In the 1960s, a number of technical developments occurred that caused a great outpouring of new findings in the field of oculomotor neurophysiology and with it, the means to try to interpret this almost overwhelming mass of data. This paper will review those developments and try to give a feeling, for the non-specialist, of the progress made and where we stand today.

Technological Advances

Signals in Awake Animals

The single, most important technical advance in all of motor physiology was the development, by the late Ed Evarts at the National Institute of Mental Health, of the method of recording from single neurons in alert, behaving animals. A chamber is implanted over a trephine hole in the skull through which, upon recovery, metal microelectrodes can be advanced to any region within the skull to record the extracellular spikes generated by its neurons. Prior to this, motor physiologists could study motor behavior in unanesthetized animals only after lesions or the chronic placement of fixed stimulating electrodes—both techniques useful for localization, but only in a gross way. Electrophysiology required anesthesia and largely permitted only circuit tracing as an adjunct to anatomical techniques. At the heart of motor physiology is the question of how sensory signals are processed by neurons to become motor commands. Signal processing is at the heart of understanding, and Evarts allowed us to see these signals for the first time.

Ironically, this development has not touched off the explosion in research in the control of limb movements that it did in the oculomotor system, for the simple reason that the latter is contained entirely within the cranial vault. Recordings from cerebellum, motor cortex, basal ganglia, etc. in monkeys trained to make limb movements have generated many new data but they cannot be interpreted in any basic way because these signals are so far removed from the motoneurons in the spinal cord. Mechanical instability in the cord has so far prevented recording the complex signal processing that goes on there and until this technical problem is overcome, and it is only a technical problem, progress in spinal control of movement will remain seriously retarded. In the oculomotor system, on the other hand, we can start with the motoneurons (nowadays called the bottom-up approach) and try to move up through more and more complex layers of signal processing.

Straight from industrial electrical engineering, my biological naiveté led me to adapt Evarts' technique to the oculomotor system, in the mid-1960s, not realizing that I was treading on formidable state-of-the-art territory. But it was an idea whose time had come. I used it initially to record from the oculomotor nucleus. Eric Luschei, at the University of Washington, was, at the time, recording from jaw motoneurons, so that when Albert Fuchs, my first graduate student, joined that faculty in 1969, he and Eric could collaborate at once in a study of the nearby abducens nuclei. Meanwhile, Peter Schiller, at MIT, also had seen the power of this technique, so that in 1970 three papers appeared on the behavior of ocular motoneurons during eye movements in alert monkeys. These studies opened the floodgates; for the next 17 years, and continuing today, investigators are thrusting their microelectrodes into every oculomotor nook and cranny of the cranial vault.

Tracers

A second, important, technical innovation was the development of tracer techniques. When Graybiel and Hartwig first applied this technique to the ocu-
lomotor system, by putting horseradish peroxidase (HRP) into the oculomotor nucleus, they paved the way for a number of major discoveries. Anatomists had for decades assured us that the abducens nucleus contained only motoneurons of the lateral rectus muscles. These pioneers, however, found that roughly half of this nucleus consisted of internuclear neurons that relayed horizontal oculomotor commands to medial-rectus motoneurons. Old hat now—it’s easy to forget the flap of activity this caused just after 1974.

They also found that HRP was transported to the nucleus prepositus hypoglossi, a perihypoglossal nucleus whose name indicates how misunderstood it was by early anatomists. It is a hotbed of oculomotor activity, as we will see below. Subsequently, there appeared a regular parade of nuclei: the nucleus of the optic tract; the rostral interstitial nucleus of the medial longitudinal fasciculus; the nucleus reticularis tegmenti pontis and so on—nuclei lying on the dusty shelves of neuroanatomy and now suddenly propelled into the limelight of oculomotor neurophysiology by tracer techniques.

Computers

Among the technological advances, that we so take for granted that we don’t even think about, is the digital computer. As someone who, as late as 1975, was still analyzing spike trains by hand, I can attest to the orders of magnitude of time saved by letting the computer do it. If one is studying signal processing by the nervous system, it is vital to quantitate those signals at least as rapidly as they can be acquired.

Eye-Movement Recording

The fourth advance was a technique I devised for measuring eye movements more accurately. Coming from a company that made magnetic devices, I tended first to see if I could solve a problem by a magnetic method. Engineers explore the shapes of magnetic fields by using a search coil in which is induced a voltage proportional to the field strength and the angle between the plane of the coil and the direction of the field lines. If the field is uniform and the coil is somehow fastened to the eye, the induced voltage measures the angle of the coil and so the eye. The design of the coil and the magnetic fields was easy, but how did one implant such a coil in a monkey’s eye? I owe a great deal to Al Fuchs in this regard: as two electrical engineers, we spent a year bumbling about learning the rudiments of extracocular surgery before getting the hang of what is now a routine, 30 min procedure.

This technique in animals offers a chronic, objectively-calibrated method of recording any eye movement from the smallest to the largest. These features have led it to become a standard technique in oculomotor laboratories worldwide. H. Collewijn, in Rotterdam, extended it to human research by embedding the coil in a soft, annular, scleral contact lens (it does not touch the cornea) and this technique has now expanded the method into most human, basic and clinical, oculomotor laboratories as well. The electro-oculargram is still a valuable war horse in this field, and when its drift and noisiness are countered with a few simple precautions, its value should not be underrated. The eye-coil/magnetic-field method was by no means essential to the information explosion in this field, but its greater accuracy did, at least, facilitate it.

The Systems Approach

The final advance is conceptual and not all embrace it. It is the application of systems analysis to the study of eye movements. This results in the appearance of models of the oculomotor system which some classically-trained physiologists regard with suspicion. Let me define the term, model. The philosophy of science identifies something called the scientific method: given a set of observations (nowadays called a data base), one constructs a hypothesis to explain them. One next devises an experiment to test the hypothesis. The results could support or destroy the hypothesis but usually it adds to the data base and requires modification of the hypothesis. These steps are repeated until the hypothesis is rejected or seems to pass all tests and becomes a theory.

Making a hypothesis is completely subjective. Into it goes experience, insight, intuition and luck. Hypotheses can be qualitative, like Darwin’s theory of evolution. In studying brain function, they usually must be quantitative and involve feedback loops, time constants, nonlinearities, maps, complex connectivities, etc., and cannot even be formulated without a wiring or block diagram, such as engineers use in nonbiological control and information-processing systems. This is a model. It is still a hypothesis, but it is sufficiently complex that the language of systems analysis is needed just to state it. To test the hypothesis requires predicting what this model will do in various experimental situations. Techniques for doing this have long been developed by engineers and are known, of course, as systems analysis.

Thus, models are simply hypotheses and systems analysis is just the means developed to cope with such hypotheses. To be against models is to be against hypotheses which, in science, is like being against motherhood and apple pie. Why do some people dis-
trust models? All models contain assumptions (the artistry of hypothesizing) as well as facts. If a model contains lots of facts, one or two assumptions, and is testable, it is accepted as reasonable. If it is 10% fact and 90% assumptions and cannot be tested, it is not of much practical use so it is ignored by practicing physiologists. Fortunately, due to an abundance of data and many simplifying features in the oculomotor system, oculomotor models tend to be of the former kind and their ability to explain a number of clinical disorders has led, today, not only to an acceptance of these hypotheses but to an acceptance of systems analysis as an appropriate tool in analyzing the oculomotor system. The current literature, clinical and basic, abounds with Laplace transforms, Bode diagrams, phase shifts, time constants, etc.—concepts that 25 years ago were foreign to this field. I confess to playing a major role in helping to effect this change which I regard as essential in the maturation of all of neurophysiology.

Windfalls

The Vestibulo-Ocular Reflex

What have we learned with all these new techniques? Let's start with the vestibulo-ocular reflex because it is the simplest of all the oculomotor subsystems and forms a basis, phylogenetically, on which most other systems are built. The results of the three studies of motoneurons in 1970 can be expressed most succinctly by the equation shown on the right in Figure 1. In addition to a background discharge rate, \( R_0 \), seen when a monkey looks straight ahead, the rate increases at the rate \( k \) (spikes/sec)/(deg) for each deg of eye deviation, \( E \), in the pulling direction of the muscle, and at the rate \( r \) (spikes/sec)/(deg/sec) for each deg/sec of eye velocity, \( E' \), in that direction. Because \( R \) reflects muscle force, \( k \) represents the elastic elements of the orbit, and \( r \) the viscous elements. Different motoneurons in the pool have different values for \( R_0 \), \( k \) and \( r \), but Figure 1 shows the values for the average neuron.

Several important motor principles emerge from these findings. Motoneurons are recruited into the active pool in a fixed order known as the rule of rank order of recruitment. (Other than using references to acknowledge my great debt to my students and colleagues, I shall not burden the reader with references to the well-accepted. They may be found in reviews such as\(^8\).) Motoneurons strictly obey reciprocal innervation: when motoneurons of a lateral rectus increase their rates, those of the medial rectus decrease them; eye muscles never cocontract. There does not exist one group of motoneurons (phasic) that just make saccades while another (tonic) just engage in fixation; that would violate rank order of recruitment and that does not happen. It would be impossible to write an equation, such as that in Figure 1, for a
motoneuron in the spinal cord because cocontraction frequently occurs in limb muscles, making a unique relationship between muscle force and joint angle impossible. Also, we do not pick up objects with our eye muscles; limbs must deal with a variety of loads, further dissociating force from position. Because the eye lives in an ivory tower and need not deal with external forces and objects, it really does not need a stretch reflex and, when Ed Keller joined our laboratory, he settled this age-old problem by showing that there was no stretch reflex in extraocular muscles. These toneurons.

To maintain a predominance of direct canal-eye reflexes, matrices and tensors\(^\text{11}\) and from these studies has come a general impression that the canals have largely imposed their behavior on the entire reflex. It can be shown, for example, that the location of the vertical canals, lying 45 deg off the sagittal plane, is not a caprice of evolution, it is the only orientation that optimizes the accuracy of canal transduction.\(^\text{11}\) To maintain a predominance of direct canal-eye muscle projections, the orientations of the eye muscles themselves have tended to remain near the canal planes not only in lateral-eyed, afoveate animals, but in frontal-eyed, foveate animals as well.\(^\text{12}\) Thus, our vertical recti have not evolved to move our eyes straight up and down, but have retained their ties to the canals rather than to our percepts of visual space.

Similarly, the resting discharge rate (90 spikes/sec, Fig. 1) seems to have imposed itself on the whole reflex. It is thought that this high rate evolved so that one canal could take over if the other were lost through push-pull connections. In any event, this high background rate is seen throughout this short reflex arc; all its neurons have similar high rates including the motoneurons, at least in the awake state. This high rate also results in linearity. In the canals, this shows up as a push-pull, head-velocity signal above and below the background rate, thus avoiding the major nonlinearity in neurological systems: discharge rate cannot be less than zero. This linearity is also seen throughout the reflex as illustrated by the motoneurons. Thus, in primates, the canals have imposed on the entire reflex: direction of action, high background activity and linearity. The latter property has also been a great help in analyzing this reflex.

Figure 1 shows other unusual features of this reflex: it shows how the sensory signal, \(H'\), becomes a motoneuron command, \(E'_v\) (the minus sign indicates only that a canal sensing a rightward head movement causes a leftward eye movement). There are very few sensory-motor systems in which one can pinpoint where a signal stops being sensory and begins being motor, but it is possible here—at the second-order vestibular neuron. Another feature is revealed here: if we did not know that the purpose of the reflex was to make eye velocity equal and opposite to head velocity, we would not recognize the signal in the vestibular nucleus as an eye velocity command. Knowing the purpose of a sensory-motor system, as we do for eye movements, is an enormous advantage. In other systems, the visual system not excluded, one usually does not know what is being done, let alone how.

From this work on the sensory and motor periphery, it is possible to state what central processing must be done in between. As shown in Figure 1, the eye velocity command, \(E'_v\), (or \(-H'\)) passes directly to the motoneurons to satisfy their need for that signal. This is a direct projection in the medial longitudinal fasciculus (mlf) as required by anatomy and signal processing. (I have used primes when it seems useful to bear in mind that these are not actual physical variables, such as \(E_v\), but only the neurally encoded commands for them.) It has long been known that there was a parallel pathway, probably reticular, that “contributed” somehow to the reflex. Figure 1 states precisely what that contribution is. The motoneurons need an eye position command as well and the only way to obtain it is by integrating the velocity command from the vestibular nucleus. The need for a neural integrator was apparent as soon as anyone trained in systems analysis sat down and looked at this reflex. The problem was never whether it existed (as some thought); the problem was where it was located and how it worked.

To try and show in the 1960s that an integrator did exist, Alex Skavenski and I used a sine wave argument.\(^\text{13}\) We rotated monkeys sinuosoidally, recorded the sinusoidal modulation of the motoneurons and demonstrated the 90 deg phase lag associated with integration. Next, Jordan Pola joined our laboratory to test the model in Figure 1 which predicts that the mlf should carry the signal \(E_v\). It did, but to our sur-

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No. 12 THE WINDFALLS OF TECHNOLOGY IN THE OCULOMOTOR SYSTEM / Robinson 1915
prise it carried other signals as well\textsuperscript{14} and showed the model to be wrong. The mlf also carried a command for eye velocity for smooth pursuit, \(E'_p\), and it paused (ceased firing) during all rapid eye movements (saccades, quick phases of nystagmus). The latter feature reflects the turning off of the vestibulo-ocular reflex during large changes of gaze by coordinated eye and head movements. When Vintsas Laurutis joined us in 1984, from the Kaunas Polytechnic Institute in Lithuania, USSR, we showed this disconnection behaviorally in humans.\textsuperscript{15} Since the vestibulo-ocular reflex opposes motion of the eye in space, it would slow the eye down and greatly prolong the time needed to make such gaze shifts—so, it is turned off.

But the most surprising signal found on the mlf was the eye position command \(E'\). This means that part of the integrator output feeds back onto these second-order cells. This isn’t so surprising now that we know that the integrator is, in part, right in the vestibular nucleus itself (see below), but this was the first indication of messy wiring in this reflex. One could attempt to patch up the wiring in Figure 1, but as we will soon see, things get messier. Consequently, Figure 1 must be regarded as a diagram of what signal processing must be done but does not show how it is done with real neurons.

More evidence for messy wiring came when Dave Tomlinson joined the laboratory to finish our 15 year odyssey of 3 mm, from the abducens to the vestibular nuclei.\textsuperscript{16} We found a variety of cell types but they could all be described by:

\[
R = R_0 + kE' + rE_p + rE_v + rE_r,
\]  
where \(rE_p\) and \(rE_v\) are eye-velocity terms for pursuit and rapid eye movements respectively. Some, that we called position cells, carried only the \(kE'\) signal; others, called position-vestibular cells, also carried the \(rE_v\) term. Cells with a significant \(rE_v\) component had the term burst in their labels, and so on. We found cells with all combinations of these terms. Note that in Figure 1 only four cell types are needed, each carrying either \(E'\), \(E_p\), \(E_v\), or \(E_r\). Only the motorneurons need to combine these signals. Figure 1 is laid out as an engineer would conceive it but the design of this system obviously uses different rules. It is a bit as though one started with a group of interconnected neurons that received the observed signals \(E_p\), \(E_v\), and \(E_r\) and which, in development, had “useful” synapses strengthened and “useless” synapses removed. Although this is glib, at least it would result in the “hidden” neurons in this learning network—those between the input and output—having the observed messiness and carrying many different combinations of the signal elements in equation (1).

Moreover, if “useful” means the production of the time integral of the input signals as well, one is describing the neural integrator, and Tomlinson and I began to suspect that the neural integrator was right under our noses. For a long time it was thought that the integrator was, by default, in the paramedian pontine reticular formation (pprf), since that is often used as the garbage dump of the brain stem, and it was known to be very important for eye movements. Then Henn and his group in Zürich showed that neurotoxin lesions of the ppf eliminated saccades but not gaze-holding (another way of saying what the integrator does). This negative finding reinforced our idea that the integrator was in the vestibular nucleus (vn).

At this point (1982), Steve Cannon began his research in the laboratory and set out to show that neurotoxin lesions of the vn abolished integration in the alert monkey. Recall that Ann Graybiel\textsuperscript{1} discovered the oculomotor nature of the nucleus prepositus hypoglossi (nph) when she and Hartwig first showed by tracers that it projected directly to the motoneurons. Bob Baker and colleagues,\textsuperscript{17} on the basis of its extensive connections with other oculomotor areas, suggested it might be the site of the integrator, and Cheron et al\textsuperscript{18} were just beginning lesion studies of nph in Belgium. Consequently, we suspected that both nph and vn were involved—the two touch each other just under the floor of the 4th ventricle at the level of the rostral-medial vn.

Bilateral lesions at the junction of nph and vn knocked out the integrator completely.\textsuperscript{19} Figure 1 shows that without the integrator the eye will respond only to the \(E'\) commands with the result that eye position will reflect the eye velocity command for saccades, the vestibulo-ocular reflex and pursuit, and this is just what was found. This not only established the location of the integrator but, as we hypothesized in Figure 1, there was only one integrator shared by all conjugate systems. We went on to show that a simple neural network could be proposed to perform integration\textsuperscript{20,21} but it remains, for now, only a demonstration of feasibility and a hypothesis. Tom Anastasio recently joined our laboratory to record from the neurons in the nph of the alert monkey to add to the database for such hypotheses.

So, in 1987, we stand with a fairly comprehensive understanding of this most basic oculomotor subsystem. We can summarize its signal processing, characterized mainly by the integrator; we know where it is located and have ideas how it may work. We know most of the important anatomical connections and even know the signals flowing along these wires. There are, of course, many interesting, unsolved problems that occur when this reflex works in conjunction with other systems, such as mental set, pur-
suit, convergence, the otolith organs and saccades. For example, Charley Barr, in our laboratory, showed back in 1976, that people could turn the gain of their reflex ($E/H$; normally near 1.0—the minus sign is usually neglected) from 0.65, doing mental arithmetic in the dark, to near 1.0 or near zero while imagining (in the dark) an object on the wall or attached to the vestibular chair. Thus, this reflex, a slave driver in lateral-eyed, afoveate animals, has been brought to heel to serve the many different demands of primates. Nevertheless, this subsystem is probably the best-understood, sensory-to-motor system in mammalian physiology. And it is a good thing since, as Figure 1 suggests, it is the basement machinery for all other conjugate oculomotor systems.

The Saccadic System

In 1972, Fuchs and Luschei did a systematic search of the monkey brain stem looking for eye-movement related neurons. They found many cells in the pprf that began bursting at high rates in association with saccades and were silent at all other times. They led saccades by about 10 msec and were called medium-burst neurons but we will call them burst neurons here for short. These are the cells shown in Figure 1. When Jan van Gisbergen joined us in 1974, we recorded their instantaneous discharge rates and felt that they could be thought of as an eye velocity command, $E'$. Just as for the vestibular command, $E'$, it is necessary to send $E'$ directly to the motoneurons and into the neural integrator which converts this pulse to a step. The pulse and step are then combined on the motoneuron, as shown in Figure 2A. These connections for the burst neurons have now been confirmed and there is no question that these neurons are the final outlet of the saccadic system—they create the final product.

One of the pleasures of thinking about eye movement control from a systems standpoint is providing mechanistic explanations of oculomotor disorders. It is very satisfying to see an abnormal eye movement and pinpoint the lesion on a diagram such as Figure 1 or 2. It was, of course, Dave Zee who turned the attention of the laboratory to patients and their disorders. One very common disorder seen in the clinic is gaze-paretic nystagmus. It reflects a malfunction of the integrator. Figure 2A and B show that the integrator produces the step of activity that holds the eye in place after the saccade is over. Thus, it is very easy to check the integrity of someone’s integrator; just ask them to hold their eyes to one side in the dark. In affected patients, even in the light, their eyes will slide back, roughly exponentially, toward the center (Fig. 2C). To obey instructions, they then make repeated saccades, after each backslide, to regain eccentricity and so generate a nystagmus. As we have seen, the integrator is in the nph-vn complex but we should hasten to add that its performance is, like everything else in motor control, continuously adjusted by the cerebellum, in this case the flocculus, and “the leaky integrator symptom” is often a sign of trouble in the roof of the fourth ventricle.

Another saccadic disorder is illustrated in Figures 2D and E. A little post-saccadic drift of the eye had been noted in normal subjects and all agreed that it was due to a pulse-step mismatch. If the pulse in $R_m$ is too small (or too large) for the step, the rapid part of the saccade will be too small (or too large) and the eye will then slide onward (or backward), exponentially, to its final position. Pathological exaggerations of this occur when one muscle is palsied or in internuclear ophthalmoplegia, in which a lesion of the mlf distorts the signals rising in this tract to the motoneurons of the medial rectus. Again, clinical signs are explained by simple disorders of the circuit in Figure 2A.

When Lance Optican began working on saccadic plasticity in the laboratory around 1972, his main concern was the elimination of gross saccadic dysmetria caused by weakening the muscles of one eye in a monkey. We will return to this subject later on, but weakening the muscles also caused a pulse-step mis-
match and Lance noticed that whether the monkey wore a patch over its good eye or weak eye, the visually experienced eye always eliminated its post-saccadic drift. This showed, as one might have guessed, that this drift was another form of dysmetria under the control of motor plasticity. By chance, Dave Zee had some flocculectomized monkeys in the laboratory and Lance quickly observed that they had post-saccadic drift that did not get better. When Lance did a postdoctoral fellowship with Fred Miles at the NEI, they showed that post-saccadic drift can be induced.25 They arranged that a large, contour-rich pattern should drift briefly to the left whenever the monkey made a saccade to the right and vice versa. This idiot paradigm fooled the flocculus, which evidently regards retinal image slip as the error signal, into thinking that the monkey had post-saccadic drift and "re-pairing" it. As a result, when the monkey made a saccade in the dark after such training, its eyes drifted backward as in Figure 2E. Removal of the flocculus blocked such changes.26

When Zoi Kapoula joined our laboratory from Paris, she discovered that most normal subjects have an onward post-saccadic drift (Fig. 2D) in the adducting eye but not the abducting.27 This was eliminated in the viewing eye when the other eye was patched for three days28 indicating, again, plastic control of post-saccadic drift. In collaboration with Optican and Miles, she is currently demonstrating that the same paradigm that worked with monkeys also induces post-saccadic drift in humans. So again, if we see post-saccadic drift at the bedside, we know what causes it. If we see it persist for days, we suspect floccular lesions. When Herschel Goldstein, in our laboratory, took a closer look at the pulse and step, he found that the pattern of innervation was really a pulse-slide-step as in Figure 2F. The slide compensated for slowly relaxing viscoelasticities in the plant29 and we now realize that plastic manipulation of the slide has as much to do with holding the eye still after a saccade as does the matching of the pulse and step.25

Figure 2, then, coupled with circuits to and from the cerebellum to alter the gains of the direct and integral pathways, can explain many perisaccadic disorders seen at the bedside or, since many of these movements are so brief, recorded in the laboratory. But what of higher centers that tell the burst cells what to do? Dave Zee and I ventured into this area when Dave found a charming, young lady who had slow saccades accompanying spinocerebellar degeneration. He realized that she provided an excellent opportunity to test two sacred cows in oculomotor physiology: one was that saccades were ballistic—once started they could not be altered but ran their course to completion; the other was that there was an obligatory refractory period of at least 200 msec after one saccade before the next can occur.

He tested these ideas by asking the young lady to track a target that jumped once and then, just before or during her first (slow) saccade, jumped again to another position. He found that she could stop her saccade in midflight and start another immediately.30 This behavior broke both rules. Subsequent work with normals by others has verified these findings, although one should hasten to add that both rules do describe normal behavior roughly, just not absolutely. Dave's work was a brilliant example of using clinical material to investigate basic questions.

When Dave showed me these records I was struck by the similarity in behavior to servo control systems I used to design in industry. They were called bang-bang systems because, like the young lady's eyes, they could only run full tilt in one direction or the other until they abruptly came to rest on target. This led us to propose what is now known as the local feedback model shown in Figure 3.30 The basic question it addresses is, how does the system know when to stop a saccade so it lands on target? If it is not really ballistic,
it can't be preprogrammed. We allowed feedback to do this for us. The output of the integrator is a copy of current, instantaneous eye position. We hypothesized that higher centers can create the signal for a desired eye position, $E_D$. The difference between them is motor error, $e_m$, and this drives the burst neurons with a mild, saturating nonlinearity $f(e_m)$. When $E'$ equals $E_D$, $e_m$ (and $f(e_m)$) become zero and the eye automatically stops on target.

One danger of feedback is instability and indeed, to make saccades very fast, the gain $f(e_m)$ must be so large that, given the small delays (10–20 msec) in any neural circuit, this system is unstable. Nature has found an ingenious way to stop the system from oscillating. Pause cells, lying on the midline in the caudal pons, discharge continuously except during saccades when they pause. They inhibit burst cells and so shut off the whole saccadic system when saccades are not wanted. This very effectively prevents unwanted oscillations. This clever scheme allows the system to have its cake and eat it too: it can have very high gains to be fast, yet not have to worry about oscillations. To initiate a saccade, the pause cells must be momentarily shut off by a trigger signal (trig, Fig. 3). This releases the burst neurons to begin responding to $E_D$. To prevent the pause cells from stopping the saccade prematurely in the model when trig disappears, the burst itself keeps the pause cells off through the latch connection until the saccade has run its course. Then the pause cells come back on to suppress oscillations.

Well, not quite. There are a number of situations, normal and pathological, where one does see saccadic oscillations. Dynamic overshoot (Fig. 3B) is a small saccade that immediately follows an initial saccade—a half cycle of oscillation. Voluntary nystagmus (Fig. 3C) is the peculiar ability of about 10% of us to produce a momentary string of back-to-back saccades—saccadic oscillations. During microsaccades (Fig. 3D) it is common to see two or three microsaccades occur, one right after the other. More interesting is that during certain pathologies one sees a gross exaggeration of these phenomena known, clinically, as ocular flutter (Fig. 3E). By fiddling about with the pause and latch circuits, we were able to model all these phenomena.23,31 If this model, or something like it, is correct, yet another saccadic disorder will have been explained. I should add that this model was not originally proposed to account for such exotic behavior as ocular flutter but merely to provide a way to stop the eye automatically on target, to avoid alternatives such as preprogramming, and, through a single nonlinearity $f(e_m)$, to account for the main characteristics of saccades—the relationship between size, duration and velocity.

While many of the connections in Figure 3 exist, we do not yet have enough evidence to reject it or revise it. Like all good hypotheses, it has challenged the field and, over the last 10 years, stimulated a lot of good research which is what a hypothesis is supposed to do. Alternative models are now appearing (eg Scudder), as they should. They vary in ways thought to comply better with recordings from single neurons but they all retain the main feature of local feedback. The main point, going back to the young lady with slow saccades, is that the evolution of this model is a superb example of interaction between basic research and clinical investigation.

I confess to a great reluctance to stray too far away from the motoneuron without knowing what is going on in between. Our main excursions into higher realms occurred early on when we realized that, with the new alert monkey preparation, almost all of the pre-1960 studies of eye movements evoked by stimulation of various brain structures needed to be done again. Al Fuchs and I, back in 1969, attacked one of the more obvious targets—the frontal eye fields.32 We showed that stimulation (with currents much lower than previously required) evoked all-or-nothing saccades and that there was a sort of map of saccade size and direction there. A second point of attack was the superior colliculi, where I showed in 1972, the now well known motor map of evoked-saccade size and direction in the deep layers that coincided with the visual retinotopic map in the superficial layer.33

When Sam Ron joined us around that time, he applied the same logic to the cerebellum and systematically explored that structure with a stimulating electrode. He revealed the importance of the vermis near lobes V and VI as a saccadic hot spot and showed that evoked saccades were not all-or-nothing but depended on stimulus parameters, indicating an involvement within the pulse generator circuits themselves.34 These early studies have since been redone with even lower stimulus currents (eg 20 μA) but without significant new surprises. Other studies using lesions or single unit recordings have now shown a role of the frontal eye fields and cerebellar vermis in smooth pursuit. Evidently we were misled in these early investigations into thinking that we were studying saccade-only areas but apparently the threshold for saccades is so much lower than for pursuit that we failed to recognize any involvement of the latter. Thus, things get more complicated.

Fortunately, others have charged ahead, where we have hesitated, by recording from suprapontine areas. David Sparks and colleagues have made intensive investigations of the superior colliculi (eg), Mickey Goldberg and colleagues have explored the frontal eye fields,39 Bob Wurtz and colleagues have exam-
ined the substantia nigra, the Schlags have looked at the internal medullary lamina and the supplementary motor area and Mountcastle and colleagues have examined the parietal cortex. These results are interesting and tantalizing but so far they cannot be assembled into schemes that can assign functional roles to each area and describe how their signals are processed in finally reaching the burst neurons in Figure 3. They do, however, give us much to think about.

Smooth Pursuit

For some reason saccades have held the spotlight in oculomotor research and it is only in the last few years that studies of the pursuit system have proliferated. As Figure 1 indicates, the pursuit command arrives in the pons as a velocity signal. Zee et al have shown the flocculus to be important for pursuit, and others (eg) have found many Purkinje cells there that carry the pursuit velocity command. These cells may relay their signals, on their way to the motoneurons and integrator, through cells clustered just caudal to the abducens nuclei. Recent work of others now suggest a pathway, at least skeletal, originating in the middle temporal lobe, descending to the dorsolateral pontine nuclei, ascending to the cerebellum — vermis and flocculus — and finally returning, as shown, to the motoneurons and the final common integrator.

Our contribution has largely been confined to behavior. We have shown that the upper limit of human pursuit velocity is close to 100 deg/sec. We have been concerned, from a clinical standpoint, about what gains (eye velocity/target velocity) are normal. Oculomotor students and colleagues tend to have gains around 0.9—0.95. These high gains appear to be less related to experience than a knowledge of expected behavior. In a recent study of patients with schizophrenia, we found that naive, unmotivated control subjects with no knowledge of eye movements had gains around 0.7 for targets moving in unpredictable ramps at 30 deg/sec (the patients had gains of 0.3, unpublished observations). In a recent analysis of pursuit, to form a data base for a model, we found that subjects often had gains greater than 1.0 but what was more interesting was that at the onset of ramp tracking there was overshoot and ringing of the eye velocity (at about 4 Hz) that was completely missing when tracking stopped. We believe that this is evidence that the pursuit system is switched on during tracking (much like saccades in Figure 3) and then switched off to be replaced by fixation — a distinct neurological system. Put another way, fixation is not pursuit at zero velocity.

Motor Plasticity

Beyond signal processing, another interest of our laboratory has been the discovery and subsequent demonstrations of ubiquity of motor learning in the oculomotor system. In the beginning, the field owes a great debt to Geoffrey Melvill Jones of McGill University and Masao Ito of Tokyo University. I well remember the XXV International Physiological Congress in Munich in 1971. Geoffrey first brought to everyone's attention his discovery with Gonshor that the gain of the vestibulo-ocular reflex could be changed by dissociating head movements and the expected slip of images on the retina with reversing prisms, while Masao pointed out a theoretical mechanism via a visual pathway to the flocculus that could effect such changes (see Ito for a comprehensive review). I was very impressed and when, after a year back at Hopkins, no one had published results in an animal model, I decided to induce plastic gain changes in the cat and show that flocculectomy abolished such changes. As I expected, Masao had exactly the same plan for the rabbit and published his results in 1974. Nevertheless, my efforts did help because the "normal" gain of the reflex in the albino rabbit was 0.24 and the induced changes were about 0.14, whereas in the cat, the normal gain was 0.90 and the changes, induced by reversing prisms and abolished by flocculectomy, were large (0.80) showing clear results that needed no statistics to verify. Since then, it has been shown that with such visual-vestibular dissociation the gain can be driven up or down in humans, monkeys, cats, rabbits, chicken and goldfish; the governing principle being that the gain always be adjusted so that images do not slip (unduly) on the retina when the head turns.

When Gen Haddad joined the laboratory, we confirmed that lesions of the inferior olive also abolished gain plasticity. Since then, Miyashita, in Tokyo, has shown conclusively that the climbing fiber-Purkinje cell pathway is essential for this form of motor learning. Gen also showed that flocculectomy in the cat did not effect the recovery (suppression of nystagmus) after a unilateral lesion of the vestibular nerve. We call this balance control. This is important because it had been argued that since loss of Purkinje cells did not abolish balance control (indeed loss of the entire cerebellum does not abolish it) then Purkinje cells had nothing to do with any form of motor learning. This is clearly premature; as has already been mentioned, the climbing fiber-Purkinje cell pathway is essential for gain control. What our finding does mean is that balance control is much more complex, depends only secondarily on the cerebellum and depends on many other pathways, especially those from the spinal cord.
When Joe Demer did his thesis project with us, we set out to do a definitive behavioral test of the controversy between Ito (modifiable synapses in motor learning are between the parallel T fibers and the Purkinje cell dendrites) and the alternative theory (learning occurs outside the cerebellum and just happens to pass through the climbing fiber-Purkinje cell pathway on its way out to the eye). We would modify the gain of a cat’s vestibulo-ocular reflex, say to 1.5 by magnifying goggles, then we would anesthetize the climbing fibers by injecting lidocaine into the inferior olive. If Ito were right, the learning should be retained and the gain stay at 1.5. If the alternative theory were correct, the learning would be abolished and the gain should return to 0.9. We did the experiment; the gain rose to 2.0. Such is biological research. However, the gain, after lidocaine, was affected by the adapted gain before, by about half what would be predicted by Ito’s theory. Anne Luebke, a student in our laboratory, is currently trying to get to the bottom of these confusing results.

Our main contributions to motor plasticity so far have been to demonstrate that it is ubiquitous. When we began to use vectors and matrices as tools to examine the vestibulo-ocular reflex in all three dimensions, it seemed clear that the gains between horizontal canals and vertical eye muscles or vertical canals and horizontal muscles, must be just as adjustable as, say, horizontal to horizontal. This is called cross-axis plasticity. Lex Schultheis did his thesis project in this area. He rotated cats in pitch in the presence of a synchronously horizontally-moving optokinetic drum and showed that after several hours of training, excitation of the vertical canals in the dark produced reflexive horizontal eye movements. Thus, we twisted the reflex. This ability was, not surprisingly, abolished by flocculectomy. Lance Optican’s contribution has already been mentioned in regard to demonstrating plastic control of the saccadic pulse and step (now the pulse-slide-step) to eliminate post-saccadic drift. His main effort initially, of course, was to show that the size of saccades in general was under such control. This was not very surprising. Once a saccade is triggered in Figure 3, it runs its course so rapidly that there is no time for visual feedback to alter E_p. That is why saccades appear, superficially, to be ballistic. Thus, during a saccade, the system, just like the vestibulo-ocular reflex, is running open-loop; that is, without the benefit of negative (visual) feedback. This demands, on theoretical grounds, that the system maintain calibration through motor learning. Lance also showed that this motor learning was again abolished by cerebellar lesions.

Subsequently, it was shown that background vergence tone and the amount of accommodative vergence induced by accommodation (the AC/A ratio) were also under plastic control. Since the optokinetic system is the visual compliment of the vestibulo-ocular reflex, it automatically comes under the control of motor learning. Thus, only the smooth pursuit system, of all the oculomotor systems, remained untested. Since it is a negative feedback tracking system that is considerably slower than the saccadic system, one might think that the visual feedback would be enough and plasticity was not necessary, but Lance and Dave Zee reasoned that in the first 130 msec after the eye began to move (this is the latency or delay in the loop) acceleration was responding to the visual system’s appreciation of initial target motion in the previous 130 msec and the movement could not be modified by vision for another 130 msec. Thus, this system, too, was behaving, if only momentarily, as an open-loop system. By using patients with a muscle paresis, and requiring the patient to view for a week first with only the paretic eye and then the good eye, they demonstrated large, plastic changes in pursuit gain.

By now, of course, motor plasticity is accepted everywhere in the oculomotor system. Whenever it has been investigated, cerebellar lesions almost always interfere with it. These facts obviously have a great influence on how one interprets oculomotor disorders with regard to time available for plastic readjustments (recovery) and cerebellar involvement. Many rapid visuomotor acts involving limb muscles (reaching, postural recovery) come under exactly the same theoretical considerations that now, 17 years later, make motor learning in the oculomotor system taken for granted. No one supposes that the same sort of motor learning does not also apply to motor control in general and few believe that the cerebellum is not involved in an important way. That is why it is so critical to work out how plastic changes occur in the simple vestibulo-ocular reflex, because then we will very likely know how it is done everywhere.

A Strabismus Model

As a bioengineer, I wondered, a long time ago, why the biomechanics of the eye, strabismus and its surgery had not been worked out. After all, it is just six muscles attached to a ball, and muscles act like rubber bands, etc. So, as a hobby on the side, I worked out all the equations and by about 1965 had a program running in Fortran. I guessed the spring coefficient of the muscles. The program told me that the only stable position of the eye was flipped over straight back into the orbit. That is what models are for: to tell you when it is time to go back to the laboratory. What I needed to know was the relationship between length, tension and innervation of...
human extraocular muscles. I put the program away in a drawer and forgot about it.

Two years later Arthur Jampolsky, of the Smith-Kettlewell Institute of Visual Sciences (SKIVS), invited me to come out for a visit and to suggest a research project we could do together. Boy, did I have a project in mind! Arthur was as good as his word and arranged to have patients undergo strabismus surgery with local anesthesia so that while, with a strain gauge mounted on a microdrive, we measured the length and force of a detached muscle, the patient could change innervation naturally by looking at target lamps arrayed over the surgery table with the other eye. The results were just what were needed. Armed with these vital data, I revised my squint model and published it in this Journal in 1975. The model not only describes how six muscles cooperate to point the eye in any given direction but pathologies can be interpreted as “surgery” then performed on the model to see which manipulation would give best results.

Joel Miller joined us in 1979 and converted the model to the UNIX operating system, adding many improvements and making it simple to operate. One benefit of all this was to point out again the need for further physiological research, in particular, how much do the tendons of the horizontal recti slip sideways over the sclera when the eyes look up or down? The answer means a significant difference in the action of these muscles in secondary and tertiary positions. Joel and his colleagues (by this time he had moved to SKIVS) attached radio-opaque markers to the horizontal recti of muscles in monkeys and found remarkably little side slipping, indicating that the action of the muscles with respect to the orbit was relatively independent of eye position. This abstract was awarded the Fight for Sight Citation for outstanding achievement in basic research at the 1984 ARVO meeting.

Nevertheless, progress has been slow in this area because so few people are interested in squint. In a field preoccupied with vision, there is something mundane about working on muscle mechanics—a sort of parallel with garage mechanics—which, unfortunately, puts it close to the bottom of our collective priority list. Strabismus surgeons themselves contribute to this image: a little resection here, a little recesson there; who needs to know about muscle mechanics or consult a computer program? Nevertheless, it is an interesting and important part of our field and I still hope that our SQUINT Program will find its way into clinical applications.

Concluding Remarks

At the risk of appearing to ramble, I have tried to give an impression of the exciting results that have come tumbling out of the past two decades. As is often the case in integrative neurophysiology, progress is not made by adding one piece to the puzzle, it is made by fitting many pieces together to form a functional, sensory-motor picture of how the brain, or at least a bit of it, works. So it is in the oculomotor system; it is the overall picture that is important, not any one detail, and I have tried to sketch this overall picture. When the windfalls of technology offer us such a rich data base, we are challenged to the next step: to interpret these data. In integrative neurophysiology these interpretations, or models, take on the prickly forms of wiring diagrams and mathematics, simple at first, as represented currently in the oculomotor system, but bound to get more and more complicated as we probe the incredible capacities of the human brain. If we need complicated circuit diagrams to explain how a transistor radio works, what will the circuit diagram look like if we ever explain the saccadic system? In another 20 years, what will we think of these first, simple steps?

References

12. Simpson JI and Graf W: Eye-muscle geometry and compensatory eye movements in lateral-eyed and frontal-eyed animals. In Vestibular and Oculomotor Physiology: Internatl. Meeting


56. Miyashita Y: Differential roles of the climbing and mossy fiber visual pathways in vision-guided modification of the vesti-


