Papers and Originals

The Twilight Land of Change and Decay*

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Few would deny the poetical genius of Samuel Taylor Coleridge, but "the truth about Coleridge the talker seems to have been that he rapt some listeners to the seventh heaven; bored others to extinction; and made one foolish girl giggle irrepressibly. But there is one point upon which all who listened are agreed; not one of them could remember a single word he said" (Virginia Woolf, 1961). With such a warning in mind I embark upon the task you have seen fit to entrust to me, not hedged in by fashion or tradition, which means that I myself, as your President, must shoulder full responsibility for what I am about to say. I feel free on many counts to devote these moments of fellowship and mutual aid to an inquiry into the philosophy that guides our science, especially as it bears upon our future. Lest there be any among you who take alarm at the intrusion of theoretical principles into what you quite reasonably regard as a practical enterprise, I hasten to assure you of my intent to avoid anything that betrays a bias for pure theory on the one hand and working-day pragmatic pathology on the other.

An Ideal to Strive For

We must never lose sight of the true source of inspiration of all great enterprises; I refer to an ideal to be fought for against all odds, that springs from our inmost hearts and refuses to be deterred by obstacles of planning, political manoeuvring, personal ambitions, and the like. From what I have already experienced during the birth pangs of the College I have no doubt that the enthusiasm of our younger members will supply the driving energy for many years to come. And, quite properly, we shall depend on our older, experienced colleagues for the wise and skilful canalization of this energy into regions rich in potential for progress and unbounded development. "To old age belongs the old man's business," says Nietzsche, "of looking back and casting up his accounts, of seeking consolation in the memories of the past, in historical culture."

But what of this ideal that I maintain to be our first consideration? It is, I believe, no more than that which fashions the history and endeavour of science in general manifesting itself in a burning conviction that objective truth and rules for discovering it exist and that on such a basis unanimity is possible and desirable. This unanimity must be achieved without coercion, personal argument, or appeal to authority (Rapport, 1957). And what exactly are these rules that should guide us in our search for truth and all that stems from its attainment? Allow me for a few minutes to recapitulate the history of their discovery and consolidation, for this achievement is just as much a part of pathology as it is of the natural sciences.

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Evolution of Scientific Thinking

Man, it would seem, has always been given to observing. Primitive folklore represents part of those observations that have escaped the ravages of time. If we add archaeological evidence to these age-old legends and sayings we derive a fairly complete index of ancestral workings of the mind aimed, in the first instance, at survival of the individual and of the race. Repeated sifting of this knowledge ushered in a hazy appreciation of certain vital codes which forestalled rules for conduct, tribal protection, and the placation of the untamed forces of Earth and the firmament that encloses it. Thus emerged a sense of the value of experience, and the dim gropings after some sort of meaning in this hoarded treasure. Thus, too, was born the overpowering feeling that supernatural powers intervene between man and his ever-threatening environment which can be placated by sacrifice and ritual.

With the expansion of the treasure-houses of experience, specialization was inevitable, and there emerged the food-provider, the master craftsman, the priest and soothsayer, and the physician. Even when the first tiny city-states grew up as havens of protection and storehouses of grain, and man groped his way along the margins of the restless sea in his quest for an easier existence, the conflict with Nature still challenged his maturing imagination no less than his physical endurance. Babylonian and Egyptian records at the very dawn of documented history tell us of a great wealth of observation about man and his environment, cosmic phenomena, and the scourges of Nature. Herein we decipher the drift towards a kind of empiricism, as periodic phenomena of the heavenly bodies and their wayward companions the comets, the seasonal ravages of the great rivers, the change and decay of living things, were in turn noted and puzzled over. This in turn conceived a crude form of mathematics and physical science, a biology built upon the perception of Nature's most obvious manifestations.

Greek Contributions

Unrestricted observation, tinged with a vague desire to find an underlying purpose, gave birth to empiricism built upon observation and rudimentary experimentation, a form of trial and error. Its glorious fruition in the Greek city-states culminated in the genius of Aristotle. In him we see the messenger who endeavours to bring order into the world through scrutiny and simplification. His place in history is even more astonishing as one who realized the supreme importance of logic and the need to state the so-called laws of logic in a form that is clear and easily made use of in regular life.

But the Grecian contribution that excites admiration and awe is the attempt to erect a science by assuming certain basic, consistent postulates with which, in turn, are resolved the complexities of knowledge as it is stumbled upon by the curious and the observant. In mathematics and astronomy deduction

reached its greatest heights. But to my mind the most impressive of all the Greek contributions was their ingrained habit of questioning everything in life so that behaviour and belief might be simplified and some sort of order established. This precept burns through the great tragedies of Aeschylus, Sophocles, and above all Euripides, no less than in the inspired Socratic dialogues and the *Republic* of Plato. Think for a moment of Socrates, for whom "the unexamined life is not worth living." But do not forget that this sombre probing of all that came beneath the scrutiny of the intellectual Greek was watered down by a distinct capacity for mischief. Richard Hofstadter (1963), in contrasting the modern professional man who lives for ideas with the journeyman who lives off ideas, protests against the grotesque life when "intellect gets swallowed by fanaticism and piety." For this a counterpoise is needed, something to prevent it from being exercised in an arid, rigid way. Hofstadter suggests that such a counterpoise exists even in the most intellectual temperament as the quality of playfulness. "Man is perfectly human only when he plays," said Schiller, and nowhere do we see this amalgam of high thinking and joyousness more subtly fashioned and embellished than among the Greeks.

Inspiration of the Renaissance

For more than two thousand years thereafter the unhappy, restless West lay dormant in a miasma of intellectual stagnation and decay through which penetrated a few solitary rays of percipience and ancient wisdom, lovingly fostered in the monasteries or cherished as a peculiar treasure by the wild, tempestuous hoards of Islam. From one of those moments in history when catastrophe threatened to overwhelm the world in chaos there emerged a period of enlightenment and rebirth of the mind and soul which we call the Renaissance. Two men of genius appeared in Italy, Leonardo da Vinci and Machiavelli, the one a master of the arts and science no less than an inspired anatomist and engineer, the other a diplomat and political scientist. Both grasped the essential point about modern scientific method, that it progresses through the combined use of empiricism and rationalism. Nature speaks to us in detail, and it is only through the detail that we can find her grand design (Olschki, 1945; Bronowski and Mazlish, 1960). This we do by establishing a unity or simplicity in natural phenomena, expressed in laws and simple hypotheses, which inspire us through their neat and elegant pattern with a sense of beauty and a theory of aesthetics. To Copernicus and Galileo, to Newton and the pioneers of the great scientific societies, we owe this landmark in our intellectual journey through the ages. And no small debt is owed to the philosophers, from Francis Bacon to Emanuel Kant, who saw the world as an "endless chain of cause and effect," re-emphasized the place occupied by experience in the acquisition of knowledge, but warned us that the observer himself enters into all such discoveries and interpretations.

Should we wish to frame a code of behaviour suited for the scientific exploration of anything in life that arouses our curiosity we can do no better than follow the dicta of René Descartes: "Carefully to avoid precipitancy and prejudice, to comprise nothing more in my judgment than what was presented to my mind so clearly and distinctly as to exclude all ground of doubt . . . to conduct my thoughts in such order that, by commencing with objects the simplest and easiest to know, I might ascend by little and little, and, as it were, step by step, to the knowledge of the more complex; assigning in thought a certain order even to those objects which in their own nature do not stand in a relation of antecedence and sequence; and in every case to make enumeration so complete, and reviews so general, that I might be assured that nothing was omitted."

To these we may add the saying of Leonardo: "Science is the captain and practice the soldiers; both must march together." And above all we must cultivate the art of clear expression, both in dealing with our colleagues and patients and with our reports

to our brothers in practice. Our great prototype, the Royal Society of London, asked its Fellows to report their findings "without amplifications, digressions, and swellings of style; to return back to the primitive purity and shortness, when men delivered as many things almost in an equal number of words." The Society wished to exact "from all their members a close, naked, natural way of speaking, positive expressions, clear senses, a native easiness, bringing all things as near the mathematical plainness as they can" (quoted from Hearnshaw, 1928).¹

I must take the hint, and hurry on to matters no less important though I fear still cloaked with obscurity.

Uncertainty and Doubt in the Twilight Land of Pathology

Uncertainty about just what we are to conclude from a body of careful observation has long since made many of us sceptical and prone to doubt our inferences. Hence we have groped for the statistical approach. But how much more does our own personality and mental equipment influence us in drawing conclusions? Can we train ourselves to become detached from all such handicaps when we attempt the assessment of data obtained by a group of highly trained observers working under identical conditions? I believe that all thoughtful pathologists have faced this problem many times and have achieved some sort of a compromise with increasing experience. They, like their colleagues engaged with physical phenomena divorced from matters implicit in the living state, learn that there is no such thing as absolute knowledge. For ordinary-day purposes a coarse approximation to the truth more than suffices for diagnosis and treatment of disease.

We can still afford to be governed by working-rules that give us an overall statistical view of distorted functioning in organs without being concerned with the basic components, the postulates, as it were, of disease that allow of no further analysis. In this respect we stand in much the same relation to the fundamentals of biology as the Newtonian world contrasts with the Einstein outlook. We accept a model of life and its upsets that is perhaps crude and oversimplified, yet works under the restrictions of technique and intelligence that have hitherto satisfied us. But the time is rapidly approaching when we shall no longer be able to ignore the new trends and evaluations consequent upon changing techniques and ways of thought, and we shall realize, with dismay, that we have been living in a twilight land into which must penetrate the shafts of light from a clearer, luminous world of knowledge. No longer will we say with Euripides, "After all, wisdom is only happening to guess right," for we shall have fully realized with Shakespeare that

"—our virtues
Lie in the interpretation of the time."

Meanwhile we must endeavour to strike a balance between ourselves and our environment in the most general sense of the term consequent upon the opening up of these new worlds of thought and understanding. A new sort of plan will have to be thought out; the selection of one set of appearances rather than another because it gives a better sense of the reality behind the appearances, as Bronowski (1960) neatly puts it, is the first signal of emergence from the twilight.

I realize that I am in danger of obscuring the theme that I am trying to develop largely because of this principle of uncertainty that emanates from the twilight land of knowledge; so let me turn to a region that confronts us no matter whether we labour in the hospital ward, in practice, or prefer the seclusion of a research laboratory. I refer to the surface of cells and cellular products, domains that are truly part of the twilight land of change and decay.

¹ So also Antonio Sacchini (1730–86), the pupil of Scarlatti, "chiarezza, bellazza, buona modulazione."

The Cell Surface, a "Twilight Land of Change and Decay"

Some of the confusion has grown up around the use of the terms cell surface and cell membrane. The former commits us to nothing more than vague, interfacial regions in which the outermost cellular molecular complexes come into the orbit of a cloud of ions, water, and all sorts of molecules, some very large, in transit from environment—intercellular spaces—to cell interior. It is surely a region of flux, a twilight land of change and decay. When we speak of a cell membrane we imply all of these things together with some notion of pattern or structure in the cellular molecules that are primarily concerned. Indeed, claims have been made that such a membrane can actually be separated from the main mass of the cell by micro-surgery or centrifugation. This belief has come mainly from studies on the red blood corpuscles, although direct observation of other isolated cells, grown in tissue culture and photographed by the cine-camera, also supports the concept. Pulvertaft (1949), for instance, most brilliantly has recorded rhythmic movement, called flicker or scintillation, confined to the red-cell surfaces, recalling the movement produced by wind blown over a field of wheat.

Electron-microscopic investigation of all such red-cell ghosts—that is, the surface membrane that is left behind after haemolysis and thorough washing of the erythrocyte—does indeed give evidence of a surface ultrastructure in which can be distinguished plaques or short cylinders, about 40 Å thick, 250 Å diameter, packed in hexagonal arrays over the entire surface and composed of phospholipid and cholesterol, along with protein fibres, 20 Å diameter, 100–400 Å in length, lying beneath the plaques (Dourmashkin *et al.*, 1962). These are held together by ether-extractable lipid, the arrangement of which decides whether the membrane exists as leaflets or pores (Hoffman, 1962). But, as Ponder (1961) rightly points out, the value of this kind of investigation is very much limited, since the process of preparation largely determines the chemical and physical properties of such ghosts.

Be that as it may, there is no gainsaying the research that has followed the pioneering observations of Overton, which points to the existence of a specialized surface region, a few molecules in depth, which cannot be removed or even badly damaged without the cell dying. Beneath this extenuated plasma membrane lies the ectoplasm.

The evidence for a surface region is threefold:

1. At the surface of the cell is a very thin layer of cytoplasm that is a very poor conductor of electricity in contrast to the interior that is a good conductor (Jacobs, 1962).
2. Things that fail to cross the surface of the cell in either direction diffuse rapidly and freely within the cell boundaries when introduced into the interior of the cell (Chambers, 1922).
3. Investigations into the permeability of cells for solutes show that the part of the cell that regulates the rate of uptake of such solutes is at or very near to its surface (Jacobs and Corson, 1934; Edelberg, 1952).

Such a surface region exhibits a preference in permeability for lipid-soluble substances, has a low surface tension, and contains enough extractable lipid, at any rate in the red blood corpuscle, to form a bimolecular leaflet (Gorter and Grendel, 1925). Grendel concluded that this layer is composed of cholesterol, cephalin and lecithin, and sphingomyelin; the double lipid layer has an average thickness of 30–55 Å. Further studies on a broad base favour the idea that the "blanket permeability" properties of the cell membrane, as Davson (1962) has it, might well be accounted for by a thin layer of lipid stabilized by protein, since the surface tension at the cell surface is much lower than that of a purely lipid layer. Hence Danielli long ago suggested that the cell surface membrane consists of a bimolecular lipid layer, on each side of which is a monolayer of denatured protein, and a secondary layer of a globular native protein. Van der Waal's forces probably hold

together the lipid molecules in a side-to-side aggregation, with protein side-chains penetrating the lipid surfaces and stabilizing the film by their own Van der Waal's forces (Schulman and Rideal, 1937). Various proteins have indeed been isolated from red-cell ghosts, including several enzymes such as ATP-ase and a phosphatase (Glynn, 1959). The membrane, however, is not homogeneous, and we must postulate specialized regions which give to the membrane some of the characteristics of pores and of enzymes. These are concerned in accelerating transport of specific molecules through the cellular barriers, and in the cell's response to narcotics and to heavy metals such as copper (Davson, 1962). Above all, the idea of such specialized regions is needed to explain active transport of certain molecules and ions into or out of the cell. Quite likely these regions are needed for the metabolic reactions that provide energy used in the transport of the molecules and ions concerned. I shall return to these topics in a moment or two.

Investigations into the Plasma Membrane

Two recent developments in the exploration of the plasma membrane illustrate the complexity of this problem and the need for its advancement on the broadest lines.

1. New fixatives of cells that favour high-resolution electron-microscopic studies of membranes appear to give a truer reflection of the underlying molecular architecture than heretofore and favour the idea of a lamellated bimolecular structure of lipid and protein of total thickness about 75 Å (Robertson, 1959, 1960). A similar pattern is found in the endoplasmic reticulum, Golgi apparatus, and mitochondria of animals, plants, bacteria, and even certain viruses parasitized within the interior of a cell. Contact between adjacent cells is largely determined by the lamellated membranes and their adhesive properties aided by little tags called desmosomes which afford points of especially strong adhesion. These observations may well indicate important lines of investigation into tumour growth, for explanted non-malignant cells after division move into position to form aggregates like adult tissue, and when they touch each other their movement becomes inhibited. This is the contact inhibition of Abercrombie. Cancer cells show no such inhibition (Abercrombie and Heaysman, 1953; Abercrombie and Ambrose, 1962).

2. There is still much to be said in favour of the use of models of cell components for following cell processes. Recently A. D. Bangham and his colleagues have submitted a model of the plasma membrane composed of lecithin, with or without cholesterol, in aqueous dispersion to electron-microscopic examination after negative staining with potassium phosphotungstate. They have detected spherulites in these dispersions that are composed of concentric lamellae. The latter, in turn, consist of a lipid layer roughly 44.2 Å wide, and a water compartment 25 Å wide. Rod-shaped elements with a breadth of 10.2 Å lie at right angles to the long axis of the lamellae. These most likely are groups of lipid molecules (Bangham and Horne, 1962, 1964).

In the presence of saponin, which you will recall is a surface-active toxic compound well known for its lytic action on red corpuscles, or of lysolecithin, a hydrolytic breakdown product of lecithin produced by an intracellular phospholipase, or after exposure to various venoms, these spherulites change and tubules penetrate them at right angles to the planes of the lamellae, giving an array of minute perforations. Evidently these agents can penetrate tightly packed leaflets of mixed lipids encountered in such molecular membrane, and possibly those found within a biological cell membrane, thereby disturbing the electrostatic interfacial or intermolecular forces that maintain the integrity of bimolecular structures. Instability and eventually emulsification or micellization of the leaflet follow. This overall surface charge of membranes estimated as zeta potential is important for the normal metabolism of cells, especially when certain enzymes—for example, lecithinases—are concerned in maintaining the

integrity of the plasma membrane and, no doubt, its permeability.

Bound up, too, with this kind of investigation are such important matters as the clotting of blood (Bangham, 1961), the mechanism of ionic detergents, the potency of local anaesthetics (Skou, 1954), the mode of action of certain toxic compounds on various cell organelles and specialized membranes such as the myelin membrane of myelinated nerves (Thompson, 1964), and, as I have suggested elsewhere, the properties of bile (Cameron and Hou, 1962). Even more intriguing is the suggestion that a bimolecular membrane damaged by an undue accumulation of surface-active anions, especially fatty acids, causing discrete areas of micellization and emulsification, might be reconstituted by incorporation of surface-active cations at the site of damage. In other words, cellular injury initiated at cell surfaces should be reversed by due attention to these principles. Already Bangham, Rees, and Valerie Shotlander (1962) have shown that liver necrosis in rats resulting from exposure to carbon tetrachloride is prevented by intraperitoneal administration of a simple long-chain cation such as stearyl amine or cetyl trimethyl ammonium bromide. Their results also suggest that it is the presence of positive charges at the cell interface that prevents the development of necrotic lesions in the cell. We would all agree that any research that gives hope for the prevention and cure of serious cellular injury must be pursued with vigour.

Essential Movement

Amidst the complications and uncertainties of this aspect of cell life and death, this "twilight land of change and decay," one problem stands out very plainly, the movement in and out of things that are essential to the integrity and future of the cell. Whether they be food, excretory products, the gases of respiration, some or all are transported by the bubble mechanism of pinocytosis. These to-and-fro exchanges, especially when they affect defence, must not be forgotten in planning the strategy of future attacks upon disease. We have been forcibly reminded of the importance of such movements by the enzymic leakage from various kinds of cell which now is being fashioned into a powerful means of diagnosis and prognosis of disease. I single out relevant studies on cardiac infarction, liver necrosis, and muscular dystrophy.

For less complex matter, notably ions, water, and non-electrolytes, two mechanisms are placed at the disposal of the cell (Ussing, 1960): (1) *passive diffusion* or leakage from the diffusion membrane, whereby ions move downhill, as it were, in the direction of their electrochemical gradient; (2) *active transport*, in which ions move uphill against such potential gradients as in the exchange of K ions outside the cell for Na ions inside. Energy has to be expended to overcome the inherent resistance of the cell membrane—a lipid barrier—and moving the ions about the cell (see Conway, 1957; Hogben, 1962). Pumping stations have been postulated as the machines concerned in active transport, the pump itself resembling ATP-ase, with ATP acting as the main source of energy for the pump (Dunham and Glynn, 1961). Passage through the cell membrane is expedited by lipid-soluble "carriers" that take up ions at the surfaces and transport them across the membrane in a shuttle service.

Recent studies suggest that the respiratory chain assemblies and the phosphorylating enzymes which prepare the fuel are located in the mitochondrial membranes: the Krebs-cycle enzymes, the fatty-acid cycle, and their ancillary systems that stoke the carriers with fuel reside in the matrix (Fernández-Morán, 1962). All of this makes cheering reading and encourages us to expect a much more precise chemical model

of cellular function in health and disease at a not-too-distant future, replacing the older ideas of vaguely connected disjointed functions by a common plan of interlacing enzymic chain reactions which can be switched one way or another to subserve metabolism, respiration, and the other functions of the cell. We are about to cross the barrier that separates our world of gross structure and function from the submicroscopic and molecular domain, and with dismay we find ourselves confronted with the mysteries of the atomic and subatomic cosmos where events and observer are no longer separable. But courage! Man's determination and faith will find a way out of this labyrinth of frustration and disorder, for we stand at the threshold of the mansions of the mind, whose exploration will in the process of time reveal a new unthought-of universal science.

Meanwhile our particular mission as a College, though modest, is clear enough. We must stand together in the determined effort to preserve the highest ideals of service and advancement in our profession, free from any kind of distinction or personal ambition, serene in our faith in the future and aims of our fraternity. Without doubt disappointments will come our way and many obstacles must be surmounted, but they should give us little concern while we share the purest ideals. Take consolation, my brothers, for the weariness and setbacks of life in the immortal lines of Euripides:

"Gods manifest themselves in many forms,
Bring many matters to surprising ends;
The things we thought would happen do not happen;
Things unexpected God makes possible,
And that is what has happened here today!"

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