholine. They completely missed its neuromuscular blocking effect because they worked on animals *curarized* at the onset of the experiment. As a result, succiuylcholine never entered medical practice until 1949. Was this a missed opportunity for use of muscle relaxants in the practice of medicine and anesthesiology? Maybe not, for these reasons: (*1*) few surgeons or anesthetists in the early 1900s knew how to maintain artificial ventilation in man, (*2*) the deliberate paralysis of skeletal muscles, including the muscles of respiration, probably had to await the development of a new specialty of professional, medically trained anesthetists (in the 1940s), and *(3)* Meltzer and Auer in their experimental studies of insufflation respiration in dogs (27) routinely gave their animals an intravenous injection of curare sufficient to abolish any spontaneous or reflex movements. Though they stated that the dog's "life is as safe [with curare] as under regular artificial respiration," they never proposed its clinical use, nor did anyone else until 1942. I doubt that availability of a pure agent, such as succinylcholine, would have made surgeons any more comfortable about operating on a paralyzed patient.

Diphenylhydantoin (dilantin) was used for 20 years to decrease the excitability of cells in the motor cortex of epileptic patients before Leonard first used it to control ventricular tachycardia in man (28).

Local anesthetics were used experimental-ly for 48 years to reduce cardiac excitability in animals before James Southworth and associates finally used lidocaine to reverse ventricular fibrillation in man (29). Plenty of time for missed opportunities over these two decades, especially since it encompassed the important decades in which cardiac surgery began and matured.

Ganglionic blocking agents were known as early as 1915, when Burn and Dale clearly recognized that tetraethylammonium was a ganglionic "paralyzing" agent capable of blocking sympathetic nerve impulses to the heart and arterioles. But it was not until 1946 that Lyons and associates (30) used it to lower frood pressure in hypertensive patients by performing a "chemical sympathectomy." Were there missed opportunities for its use during this 31-year period? Probably "yes" in the 1930s and thereafter, but probably "no" before, because most physiccians believed that patients with hypertension had initial renal disease and reduced renal blood flow. They believed that their resulting hypertension was compensatory or essential to maintain renal circulation and prolong the patient's life, even though it eventually caused cardiac hypertrophy and heart failure.

Concluding Remarks

Much has been said and written about lags between initial scientific discovery and final clinical application. In many instances, the lag was unavoidable because whole new branches of science had to come into being before the initial discovery could move forward (e.g., the invention of the microscope could not lead to antibiotics until it first led to the discovery of microbes, the germ theory of disease and the sciences of microbiology and pharmacology). Sometimes, however, an individual made observations crucial to an important next or even final step but didn't realize their significance. These "missed opportunities" cannot be la-belled scientific discoveries "locked up" in a laboratory by an unconcerned scientist. They are an almost inevitable result of the background, training and environment of that scientist and his immediate goals and preoccupations that blind him to a new concept. It has been said that the eye often sees only that behind it and not what is in front of it. If it is any consolation to those who missed magnificent opportunities, remember that the world's greatest inventor, Thomas Edison, failed to see any useful application at all for his greatest scientific discovery, the "Edison effect," which later was the basis for the audion or vacuum tube that permitted the development of radio. And missed opportunities are not limited to science: Winston Churchill said, "Men occasionally stumble over the truth, but most of them pick themselves up and hurry off as if nothing had happened."

JULIUS H. COMROE, JR.

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