THE BIOLOGY OF SCHIZOPHRENIA

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By R. G. HOSKINS, Ph.D., M.D.

Director of Research, Memorial Foundation for Neuro-Endocrine Research, Harvard Medical School

AND

Worcester State Hospital

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PREFACE

THE subject matter of this little book is made up of a slightly amplified version of material that was presented as the three Salmon Memorial Lectures at the Academy of Medicine in New York on the evenings of November 2, 9, and 16, 1945. Hitherto, the Salmon Lectures have been delivered exclusively by psychiatrists. The invitation, this year, to a physiologist was motivated primarily by the fact that I had been privileged to serve, since 1927, as the Director of Research at the Worcester State Hospital, where a somewhat intensive study of the schizophrenia problem has been in operation for the past 18 years.

In 1926, under the leadership of Mrs. Stanley McCormick, the Memorial Foundation for Neuro-Endocrine Research was organized. From the beginning Mrs. McCormick has served as president of the Broad of Trustees. The selection of myself as Director of Research of the Foundation was motivated by a hope that an approach to the problem of schizophrenia (dementia praecox) at the physiological level might throw important additional light on the nature of the disorder and might indeed lead to a fundamental solution. In addition to participating in the activities of the Research Service of the Worcester State Hospital, the Foundation has carried on through most of the intervening period a series of researches at the Harvard Medical School on certain aspects of endocrine biology that seemed to offer promise of improving insight into the nature of the psychosis.

In these lectures an attempt has been made to survey the psychosis primarily as a special manifestation in the biology of man as a product of integrative evolution. In discussing the evolutionary process I was necessarily concerned with the overall problem of values; the question of the origin, nature, and ultimate destiny of man is involved. The temptation has been difficult to withstand to come to grips with the problem of

cosmic purposiveness—a problem in which I am by no means uninterested. It has seemed expedient, however, to attempt to stay within the framework of human evolution and to assume, as the only purpose involved, the survival of species. This purpose is so clearly evident throughout organic nature that it can perhaps be accepted without cavil by all intelligent readers. I have dealt briefly with the biology of ethics, not as a part of an over-all purpose but as a means to the implementation of the survival value of gregariousness. I have been concerned to speak only the truth, though not necessarily the whole truth. The span of evolution from electron to society is as great, I think, as the available scientific evidence is able to reach. With Sherrington, I have intentionally left open the possibility that there may exist within the cosmos a higher emergence, but one with which the scientist, as such, has no competence to deal.

My thanks for aid in carrying out the current task and furthering the work upon which these lectures are based are due to so many individuals as to preclude the listing of them. A word of special gratitude may be spoken, however, to all the many colleagues who have shared in the researches themselves. Specific mention should be made of my obligation to my colleagues Drs. David Shakow and Harry Freeman, who aided directly in compiling certain of the data that were used in the writing of the lectures.

It is my hope that this book may prove of some aid to non-psychiatrists in obtaining a comprehension of a very baffling subject, to beginners in research in the field by offering certain suggestions regarding the many problems that are presented, but most of all to intelligent laymen who may be encouraged to exert their influence to the end of setting up a more respectable defense than has ever yet been offered against the menace of schizophrenia.

R. G. H.

SECTION ONE

THE BIOLOGY OF MAN IN RELATION TO SCHIZOPHRENIA

INTRODUCTION

THE PROBLEM of schizophrenia presents to the medical profession the outstanding challenge of our day. One fifth of all hospitalized patients in this country are victims of this single disorder. The psychosis commonly takes onset in the early years of maturity and usually persists in a greater or lesser degree of severity throughout a lifetime that is not greatly shortened. Often the end is complete disintegration of the personality. To the patient it represents separation from family and friends—literally in many cases, spiritually in all cases. It casts a pall of undeserved stigma upon the family in which it strikes and no family can know itself to be exempt. In our country approximately 150,000 able-bodied citizens are annually removed from productive pursuits to be maintained at large cost in special institutions. In addition to the institutionalized population there are many schizophrenics living outside of hospitals. At best they are inoffensive incompetents and at worst they constitute a portion of the criminally insane, with hoboes, prostitutes, and other less offensively queer people falling in between.

To a layman visiting a ward of schizophrenic patients for the first time the experience is bewildering. Here stands a youth in awkward, rigid pose, refusing all communica-

tion and apparently oblivious to, but quite aware of, all that is going on about him. There lolls another gazing into space with a vacuous, foolish grin, interrupted occasionally by self-conscious, silly laughter. In that alcove a young man is dancing with a nurse, with all the airs of the ballroom habitué that he is. An older man minces by with coy glances and seductive swaying of the hips. Two young men are playing table tennis with alert skill. Several sit reading with various degrees of intentness. One man ambles by nonchalantly pushing a swab and kneeling occasionally to kiss the floor. In that corner one loudly berates his former employer who did him deadly wrong. Three men are arguing with imaginary voices. Mostly, however, the ward is occupied by quite ordinary-appearing persons doing ordinary things in an ordinary way, albeit with a certain air of indolence as befits bored, incarcerated men. Some of them can converse easily and intelligently. Yet each patient is the victim of an ominous psychosis from which many of them, so far as we can now foresee, will never recover.

As a biological phenomenon, schizophrenia represents primarily a distortion of the personality. It is almost as varied in its individual manifestations as is human nature itself. It presents facets of interest to anyone who is concerned with man from any point of view. It offers problems in sociology, psychology, physiology, and general medicine —all of which disciplines are conventionally brought to bear in psychiatry proper. Historically the psychosis was for many centuries regarded as primarily a matter of religious concern, it being thought of, in effect, as a special variety of sin, i.e., of devil-possession—a concept that led

to much abuse of innocent victims in attempts to exorcise their in-dwelling demons. The opprobrium which in the minds of many still attaches to the disorder harks back to this early concept.

Biologists, as such, have not greatly concerned themselves with the problem of schizophrenia. But over the past 20 years it has been my somewhat unique privilege as a physiologist to have observed from a favorable vantage point many cases of the disorder and the efforts of a group of workers from several disciplines to elucidate the problems presented. It is primarily in the role of a physiologist that I propose in this and succeeding sections to invite your thoughts to schizophrenia as a manifestation of disordered biology.

The literature on so challenging a subject runs, of course, to great length. To the biologist, with his predilection for scientific explicitness, much of this literature seems somewhat inept—an attempt to compensate for frustrating ignorance by semantic adroitness. Many of the writings of psychiatrists seem addressed rather more to unprofitable sophistication than to wisdom. In opening this discussion may I therefore comment briefly on the nature of formulation itself. In an address that should be required reading for all scientists and especially social scientists, Sir James Jeans has emphasized that no verbal statement whatever can be equated with reality. Formulations in their essential nature are comparable to maps in that they symbolize by conventional signs various features of a given terrain. A map, like any other formulation, is good or bad merely in accordance with the degree of success with which it records particular relationships. A map, for example, that would be adequate

to the needs of a geologist might be quite useless for an ecologist. Throughout this discourse, then, it will be my purpose to use the simplest maps that can be made to serve the purpose of pointing out the features of the terrain that we are to traverse. In this search for cartographic simplicities I shall openly eschew attempts at verbalizing the nature of the various subjective biological manifestations such as consciousness, mind, and spirit. These are primary experiences, and, in my considered conviction, attempts to go behind primary experience are merely a verbal cushioning of our frustrations of the yearning to know the unknowable. Since we must in any case, then, deal in allegories I hope that the choice of simple formulations will not be ascribed to either indolence or willful ignorance. So far as may be I shall seek for wisdom in simplicities rather than in belabored sophistication.

The schizophrenic personality can be likened to the distorted image of a man seen in an irregularly curved mirror. The fundamental approaches to the problem of the psychosis must then be directed to the three goals: the nature of the man who has the disorder, the nature of the distorting forces, and the details of the distortions. We are constrained, therefore, to give attention first to the biology of the normal human being.

THE NATURE OF MAN

Throughout the period of recorded history the problem that has most insistently engaged the thoughts of man is that of his own nature—his origin and his destiny. Philosophers

and theologians have discussed the theme from time immemorial. At each stage of social development the best thinkers have brought together such available facts as they have regarded as relevant and have attempted to systematize the facts in a fashion to reveal their ultimate meanings. Thus the philosophies and the religious formulations of each period have mirrored both the knowledge and the ignorance of the time. In view of the human propensity to cherish the old it is not surprising that many derivatives of fundamental ignorance have been carried over from each period to the next. Always, the ideological vested interests have resisted the challenges of new knowledge, with the result that much in the way of atavistic spiritism and magic persists in common thought even today.

Perhaps the most influential fact of all time, so far as the problem of the nature of man is concerned, is the fact that people dream. Running throughout all the prescientific formulations are concepts derived from that experience. To borrow a particularization from Linton, the hunter during a given night spends many hours stalking his foe or pursuing his mate. Yet, he is reliably informed, his *body* had actually remained at home all the while in the corner of his domiciliary cave. The only possible interpretation that common sense could suggest was that man is actually a dual personality, part physical and part spiritual. He is a soul inhabiting a body. From this it followed that the visible world is populated with invisible spirits. It was again a matter of common sense to assume that spirits, like men, were either good or bad, and thus arose the concepts of gods and demons. These concepts, in more or less refined form, persist in practically all the theological formulations, even today. It would go

beyond the scope of this work to deal further with the elaborations of these concepts, with the systems of witchcraft, of propitiation, and of exorcism that dominated the minds of even the best thinkers throughout the medieval centuries. The story of the transition from the medieval prescientific to the modern scientific concepts of the nature of man has recently been engagingly told by Sherrington.

During the nineteenth century much new knowledge bearing upon the nature of man became available. The laws of physics and of chemistry became increasingly clear. In the field of biology the publication of Darwin's *Origin of Species* completely changed the ideational climate. Many a losing battle was fought by the proponents of medieval spiritism and of less ancient vitalism in one or another of its guises, but at the end of the century informed scientific thought was fairly stabilized in the doctrine of organic evolution and the theory of deterministic materialism. Basic to all physical and biological thought was the doctrine of the indivisibility of the atom. It was confidently believed that the solutions of the problems of living things would ultimately be found by extensions of knowledge regarding the nature of atoms and molecules and of the laws that govern their interactions. With nearly 100 immutable elements to work with and the almost endless possibilities of permutations among them, what more could be needed or desired? The goal of each investigator, then, was to anchor his concepts in the certitudes of physics and chemistry. As a lingering concession to vitalism, however, "life" was still largely envisaged as a mystic something that had been in some occult fashion smuggled into the physical order. It was even fairly respectable and in some curious way satisfying to many

to transfer the mystic event of creation to some other planet and to speculate even in print how primordial, ancestral, living material might have come to the earth on a falling meteor.

Among the chief heritages of knowledge carried over into the twentieth century were the recognition that all living things vary, that advantageous variations have survival value, and that in the struggle for existence the fit tend to live and propagate their species and the unfit to perish.

Then the bombshell descended and shattered to bits the firm physicochemical foundation upon which the finished science of biology was to be erected. The indivisible atom fell apart, and with the fall a complete reorientation was necessitated in biology no less than in physics itself. The over-all upshot of the new orientation has been to throw into foreground perspective the principle of *emergence* as the central feature of the universe, both "animate" and "inanimate." But of this, more later.

All philosophy must now start from the postulate that the universe is composed not primarily of nebulae, suns, planets, and other aggregations of fixed matter in ultimate molecular form but of electrical particles, the electrons, the neutrons, and the protons combined and recombined to form a series of systems of increasing complexity, from that of the atom to that of social man himself. It is to this fundamental characteristic of the cosmos that the nature of man must be related. The history of humanity, then, must needs start not with a given hour on a certain afternoon on a newly created planet a few thousands of years ago, as the good bishop announced, but in the primordial cosmic mists of a remote antiquity.

The nature of the subatomic entities of which all things are made no one but the mathematical physicist is mentally equipped really to comprehend. We are informed by no less an authority than Sir James Jeans that by no stretch of the imagination can the electron be actually visualized. It partakes largely of the nature of a mathematical construct and derives its meaning only as a part of a system that includes, as a necessary component, the human mind. To find psychology penetrating to this lowly reach of reality is truly disconcerting. To those who perversely insist upon a mechanical model of the electron, de Broglie offers such bare comfort as this. Suppose, he suggests, that we picture a violent storm at sea with high-running waves. Then in imagination take away the wind and the water. The disembodied turbulence remaining would represent the electron. This is the stuff of which the cosmos—including man himself—is compounded. This is "matter."

Much of the universe exists at the electronic level (McClung). The component entities, however, are capable of combining in a variety of ways. Astronomers tell us that in some of the dwarf stars the condensation may be so great as to give a weight of 5 tons to the cubic inch. Contrariwise, in interstellar space matter may be so diffuse that the entire tail of a comet if transferred to the surface of our earth could be contained in a pillbox. The actual form that matter takes in any given locus of the cosmos is determined mostly by the gravitational and thermal conditions then and there present. But without further digressions into cosmology, let us redirect our attention to the situation in which we find ourselves on this tiny planet and in our own fragment of eternity, today.

Matter as it falls within our immediate ken exists in a series of semistable configurations, the 94 "elements." Each elemental atom is composed of a nucleus made up of neutrons and protons and, revolving around this nucleus in one or more orbits, a fixed number of electrons. Each, then, like the arrangement of our own sun and planets, is a solar system in miniature. It is only the number and the distribution of the electrical particles that determine the properties of the atoms—fundamentally, all are made of the same primordial stuff, whether the given substance be helium gas or metallic mercury. And at this level "energy" and "matter" become interchangeable concepts.

Whence and when came the electric particles we can only speculate—and perhaps the speculation is meaningless. If one's philosophy embodies creationism it is at this level that creation must have taken place. If one believes in miracles, it is to this, the fundamental miracle of all, that his attention should most often be directed. If he prefers a theistic approach to reality he must recognize that it is through the agency of organized electric particles that God operates "His wonders to perform." This is the basic scientific truth that must be envisaged by all who would "worship in spirit and in truth."

THE PRINCIPLE OF INTEGRATIVE EVOLUTION

From this point on the story will point out how the subatomic structural stuff is combined in more and more complex systems and that with increasing complexities of organization new properties of higher and higher orders emerge.

No attempt will be made to treat the topic historically—to point out the earlier insights that foreshadowed the scientific knowledge of today. Only a few of the many orders of emergence at the various levels as now recognizable from molecule to man will be briefly discussed.

As to the nature of matter at the molecular level any of the known elements could be utilized as illustration. Suppose that we start with sodium and chlorine, recalling that each represents merely a different constellar arrangement of the same sorts of electric particles. The two constellations, however, exhibit very different properties. Chlorine is a greenish, acrid gas and sodium is a soft, gleaming metal. Under appropriate conditions these two substances interact, at the atomic level, sharing a common electron in their two outer orbits and give rise to a new, joint configuration with the emergence of a set of entirely new properties. The new substance is, of course, common table salt or sodium chloride. This relatively simple chemical reaction brings out clearly several important laws of emergence.

First of all, it would have been impossible, so far as we can now judge, to foresee a priori from all possible knowledge of chlorine and of sodium *as such* the properties of sodium chloride—for example, its crystalline structure, its solubilities, and its saline taste. This generalization holds throughout the range of integrated levels of organization. *The properties of a new emergence are not predictable from the properties of the pre-emergents.* Another characteristic of this emergence is that it disposes once and for all of the *nothing-but fallacy.* It is often stated that salt is nothing but sodium and chlorine. Similarly, behavioristic psychologists have often stated that man is nothing but a collection of

behavior patterns. As a matter of fact, salt is not sodium and chlorine in the ordinary additive sense at all but is something that is actually as different from sodium and chlorine as these elements are different from each other. The point can hardly be overemphasized, namely, that structural elements in new molecular configurations give rise to entirely new properties and these are dependent primarily upon *arrangement*. Nevertheless, the properties of sodium chloride are determined not only by the over-all constellar configuration but also by that of the constituent atoms. For example, if for sodium, in the salt molecule, hydrogen were substituted we should have not the bland salt but the highly corrosive hydrochloric acid gas. But hydrochloric acid, once formed, has identical properties the world over, whether in the human stomach or on the tinner's bench. It is only this constancy that renders possible a science of physics or of chemistry—or, indeed, of any science at all. The essence of "magic" is the repudiation of the principle of constancy of emergents.

The chief principles of integrative evolution may be further indicated in the words of Novikoff: "Each level of organization possesses unique properties of structure and of behavior which, though dependent on the properties of the constituent elements, appear only when these elements are combined in the new system. Knowledge of the laws of the lower level is necessary for a full understanding of the higher level. The laws describing the *unique* properties of each level are qualitatively distinct, and their discovery requires methods of research and analysis appropriate to the particular level. These laws express the new organizing relationships, i.e., the reciprocal relationships of elementary units

to each other and of the unit system as a whole." These laws, be it reiterated, are quite as valid at the level of "personality" —hence of schizophrenia—as they are at the simple molecular level. The emergence of new attributes arising from new special patterns of organization is a stubborn fact that permits neither denial nor rational explanation. It is creationism in the essential meaning of that term, and the term, I think, has no other valid meaning. Obviously this concept abates no whit any of the wonder or beauty of human nature in its higher manifestations. It merely focuses our attention on the magnificent potentialities of matter itself. So much then for the stuff of which we are made.

MULTIPLE COMBINATIONS

To resume the story of emergence, one of the axioms of physical chemistry is that, given any two or more soluble substances, these will unite as many different ways as attendant circumstances permit. To use a simple illustration, if one drops into a glass of water a pinch of sodium chloride and one of potassium bromide the salts will dissolve, dissociate mostly into the constituent atoms and these recombine. The final system will then contain water in several different molecular arrangements, sodium ions, potassium ions, bromine ions, chlorine ions, molecular sodium chloride, molecular sodium bromide, molecular potassium chloride, and molecular potassium bromide. In a simple water-solution system these seem to exhaust the possibilities, except, perhaps, as certain "addition" compounds might be further formed. Under other conditions, however—for

example, in the living cell and with other constituent elements added—much more complex combinations can take place. It has been roughly estimated that in "organic" matter, i.e., in the carbon-containing compounds, a million different combinations may be made, combinations sufficiently stable to persist as such, and the actual number may even be much greater. Many of these are explicitly known and the organic chemists are identifying other thousands each year. It is upon this almost infinite potentiality of recombination with the emergence of new properties in each case that the possibilities of the evolution of living things primarily depend.

EMERGENCES AT THE MOLECULAR LEVEL

Many volumes would be needed to include what is now known of the chemistry of matter. Let us be content for the moment with pointing out only a few of the many emergences that are of particular interest in their bearing upon the nature of man. One remarkable property of a considerable proportion of the known compounds is that of *crystallization.* There are, for example, in the earth today vast deposits of sodium chloride existing in the crystalline form. Such crystals are easily produced "artificially." If into any saturated or supersaturated solution of salt one introduces a granule of the same material in solid form to serve as a "template," the surrounding molecules of the salt begin at once to accumulate about this "seed" in a special arrangement through which the characteristic lattice pattern of the crystal is maintained. Given only a pabulum in kind, crystals

can grow and reproduce indefinitely. And the term *reproduce* is used advisedly because it is in this property of matter that we find the emergence in simplest form of reproduction even as seen in man.

Under some circumstances atoms can unite in larger and larger aggregates to form highly complex molecules. If the molecules become sufficiently large they may begin to approach the properties of solid matter even though existing in true solution. These giant molecules form what is known as *colloids*. Egg white may serve as an example. Again, volumes would be required to expound the known facts of colloid chemistry. Suffice it to say that colloids have numerous properties that are not seen in crystalline compounds. For example, if a dry colloid such as gelatin be placed in water it promptly absorbs a considerable quantity of the fluid. By the penetration of the water into the gel there is produced an enormous surface of contact between the water phase and the "solid" phase, and surface-tension phenomena come into play at the boundaries. These phenomena, which are lacking in ordinary solutions, give to the colloid solutions very special properties. Among them are the processes of adsorption, conditions favoring high reactivity among the adsorbed materials, and the possibilities of forming semipermeable membranes that may be electrically polarized. It is to the colloidal composition of protoplasm that many of its peculiar properties—characteristics that largely determine the properties of the evolved organism—are due.

One other important feature of chemistry, and especially the chemistry of living things, is the process known as *catalysis*. One of the most marked peculiarities of cell chemistry

is the speed with which chemical reactions take place in it. For instance, sugar dissolved in water will remain essentially intact for a long period, though potentially capable of being ultimately converted to carbon dioxide and water. But in living substance, the protoplasm, sugar may be oxidized with surprising speed, liberating heat, light, or doing work by the energy set free. The possibility of such acceleration of chemical processes is dependent upon the existence in the protoplasm of special molecules, the *enzymes*. The process of enzymatic catalysis is but one more example of the emergence of new properties resulting from special configurations of the material substratum. Among all the processes of organic evolution the emergence of catalysis would seem to be among the most important. It so greatly accelerates the speed of hydrolytic, oxidative, reductive, and condensation reactions as to add much versatility and lability to protoplasm. To revert to one of the simplest of the organic processes, the conversion of glucose to carbon dioxide and water may again be mentioned. Several stages are involved in the process and each stage is regulated by its own enzyme system. As Lawrence Henderson pointed out many years ago, these interposed enzyme directive systems serve somewhat after the fashion of traffic officers. At each stage the chemical reaction is directed into a given channel instead of one or another possible alternative channel. It seems to be primarily by this device that the unstable stuff of the human body is largely directed to specifically adapted ends. These enzyme systems are utilized both in the building up of particular molecular configurations and in degradation processes that liberate energy in quantified amounts adapted to the metabolic needs. An important possible bearing of this

topic upon the schizophrenic psychosis will claim our attention later.

Rather similar to the enzymes in their catalytic influences upon the chemical processes of the body are the *vitamins.* Indeed, some at any rate of the vitamins actually act as constituents of the enzyme systems. What is as yet known of the functions of these substances is derived largely from observations on the unfortunate results that accrue when they are taken in inadequate amounts. According to our observations, vitamin deficiencies are common among schizophrenics and the possibility must be envisioned that the schizophrenic process might conceivably be importantly influenced by disturbances in vitamin regulation.

Another significant group of regulatory substances, though one that is of relatively late appearance in the evolutionary scheme, is that of the various *hormones.* These are special chemical substances that are formed in a few discrete portions of the body, the endocrine glands, and carried through the circulation to exert particular stimulating or inhibiting effects in other portions of the body. Their precise mode of operation is for the most part not clearly known but their action seems to be closely allied to that of the catalysts proper in that they selectively influence the speed or extent of particular chemical processes in the metabolic total. Disturbances of hormonal physiology have often been postulated as important etiological factors in schizophrenia.

PROTEINS AND PROTOPLASM

Among the many complex molecules found in the living body, perhaps the most important are the various *proteins.*

It is primarily of these substances that the bodily machinery is constructed. The proteins are among the largest of all known molecules. By various methods and especially by the use of digestive enzymes they can be broken down into smaller constituent bodies, the *amino acids.* From protein digests 22 different amino acids have been isolated. Of these, 10 are known to be specifically necessary for bodily health and must be supplied as such. Of these indispensable amino acids, some are necessary for the maintenance of the structural integrity of the body, some for growth, some for reproduction, and some for the processes of differentiation and maturity of the individual tissues or of the body itself. Although the individual tissues in which the structural protein molecules occur tend to resemble each other closely from one species to another, the fact that they are specifically different, chemically, can easily be demonstrated by biological tests. Proteins cannot for the most part be injected from one species to another but can be utilizable only after they are broken down by the digestive processes and reconstituted into the particular pattern characteristic of the recipient species. This important aspect of biochemistry has poignant meaning to victims of allergy, who may react extensively and very uncomfortably to the introduction into the body of "foreign" proteins. A possibly important relationship of amino-acid metabolism to the schizophrenic psychosis will be discussed subsequently.

One of the earliest emergents in the evolution of living matter is that of *protoplasm,* often referred to as the living substance, proper. At any rate it certainly forms the matrix in which the chemical processes upon which life depends take place. Its microscopic structure is that of an emulsion

or "foam," the solid part of which, the gel, is made up of a complex system of colloids of a nature still largely unknown but which includes not only protein but fatlike bodies and carbohydrate as well. The gel is seldom uniform but is differentiated physically and chemically in different parts of the cell. The fluid part of the emulsion is made up of water in which are dissolved a variety of salts. Protoplasm is chemically unstable and throughout life is constantly in a state of metabolic flux. Every activity in protoplasm, whether secretion of a gland, contraction of a muscle fiber, or passage of a nerve impulse, is accompanied by an electrical disturbance in the protoplasm. Every living cell is therefore in effect an electric battery, a fact that has often led to the overfacile statement that life itself is merely electricity.

THE EMERGENCE OF LIFE

The different levels of matter in the evolutionary hierarchies are somewhat distinct but not completely delineated from each other. "No boundary in nature is fixed and no category airtight. *'Mesoforms'* are found at the transition point of one level to the next" (Novikoff). In other words, emergence is likely to appear not in sharp steps but as a somewhat gradual process. It would seem that "life" emerged in this fashion. As previously noted "living" and "nonliving" materials were very generally thought of a century ago as constituting distinct orders of nature. It was supposed that many of the substances found in the living organism would remain forever beyond the art of the chemist to reproduce. The monumental first onslaught on this

unprofitable though venerable theory was the artificial production of a very characteristic biological substance, *urea,* by Woehler in 1828. One other principal onslaught was the discovery that enzymes would often function outside the cell approximately as well as inside. In the succeeding years more and more ground has been cut from under the "vitalists" and but a relatively slight extrapolation of known knowledge will suffice to complete the job. Almost the final *coup de grâce* has been the discovery and isolation of the viruses. These, in sequence through the Rickettsial bodies and the vaccinias, almost bridge the final gap between living cells and lifeless crystals.

The viruses are the agencies by which numerous diseases —for example, the *mosaic disease* of tobacco plants—are transmitted. They, like chromatin, are made up fundamentally of crystals of nucleoprotein which, like other crystals, have the property of propagation. They differ from such things as salt crystals, however, in that they are able to abstract atoms and elaborate the molecules needed for growth and reproduction from a pabulum that does not contain them preformed. There is one limitation upon their propagation. They are able, so far as we now know, to abstract and organize the material necessary for their growth only from a substrate that is already in part prepared by other organisms. It will not be until investigators are able to propagate viruses upon an "inanimate" substrate that the last step will have been taken. It may be surmised that this will depend upon the introduction of one or more appropriate catalysts into the pabulum.

As a matter of fact, the distinction between "living" and "lifeless" is much more highly regarded by the layman than

by the biologist. And no actual philosophical advantage accrues by interpolating a special mystery of creation between the nonliving protein crystal—for example, that of egg white—and the living virus crystal. It is quite as easy and quite as satisfying in the last analysis to assume that electrons, neutrons, and protons have the potential property of entering into a system from which emerge the joint properties of reproduction and of metabolism that constitute "life" in its lowest manifestation as to assume that this one particular emergence was specially ordained. Actually if we assume creationism at this stage it is logically necessary to assume it at several other and higher stages—for example, that at which consciousness emerged. Either alternative is equally adaptable to the usages of theology, but the theologian would reap a strategic advantage by taking his place in the vanguard rather than by continuing in his accustomed place among the reluctant followers of the newer scientific thought. The revelations to Darwin or to Morgan are actually quite as valid and as binding as are the revelations to Moses or to Thomas Aquinas.

Altogether it seems highly probable that life emerged at a precellular level. It may not be too hazardous to venture a guess that the most primitive organism consisted of a mere naked bit of nucleoprotein—no doubt of submicroscopic dimensions. This may indeed have been the first appearance of the *gene* from which the *chromosomes* of higher organisms evolved. Perhaps even at this early stage the gene assumed the control of its immediate environment, which property is its most outstanding characteristic in all the higher forms of life. It is tempting to assume that the gene organized its bit of environment in minute globular form

surrounded by a physicochemical interface. This gene was then perhaps joined by a second and that by a third in the additive linear order which is apparent in the finished chromosome as it is seen in animals of today. On such a hypothesis the dominated environmental mass—the primitive cytoplasm—of each gene would fuse and the limiting boundaries become confluent—as occurs when two neighboring soap bubbles join to make a larger bubble. Subsequently, individual primitive chromosomes thus derived might have entered into a system of symbiosis, with the cytoplasmic masses again mingled and confined within a further confluent limiting membrane—ultimately the cell wall. The foregoing conjecture seems to me to be compatible with the facts as we know them today.

ANIMAL STRUCTURAL PATTERNS

Although there are known exceptions to the rule, living material as we know it, both in plants and in animals, is characteristically organized into minute compartments known as *cells*. The cells vary a great deal in size from one place of occurrence to another but have diameters of the general magnitude of 1/1,000 of an inch. The animal cell is enclosed within a cell wall, a structure that represents essentially a condensation of the outer portion of the protoplasm to form a semipermeable membrane. Through this membrane take place all the exchanges between the cell and its environment that are incident to the business of living. In most animal cells a characteristic structure known as the *nucleus* is found. This is in turn a still smaller cell-like struc-

ture that lies free-floating in the protoplasm (here known as the cytoplasm), the activities of which it dominates. The most essential feature of the nucleus is its *chromatin* which consists chemically of molecular nucleoprotein. It is through the agency of the chromatin, as will be discussed later, that hereditary qualities are transmitted from generation to generation.

Whatever may be one's taste in conjectures and whatever may have been the steps by which primitive living substance emerged, the story of evolution from the one-celled stage forward is relatively clear. It is epitomized in the individual history of each human being. As a matter of known *fact,* he begins existence as a single cell, the fertilized ovum. This cell divides into two and those again into four and so on until a cluster resembling a colony organism results. By an enormously complex series of further divisions of cells and organization of these cells, an ever increasingly intricate series of successive structural patterns results, to culminate in that most intricate of all known structures, the newborn infant. Corner has recently told this story in fascinating detail. Much evidence serves convincingly to indicate that the evolution of the species followed the same general plan as the evolution of the infant. We can continue the story of evolution then, beginning with the ancestral one-celled organism.

In the lower forms of animal life the individual, like the beginning infant, consists of a single free-living cell in which are carried out all the functions upon which existence depends. As evolutionary development proceeded the cells came to be aggregated into colonies living together in a sort of symbiotic union. It was at this level that cell differentia-

tion first emerged, those cells on the outside maintaining relationships with the environment and those on the inside specializing somewhat in metabolic activities for the benefit of the colony as a whole. Fairly early in the evolving pattern appeared still another group of cells which functioned particularly in the business of maintaining communication among the different departments of the primitive organism. Fairly well down in the scale different sorts of cells came to be fashioned into organs, such as stomachs or eyes, and the organs in turn into systems, such as the digestive system or the excretory system. The process at long last has culminated, at least for the present, in the highly intricate and multifariously integrated structure, the individual human being.

REPRODUCTION

One of the obvious limitations upon the biological efficiency of the one-celled organism is its minute size. And this is a limitation that cannot be escaped by that cell because of the elementary geometrical relationship between mass and surface area: the former increases as the cube, whereas the latter increases only as the square of the diameter; as the cell grows the relatively diminishing area exposed to the environment soon becomes too small to support the metabolic processes of the organism and growth ceases. In the evolutionary process this geometrical limitation was circumvented by the emergent process of *reproduction*. By this process a given amount of material was divided into two masses and the total relative area thereby increased. In its earliest manifestations reproduction may have been a sim-

ple budding process such as is seen in yeasts at the present time.

In the operation of simple cellular reproduction each daughter organism has precisely the properties of the mother cell. Obviously, this system of reproduction would necessarily give rise to a high degree of stereotypy of patterning which would permit survival only within the limitations of a corresponding constancy of environment. It obviously provides only a minimal possibility of adaptation to environmental changes.

This limitation, too, has been lessened by the process of *bicellular* reproduction in which such variability of patterning as had been achieved within the individual cell was pooled with that of a copartner in the reproductive process. The fundamental advantage of the method seems to reside in this augmentation of variability and consequent increase of the potentialities for adaptive evolution. In the simplest form of bisexual reproduction the two "parental" free-living cells meet, fuse, and divide. Their meeting may have been at first a matter of random chance, but early in the scale of development there appears in primitive form an "attraction between the 'sexes.' " This was presumably implemented at first merely by "chemotaxis" or "chemical attraction," itself an important emergent that is manifested in many of the primitive organic activities—an example in man is the "direction" of the outgrowing sprout of a severed nerve into the path taken by the nerve prior to its injury. As evolution progressed, however, and the reproductive processes became increasingly complicated, other emergences—what might be called *biological directives*—appeared.

Perhaps the most difficult to implement of all of the evolutionary processes were those growing out of the division of the life stream into *germ plasm* and *somatoplasm*. Grossly simplifying a highly complicated story, suffice it to state that reproductive cells came to be segregated within the bodies of the parents where they escaped the demands of most of the business of living. Their metabolic needs were met by the activities of the remainder of the body—activities that include such processes as securing food, digesting it, and disposing of waste products—in the higher forms highly complex procedures. It was left for them merely to reproduce themselves in endless series and thus carry the stream of heredity. With the germ cells thus segregated—the ova in the mothers and the spermatozoa in the fathers—two over-all problems were created. These were the bringing together of the parents and the discharge into a common environment of the reproductive cells. Of the mechanics and physiology of coitus as practiced by man and the higher vertebrates as a means of bringing the germ cells together nothing further need be said. To the various "psychological" devices that were evolved whereby the "attraction of the sexes" could be made to operate for the promotion of coitus we shall return in a later section of the discussion. The "erotic impulses" are of large moment in relation to the schizophrenic psychosis.

HEREDITY

One of the most characteristic differences between living and nonliving systems, though by no means an absolute dif-

ference, is the ability to transmit the properties of the individual to its descendants. The numerous adaptive devices by which this process is carried out are subsumed in the term *heredity*. This emergence appeared very early in the scheme of living things and is, indeed, foreshadowed in simple crystals.

The methods of implementation of organic heredity are highly intricate and in the current connection can be sketched in only the broadest outline. Suffice it for our purposes to state that the hereditary unit is the gene, which is a very minute—indeed ultramicroscopic—bit of nucleoprotein. The genes, of which the higher organisms are possessed of thousands, each differing slightly in its properties, are arranged in aggregates in linear series to form the chromosomes. The latter are plainly visible under the microscope. In the process of cell division each chromosome is drawn to a mid-cellular position, where it splits lengthwise in such fashion as to divide each component gene into equivalent halves. The two arrays of split chromosomes are withdrawn toward the poles of the dividing cell. An equatorial constriction then takes place and separates the entire cell into two daughter cells, each of which receives an exactly equal dowry of genes. In the higher forms, with each cell division throughout life this process is repeated, though with gradually accumulating differentiation of the cytoplasm. The end result may be body elements that are as different as simple gland cells on the one hand and neurons on the other. The differentiating factors seem to be carried in the cytoplasm.

In the case of sexual reproduction the two parent cells, each carrying the full complement of chromosomes—pre-

viously "reduced" by antecedent divisions—meet and fuse. The comparable chromosomes unite by pairs in such fashion as to bring together corresponding constituent genes. Thus each hereditary element appears in duplicate, one moiety being of paternal and one of maternal origin. The two genes of each pair come into intimate junction and more or less influence each other, but in the final effect on the unfolding organism one is likely to be "dominant" and the other "recessive."

How the genes actually determine the patterning of the offspring is as yet unknown. It is evident that there is no one-to-one representation of hereditary items in the individual genes, as is often thought, but each exerts its influence in relation to the genic complex as a whole. What is actually transmitted is some sort of organizing influence comparable perhaps, but in a much more complex way, to the sort of "template" influence that determines the form of a snowflake.

Through the operation of the reduction divisions in the ripening germ cells, there is a sorting of genic "determinants" so that only half of those existing in the grandparents appear in the chromosomes of the given offspring. Statistically speaking, then, each individual obtains half its hereditary characteristics from its parents, one fourth from its grandparents, one eighth from its great-grandparents, and so on in diminishing series. However, no one of us necessarily still has a bit of the genic chromatin of any given ancestor, because the number of genes is limited and in the meiotic shuffle some ancestral genes can be lost in each generation. It is thus theoretically possible that the descendants of a given John Smith may in the course of time have received nothing

whatever from him except his name. To those who desire a detailed and philosophic discussion of the subject of the cytology of heredity McClung's recent monograph can be highly recommended.

It must be recognized that what is actually transmitted is not finished characteristics such as form of nose, color of eyes, or pugnacious disposition. As Jennings has emphasized, what is passed on from parent to offspring is *potentiality* of a given development. What actually appears in the completed offspring is dependent not only on genic composition but also upon the circumstances attendant upon the unfolding process. The hereditary potentials may or may not be realized. For example, the infant is endowed at birth with a remarkable series of potentialities that are normally unfolded at the puberal period of development. One of the necessary conditions for such efflorescence is, however, the presence in the body of an adequate amount of at least the thyroid, pituitary, and gonadal hormones. If the infant is deprived of these it fails to mature, remaining throughout life, as regards sexual matters, merely an overgrown infant.

This limit on the operation of the mechanisms of heredity is often overlooked. It obviously is of the utmost significance in the philosophic aspects of the problem. Heredity does not by any means equate with inexorable fate. While it is true that the limitations upon the development of the individual are fixed and definite, and most of us are fated at birth to mediocrity, much latitude exists for promoting such development as is inherently possible. Of the two factors, "heredity" and "environment," the latter is often of the greater pragmatic importance. And this is the sum and sub-

stance of the ancient controversy regarding "nature *versus* nurture."

As will be discussed later, the importance of heredity in the etiology of schizophrenia is a lively issue. The dictum, "schizophrenics are born, not made," is still a matter of ardent debate. A fact that renders difficult a satisfying judgment is that much that is of major importance is passed along from generation to generation, not through the operation of organic heredity but through the *conditioning* of infants and children. Thus tribal and family behavior patterns may be inculcated and carried along through many generations, and organic heredity and social heredity play intermingled and often indistinguishable roles in the determination of the characteristics of the maturing individual.

DRIVES AND INSTINCTS

Early in the course of evolution there emerged a variety of methods of controlling the various structures through which the life processes are carried out. It is obvious that no organism could function without such controls, any more than could a car proceed purposefully without a driver. As one simple illustration, the possession of a digestive system would be of no value to the individual except as he had an impulse to eat. This fact becomes distressingly evident in the case of that disorder *anorexia nervosa* in which hunger and appetite have been lost or negated by psychopathological motivations. By and large it follows of necessity that all of the numerous adaptive processes by which the individual is integrated with his environment and by which integration

among the component systems of the individual is maintained must be made up of both *structural arrangements* and *directing impulses* to utilize the mechanisms. The evolutionary significance of these drives is often overlooked. Disharmonies at this biological level are of the essence of schizophrenia.

Of certain of the earliest emergent *controls,* those that can be seen in operation among unicellular organisms, nothing further will be said. These include such methods as chemotaxis and the various tropisms. Likewise at this juncture we may make but passing allusion to the action of hormones and other controlling chemical substances such as the carbon dioxide of the blood stream.

Among the most important of the adaptive mechanisms are the *reflexes.* These depend upon arrangements of functioning elements whereby a given stimulus arising in one part of the body—for example, the retina of the eye—sets up nerve impulses that are switched automatically into paths that lead to effector organs and bring about reactions that constitute appropriate responses to the stimulus. The reflexes may be relatively simple or very complex. It would go beyond the scope of this work to deal in any detail with reflex behavior. Suffice it to say that the essential feature in the control of reflex activity is the *setting of the switches.* Much of the reflex behavior is "innate"—which is to say that the patterning is laid down as a part of the general fetal structuralization of the organism.

Another moot question is where reflexes leave off and *instincts* begin. When the lips of a newborn infant are touched with any suitable object such as a fingertip, an elaborate set of muscular activities is set off. Does this

behavior represent a "sucking reflex" or a "sucking instinct"? The distinction is purely arbitrary, and so illy defined are the instincts that many psychologists repudiate both the term and the concept itself. Nevertheless, there are sorts of behavior such as nest building and the copulatory pattern for which the term instinct or some equivalent term is necessary. These activities are carried out in highly stereotyped fashion and without any previous learning process. They obviously stand in "mesoformic" relationship between pure reflexes and "willed" behavior. Like other mesoforms, they share in the qualities of both emergences between which they are interposed. Both the "innate reflexes" and the instincts are passed along from parent to offspring as set patterns, but the instincts are further characterized by awareness and by affective concomitants. The affect frequently rises to a sufficient degree of explicitness and poignancy as to constitute an *emotion*. Indeed, an emotion has been somewhat vaguely defined as "the way an instinct in operation feels to the person who experiences it."

One confusing feature regarding the instincts is that many of them come to overt expression only after a preceding process of *maturation* has occurred. For example, one compelling reason why the human infant does not take up walking immediately after birth, as does the guinea pig, is that the neural mechanisms necessary to that process are not yet completed. The same principle holds for numerous of the "engrams" (central nervous patternings) that underlie instinctual reactions.

In one category of instinctual reactions we know that the maturation mechanism is actually the appearance or augmentation of regulatory hormones. Thus if a baby rat is de-

prived of its gonads it fails completely to develop the copulatory behavior pattern. This, however, can be instated at will by the injection of appropriate hormones. It is characteristic that in lower animals this pattern appears in its completed form whether the individual has had opportunity for tutelage by companions or not and the same is true for some of the human patternings. Other examples of interposed maturation might be cited—for instance, Domm's baby chicks that were made to "crow" in a high canary treble at the age of two weeks or Wiesner and Sheard's preadolescent rats in which elaborate maternal behavior patterns were induced by injections of pituitary extract. Phenomenology of this order might appropriately be designated "chemical conditioning."

A principal, confusing element in the identification of instinctual reactions is the process of *conditioning*. Thus it is often impossible to be sure whether a given reaction is a result of a hereditary engram or whether the engram has been set up through the process of habituation. In either case, the underlying neural process is probably the same, namely, a differential lessening of interposed synaptic resistances whereby an adaptive rather than random activity takes place. And indeed, when we reflect that heredity operates merely by passing along potentialities rather than finished integrations the distinction between instinctual and acquired behavior becomes in some measure merely formal. The element of hereditary potentiality underlies both.

Schizophrenic behavior—and that pragmatically is schizophrenia—is a joint resultant of instinctual and conditioned reactions. Indeed, the long-standing controversy between psychologists and somaticists regarding the etiology of schizo-

phrenia hinges on the question which category of reactions is the more potent. There is no question, however, that in any individual case conditioning plays an important role. A few of the chief features of conditioned behavior may be underscored.

Conditioning is one of the earliest of the emergences that appear in the biological series. Indeed, it is clearly foreshadowed in many physical systems—for example, in the creasing of a sheet of paper. The essence of the conditioning process is implied in the old adage, "A burnt child dreads fire." It is probably not true, as sometimes stated, that every environmental impingement to which the human being is subjected leaves a permanent trace in its structural configuration—macroscopic, microscopic, or molecular—but it is certain that a very great many happenings do leave their traces. These vary in objective obviousness from the enlarged biceps of the blacksmith to the engram that gives rise to the subtlest affective stir experienced from a faint whiff of perfume. How the conditioning is brought about is largely a matter beyond our ken, but it must be recognized as due to some sort of spacial rearrangement at some level between that of a shift of a valence electron in a neural synapse or a reacting brain cell and the actual change in the bulk of an effector organ. And thus the conventional distinction between "functional" and "organic" becomes merely one of subtlety in modification of structure; psychology and somatics, then, in principle are one. The actual significant difference lies merely in the techniques that can effectively be brought to bear for study of the problems that are presented.

Conditioning is, of course, the basis of all learning. Its

most primitive manifestation is seen perhaps in the avoidance of harmful or dangerous things or situations—"once burned, twice shy." Thus we "learn" what is good for us or bad for us and we "remember" the lesson. Since the work of Pavlov, the conventional classic illustration of conditioning is the "teaching" of a dog to salivate at the sound of a bell, but the watering of a boy's mouth at the sight of a stick of candy serves equally well. In over-all statement, conditioning is the device by which experience is recorded and accumulated. *Instinct* represents merely racial conditioning. Conditioning at the individual conscious level is evident in *memory*. But many sorts of conditioning arise of which the individual remains entirely unconscious. For example, conditioned contraction of the pupil of the eye may be set up without one's ever having been conscious of either the conditioning process or of the resulting reaction. Higgins believes that many clinical symptoms are of this order.

Among the most fertile sources of conditioning are sensory experiences of one sort or another. Thus an infant very early "learns" that the tactile and perhaps olfactory sensations derived from the mother's body "mean" food. The scents on a lamppost "mean" to the neighborhood dog the recent presence of a friend or enemy.

Of particular importance from the standpoint of psychology and psychiatry is that manifestation of conditioning known as *symbolization*. To a dog a given scent symbolizes a given enemy. To a little boy the sight of a particular round, red object means in anticipation the delectable experience of eating an apple. But especially, after further appropriate conditioning, the spoken word "apple" comes to have the same significance, as do later a few conventional characters

in special arrangement—letters—on a blackboard or a printed page. In short, the child learns to understand, to speak, and to read a language. In his earliest experience he mostly learns to name things, then actions of things and attributes of things. Subsequently he learns to "abstract meanings" from things as well as relations between things themselves and their derived meanings. An inability thus to abstract is notable among the symptoms of schizophrenia. The conscious manipulation of words or their equivalents we designate as thinking. At the beginning of the process we have a baby crying for its mother and at the end we have a Whitehead writing profound philosophic discourse. But the process throughout is nothing more and nothing less than a simple or a complex manifestation of conditioned behavior. Conditioning can, of course, utilize many symbols other than words. The sight of the nation's flag to a lonesome tourist may give rise to an elaborate reaction pattern as may also the evocative notes of a violin. It is in the processes of conditioning and especially affective conditioning that much of the symptomatology of schizophrenia arises. It is in the use of language that the defective mental processes of the patient are largely revealed.

CONSCIOUSNESS AND AFFECT

In the exposition to this point the occasional use of the terms "consciousness" and "affect" has been unavoidable. They may now be discussed in more systematic fashion.

Perhaps the most characteristically human of all of the emergences that have appeared in the course of evolution is

that of consciousness. If it were not a matter of personal experience it would be inconceivable that such an attribute could exist. Whether, however, this emergence is in principle more remarkable than that of salinity when sodium and chlorine combine is very doubtful. Both happenings partake of the miraculous and there is small choice in miracles. When it first emerged in the course of evolution cannot be known nor can we more than surmise how far down in the scale of life anything comparable to human consciousness extends. McClung ascribes rudimentary awareness to interacting body organs and Fechner a century ago projected that faculty in rudimentary form even to trees and stones. A fact that must give us pause in retrospective projection of consciousness is that no more than an ounce of ether is needed to abolish completely any sort of awareness in a living human being in whom a myriad of biological activities are taking place. But somewhere along the evolutionary trail we must assume that the dimmest conceivable sort of awareness arose and gradually gained in explicitness and poignancy to that stage manifested by a poet composing a masterpiece or a lover in ecstatic embrace. It is perhaps not mere anthropomorphizing to assume from the behavior of my dog that he definitely knows when he is hungry, and one can more than suspect that the same is true of the trout that seizes a passing bug. But somewhere back along the course, it seems safest to assume, gradually attenuating consciousness finally fades out into mere automatism.

Actual human consciousness commonly and perhaps always is accompanied by feeling tone or *affect*. Pure affect in the sense in which the term is used in this work has only one of two attributes, namely, of pleasantness or unpleasantness.

Affect can be experienced in almost pure form when one is suddenly aroused from deep sleep. Usually, however, the affect is incorporated into an ideational complex which we speak of as an emotion such as hate, love, or fear.

It is the affective aspect of consciousness that most tempts the student of evolution to project that attribute far back toward the beginning of living things. Certainly from amoeba to man the organism acts "as if" it "sensed" the "goodness" of favorable environmental items and the "badness" of harmful items. Objectively the withdrawal of a pricked pseudopod and of a burnt finger seem to be phenomena of a quite similar order. Certainly the over-all process of evolution has operated upon a system of rewards and punishments. This fact is obviously implied in the principles of the "struggle for existence" and the "survival of the fit." The early emergence of affective awareness would have been of such obvious utility in operating that system that the temptation is strong to assume that it actually did occur. At any rate, in the culminating organism, man, it is through the agency of the emotions that daily conduct is commonly held or forced approximately within the limits that are conducive to survival. And it is of special interest in connection with the theme of this work that one of the chief characteristics of schizophrenia is the utilization of *autism,* i.e., suppressed awareness, to escape affective harassment. Anyone who recalls at all vividly, as I do, his inner experiences during early childhood realizes that there is considerable possibility of turning autism on or off at will.

There are two adaptive aspects of consciousness that demand especial attention from psychologists and psychiatrists alike. One of these is the utility of consciousness—here

the ego function—in the "testing of reality." Adaptive adjustment to any environment is possible, generally speaking, only by an organism that recognizes in some fashion its individual uniqueness in the environmental-personal totality of which it is a part, as well as the nature of its surrounding environment. Misappraisal on the latter point may readily lead to injury or sudden death—a fact of which the fly-fisherman takes planned advantage. Reality testing depends chiefly upon the reception of sensory impulses and the interpretation of these in relation to memories of previous experiences. Primary misinterpretations give rise to illusions or hallucinations and misinterpretations of relationships to delusions. Either illusions or delusions are significant in the evolutionary frame of reference merely or mostly as they lead to maladaptive reactions. Of the characteristic failure of reality testing and the resulting delusional systems of schizophrenics, more later.

A second aspect of consciousness and one that is also of major significance in relation to schizophrenia is the so-called self-regarding instinct. Running throughout the gamut of evolution is the principle of *the adaptive significance of superiority*. The fit most commonly survive, the unfit perish. The imperative evolutionary need for superiority is mirrored in the affect-laden sense of self-worth. Episodically, fear of danger or erotic desire may assume ascendancy in consciousness, but most of the time, in most people, as anthropological studies of the "status" principle show, the purpose of maintaining self-esteem at as high a level as possible affords the dominant motivation. "Keeping up with the Joneses" is not a mere foible to be amicably con-

doned—it is a fundamental biological imperative. It is imposed violation of this imperative that leads to much of the current industrial unrest. As will be discussed later, there is evidence that it is also a sense of intolerably low self-regard that is the chief precipitating factor of which the subject of schizophrenia is himself aware.

The function of consciousness has been conceptualized in several formal fashions. The dialectic literature on the subject is enormous. The oldest, chronologically, is the religious. It largely mirrors primitive, spiritistic orientations. Running throughout most formulated religions is the concept that man is fundamentally a spirit or soul, i.e., noncorporeal consciousness, temporarily inhabiting a body.

In the field of psychology proper, consciousness is dealt with especially in terms of ego concepts. They have grown out of the primitive sense of self-awareness—of all that is connoted to the man in the street by the pronoun "I." One feature of the ego experience that is of special interest to psychologists is subsumed in the terms "consciousness" and "foreconsciousness." They direct attention to a remarkable feature, "focusing of attention." From all that we know of the physiology of tissues it must be assumed that many parts of the brain are in a state of more or less continuous activity. Direct evidence that this is so is seen in the electroencephalogram. Yet of all this seething activity only a single modicum reaches subjective awareness. It is a matter of common experience that *subconscious mentation* frequently occurs. For example, when one is unable to recall a name and "directs his attention" to something else he is shortly delighted, often, to have the name "pop into his mind." Cannon has

recently emphasized that many research scientists make profitable use of this type of mentation, the results of which come into awareness in the guise of "hunches."

Of the potentially devastating effects of "suppression" of mentation and affective reactions to the subconscious level, only passing mention will be made. As is well known, such suppression plays a large role in neuroses and figures to an important degree in the mechanism of schizophrenia.

The psychoanalytic school has allegorized the faculty of consciousness in elaborate fashion. So often has the ego abstraction been characterized semantically that the name seems to have become a thing. The ego itself was used in the original Freudian allegory to mean principally the "self-preservation instinct" as contrasted with the "propagative instinct." As the "perceptive ego" it stands between the environment and the "id." It has been recently defined by Kubie as "that aspect of the personality of which the individual is partly conscious and partly unconscious, and which embraces the co-ordinated activities of the psychophysiological apparatus by means of which the individual relates himself to external realities." Judging by context, the Freudian ego seems to connote also what the man in the street means by "character" and "personal morale." In this conceptual system the central feature of schizophrenia is weakness of the ego, with various compensatory accompaniments. The analyst subdivides the "drives" that operate below the level of conscious awareness into the id, i.e., the "instinctual drives," and the "unconscious," which term would seem to have about the same connotations as the term "subconscious mentation" as used above. Perhaps the most important single contribution of psychoanalytics to psycho-

logical thought is the recognition that affective conditioning operates potently at the subconscious level. To the physiologist much that figures in the Freudian scheme seems to be nothing more than the operation of the conditioning process and the Freudian allegories to introduce an element of gratuitous obfuscation in attempts to understand the inner nature of man. Nevertheless, much of the literature on schizophrenia cannot be read intelligently without some comprehension of the analytic formulations.

Another of Freud's important contributions to the advancement of psychology was the introduction of serious consideration of *dreams*. The dream represents a manifestation of consciousness under a condition of reduced awareness. Of chief pragmatic interest is the fact that in the dream, repressed affective conditioning frequently emerges into consciousness, albeit with elaborate trappings of disguise. The dream is of interest to the biologist as affording a hint as to what may have been the mesoformic stage of consciousness as we know it in waking man.

Of two other aspects of consciousness, namely, the so-called herd instinct and the Freudian superego, we shall have occasion to make later mention.

TWO ROADS TO SURVIVAL

In the evolution of animal forms two rather distinctive patterns of survival have appeared. In some species these are seen in essentially pure form, whereas in other species they are variously intermingled. Of these patterns the one that apparently emerged the earlier is that in which any

sort of social relationship, brief reproductive episodes aside, is completely lacking. Examples of this earlier pattern are afforded by solitary wasps, turtles, and other animals that go their individual ways in general independence of their kind. This style of evolution might be designated the *idiocentric.* As applied to man and perhaps some of his nearer relatives, "egocentric" would be accurately descriptive. This pattern incorporates all the various adaptations leading up to individual personality—all the attributes connoted by the pronoun "I," in contradistinction to "we." It is made up of all the factors that would promote survival of a Robinson Crusoe cast alone upon a desert isle—the ego assets proper.

A very different and likewise a successful pattern is exemplified by such creatures as ants and bees. These forms also, of course, utilize the various adaptive devices that make for individual survival but in a fashion that is completely subservient to colony welfare. The individual is significant only as a part of an including totality—that is to say, a secondary and dominating system of survival is superimposed upon the idiocentric system.

Had human evolution taken consistently either the egoistic or the social road to survival most if not all of the difficulties that necessitate the presence of psychiatrists among us might have been avoided. It is the emergence of the superimposed social system that, in man, necessitates the pronoun "we." It involves all the changes of patterning and of personal orientation to which Robinson Crusoe turned when he was joined on the island by his man Friday. Since it is primarily from the stresses arising out of the simultaneous use of the two systems that much of the schizophrenic symp-

tomatology arises, some further attention to the *mechanisms of group survival* is demanded.

How the pattern of social living came to be instituted is, like all the other major problems of evolution, one for deduction from the evidence. It involves, of course, the general problem of the origin of all adaptive reactions. Unless one assumes creationism as running through the full gamut of evolution from amoeba to man it must be supposed that gregariousness arose on a basis of trial and error and was retained, as are adaptations generally, by virtue of its survival value. That it arose fairly early in the course of evolution is evident from the fact that gregarious living appears in many forms far below the level of man. In some instances the survival value of gregariousness seems to lie chiefly in the scope that it gives for the use of the "startle reaction," whereby any threat of danger is signaled at once to all the members of the flock. In many animal groups a further adaptation is seen in the posting of a sentinel at a vantage point from which danger can be promptly apprehended. A further elaboration of the group-survival pattern is evident in many species in which the older and stronger members of the aggregation take over the defense of the weaker members. Kropotkin has cited many examples of *mutual helpfulness* among the lower animals.

To cite one explicit example, a common experience of my early youth was the sight of a sentinel "antelope" (prong horn) standing guard on a sandhill top. Why this hungry animal sacrificed his immediate welfare to that of the herd feeding safely below presents a biological problem of major significance. The "sentinel" phenomenon includes two components, namely, what might be called "herd conscious-

ness" or "group consciousness" and, second, the obvious defensive reaction addressed to forestalling danger. It is in the interest of clear thinking to regard the two aspects of the herd instinct separately.

That any two or more animals in immediate proximity should be aware of each other just as they are aware of other objects in the environment can be taken for granted. In the same fashion a pedestrian on a busy city street is aware of other human beings about him. If, however, any occasion arises for concerted action—for example, a man falling into convulsions on the sidewalk—a new quality is at once added to the individual awareness of the people standing by. Examples might be multiplied. A passing stranger is reluctantly admitted to a wayside country home. He proves to be congenial and the following morning he departs as a friend. The phenomenon is of particular interest to the biologist in that it represents an emergence *in statu nascendi.*

How shall we designate the biological event that has taken place? A term is needed that sets forth the common element embodied in such words as friendship, love, patriotism, team spirit, religious feeling, and group morale—of that element of special awareness that is seen in almost quintessential form in an ideal honeymoon. In somewhat awkward phraseology, it is a "consciousness of *belongingness*" as contrasted with awareness of proximity. It is the intangible but very real something that makes the difference between a crowd of strangers going their individual ways and a mob engaged in a lynching. The psychoanalyst refers to it as a "transference." The term "identification" is also used, but neither is accurately descriptive. As a designation for this entity, the term "sympathy" would be precisely right, etymologically,

but through long usage it has acquired too many special connotations.

Perhaps the best available term—though used in one of its secondary meanings—is the word *empathy*, signifying, literally, "feeling into," the meaning connoted in Southard's term, the "empathic index." In the proposed usage empathy may be formally defined as "consciousness of coidentification in a social group of two or more members," though actually in some situations it may operate at a subconscious level, as is revealed, for instance, when a flash of insight makes one suddenly aware of long-standing empathy with some other person (Shakow). It implies nothing of qualitative connotation beyond a certain degree of affectivity, just as is true of the term "consciousness" as designating intra-individual feeling. Empathy often ripens into love or deepened positive empathy but it can also evolve into hate or negative empathy. It is actually the precise opposite of "indifference." Negative empathy as well as positive empathy have survival value, but for purposes of this discussion the positive aspect only will be envisioned.

THE LAWS OF EMPATHY

The laws of empathy constitute the fundamental subject matter of sociology and of ethics and they are largely utilized in religious technology; they play a large role in psychology and especially in psychiatry. They constitute what might be called the *social imperatives*, though this term should not be allowed to distract attention from their fundamental biological import as adaptive factors whereby the survival value of gregariousness is implemented.

First of all, empathy is a much more potent force than is often recognized. As a survival factor it must necessarily be so in that its essential function is often to override countervailing egoistic impulses and drive the individual on occasion literally to give his life for his friend. It is in large measure the force of empathy as exemplified in "patriotism" or in military "morale" that has recently driven thousands of soldiers to their death.

Another important characteristic of empathy is that it waxes and wanes in correlation with the prevalence of individual emotivity. Sharing an emotional experience is a well-recognized method of "breaking the ice" and getting "on friendly terms" with other people. Many a girl has got a husband by showing sympathy with a newly jilted man. It would seem that the chief utility of the cocktail hour as a social agency is the release of easy emotivity, with the consequent promotion of empathy. The religious revivalist makes frequent use of this same law as a means of "bringing sinners to salvation." It is a well-known apparent paradox that preceding acrimony enhances the vividness of connubial empathy. On the larger world scale, the promotion of empathy by shared emotion has frequently occurred. Peter the Hermit preaching the Crusades is a notable case in point. The cathedral-building era in France was largely an outcome of a special wave of conscious, vivid love of the Virgin which led men to give their lives to the construction of worthy tokens of their devotion. The remarkable group efficiency of Russia and of Germany as well as Japan in the second World War was also illustrative of the influence of affect-laden ideology. In these instances the function of em-

pathy to promote the mobilization of the individual "ego forces" and to bring into clear recognition common needs and goals is especially evident.

Another characteristic of empathy is its tendency to drain off individual egoistic emotions. The blissful oblivion of a boy in love is proverbial. Machiavelli expressed this law as a political principle in his statement that the best way to avert unrest at home is to promote a war abroad. Many will recall the marked increase in empathy that ensued upon the suspension of bank payments in 1933 and with it a widespread feeling of quiet contentment. William James cites many saints who have derived an ineffable contentment and obliviousness to hardship from religious empathy. Many other examples readily come to mind. Affective drainage is perhaps the most apparent as regards the emotions of fear and anxiety and its adaptive value in promoting confidence and valor thereby is most obvious but it functions otherwise as well.

The enhancing influence of empathy upon the "self-regarding instinct" is one of its most important adaptive usages. The arts of the demagogue amount largely to more or less subtle exploiting of this influence: the privilege of pronouncing a "we" that includes an important member of the community leads to an accretion of the "I." Organized social groups—lodges, clubs, churches, or what not—derive their appeal largely from this source. The regalia and rituals of such aggregations become satisfying symbolic tokens of personal worth.

Finally, among the uses of empathy may be mentioned its potency as an agency for the promotion of social uniformity.

Irksome as that trait may be to dissatisfied proponents of individuality it obviously makes for vigor of group impact. Under the primitive jungle conditions in which it originated such impact was no doubt a frequent determining factor in survival. Instinctively following the leader entailed not only following him into battle but also copying his attitudes and ways. "Style," then, is a particular fruit of empathy. As a single illustration, what else than the operation of a deep-seated biological urge could have induced our wives to don in the guise of hats those recent grotesqueries of the African jungle? It is in the survival value of empathy that suggestibility serves as a tribal asset and it no doubt emerged to precisely that end.

To recapitulate, empathy is a device for reorienting the ego impulses and mobilizing the individual assets in the interest of group survival. Empathy is promoted by affectivity in the members of the group and serves to drain off individual emotions. In its function of promoting group cohesion it is a potent source of enhanced personal self-regard. It exerts a major influence in determining group patterns in attitudes, thinking, conduct, and even dress. In large degree the operation of empathy has been an effective means to survival, but it often exacts a heavy penalty from the individual.

The manifestations of empathy vary widely from group to group—being determined, largely, in their initiation by environmental stresses and needs. The tribal usages thus set up tend to be perpetuated in patterning that, with the passage of time and change in circumstances, may lose its survival value and, indeed, may come to have unfavorable influences. The details of group patterning add up to *cul-*

ture, in the social-anthropological sense, and the processes of induction of such patterning in the individual to acculturation.

A knowledge of the laws of empathy and skill in applying them constitute the chief, if not the sole, stock in trade of the psychotherapist in his dealings with the schizophrenic patient.

Just as consciousness and its multifarious concomitants in the individual are represented by the "ego," group consciousness is inwardly revealed by the "superego." The latter includes both primary empathy and the conscious elements of acculturation. It represents what the individual conceives to be the tribal imperatives—the demands of ethics and of propriety. That the particularized content of the superego is derived by inculcation from the parents and subsequently from other dominant individuals is well known. In that empathy is a device for group survival, whereas egoism is addressed to individual survival, the ego (in the sense of the "socialized id") and the superego are often in conflict—and at times deadly conflict. The resolution of this conflict is a chief social function of religion—and of psychoanalysis. Persistence of unresolved ego-superego conflict is an essential element in neurosis. This conflict frequently appears also as a major item in the early psychopathology of schizophrenia.

As in case of the biological imperatives, generally, empathy is enforced primarily by a system of rewards and punishments. While an occasional hermit or predator may reach such a state of overweening egoism as to have reduced his superego largely to unprotesting silence, for all normal and most abnormal persons the demands of empathy are unes-

capable. There is nothing quite so potent as a "hurting conscience" in robbing the individual of contentment. Enforced separation from the objects toward which empathy is customarily manifested leads to a feeling of restlessness that is recognizable even in the lower animals. In man it can give rise to the agony of nostalgia. Furthermore, such separation is demoralizing, in the literal sense of that term. It robs the individual of at least a part of his sense of self-worth, and often of much of his courage. The account, for instance, has recently been cited of a weak, dependent sailor who passed successfully through a half-dozen dangerous naval attacks and emerged with his morale intact, only to succumb to a severe "combat neurosis" in a succeeding battle. The sole detectable explanation for the difference was that in next to the last battle the sailor's brother, toward whom a high degree of empathy had existed, had been killed. In the "pathological grief reaction" that has been studied by Lindemann the demoralizing effect of curtailed empathy is seen in diagrammatic clarity.

The foregoing instances illustrate the penalties for violated empathy of which the individual is himself aware. But there are other penalties that he pays unwittingly. There is a substantial modicum of truth in the assertion that the price of rugged individualism is individual neurosis. The cynical Americanism, "Oh, yeah?" expresses both a psychopathological attitude and a penalty for intentional repudiation of the claims of empathy.

The capacity for empathy, like certain of the instincts, is one that depends upon postnatal maturation. What happens when opportunity for human association is prevented

throws an interesting light upon the penalties for defective empathy.

That severance from human relationships, however brought about, is deleterious to the individual has long been recognized as a matter of folk experience. George Eliot's *Silas Marner* amounts in effect to a discussion of this theme. Healy's well-known studies in the Chicago area emphasized the "lone-wolf" way of life as an important factor in social maladjustment and consequent liability to delinquency. In so far as they go in quality and quantity, perhaps our best data are those derived from studies of so-called wolf children or other feral human beings. According to Zingg's summary, there were available, in 1942, 35 instances of such creatures which have been reported in print. In many of these cases the data are so fragmentary as to be of scant value, but in a few instances fairly adequate accounts have been written. The children fall into three general categories: those who had been incarcerated in solitude for considerable periods early in life, those who in childhood had taken to living independently in the wild, and those who had been adopted by wolves or other animals. In the first two groups acculturation of any type was largely or entirely absent. In the case of the wolf children, a profound acculturation to the animal type had been acquired.

Critics from the time of Pinel on have disparaged the evidence from these sources on the ground that the subjects have been of such intrinsically low mentality as to render difficult any evaluation of the effect of deficient acculturation as such. Zingg counters with the consideration, however, that the children must in general have had some con-

siderable mental endowment to have been able to survive on their own resources the vicissitudes of feral living.

Running throughout all of the accounts of these children is the fact that upon restoration to human contacts they were completely devoid of empathy for their own species. Their facilities for communication were reduced to the most primitive sounds or gestures. All were slow in acquiring the language habit and in most cases their linguistic accomplishments remained either absent or very modest. There was apparently a fairly definite ratio between the period in which the individual was out of human contact and the interval requisite for acquirement of language. As nearly as could be judged by their actions and such conversation as could be elicited they were highly concretistic in their mental processes. About the only emotions that could be recognized were fear and dislike of human beings. One rather remarkable feature that has been observed in these few subjects who had survived into postpuberal years was an apparently complete lack of erotic impulse. In view of these various evidences of the deleterious consequences of defective empathy, much interest attaches to the possible operation of that factor in the genesis of the symptomatology of schizophrenia. As will be discussed later, one of the primary symptoms of that psychosis is "autism" in which deficient empathy is a striking feature.

SEXUALITY AND LIBIDO

A specially focused aspect of gregariousness, and indeed the biological emergence from which general gregariousness was probably derived, is that of bisexual reproduction.

Generally speaking, all that has been said in preceding paragraphs regarding group relationships applies with particular relevance and force as between mates, and only less so as concerns offspring. It is within the family constellation that the personality commonly unfolds, and here empathic relationships have major scope for weal or for woe in determining the inner life patterns of the individual. Just as a well-integrated family in which interpersonal relationships are well adjusted affords the best sort of milieu for effective and satisfying development, likewise the family in which warring personalities dwell under the same roof affords maximal opportunities for the destructive influences of empathic strain upon the individual. As will be emphasized later, it is within the family relationship that much of the early symptomatology of schizophrenia arises and it is from intrafamilial maladjustments that numerous psychotraumatic precipitating factors in the psychosis can be found.

The primary source of the family pattern of existence is, of course, the mating impulse of the parents. Of the erotic impulse as such, little need now be said. As is well known, it arises in part from constitutional factors, but the unfolding of sexuality at the puberal stage of development is dependent, as remarked before, upon the influences of various hormones and those of the sex hormones in particular. Of the endocrine aspects of sexuality and of its part in the schizophrenic psychosis we shall have occasion to say more later. Suffice it at this juncture to comment that the erotic impulse is, and in consideration of its biological import needs must be, a powerful influence upon the individual. What but an overpowering urge could drive a woman repeatedly and with open eyes to traverse the valley of the shadow of death

and a man to mortgage his best years to the demands of paternity? Not only is sexuality the immediate basis of racial survival and of many adaptive advantages but it is also a potent source of maladaptation.

The fact that sexuality figures so largely in the psychopathology of our culture as contrasted with that, say, of the Samoans would seem to be due especially to the fact that it is, among us, a potent source of conflict and of suppression. As has often been said, perhaps were we accultured to regard eating in public as something disgraceful and coitus as a commonplace physiological event our systems of psychopathology would center around nutrition.

Under aboriginal conditions in the jungle the larger the number of warriors the stronger was the tribe. In consequence, the erotic urge would obviously be highly regarded and any dissipation of it would be recognized as inimical to tribal welfare. It was thus no doubt that sex and sin in our culture as in many others have become so nearly equated and the curtailment of reproduction come to be regarded as an affront against God and man. When our mores were being consolidated it was not foreseen that a time might come, as it has in India today, when unbridled breeding would become a source of tribal weakness and of endless human misery.

In view of its importance as a factor in the psychopathology of schizophrenia, a brief discussion of the hackneyed topic, the evolution of sexuality and of libido in the individual, may be included. For our purposes the psychoanalytic paradigm will serve especially well. It must be recognized that the delimitation of the various stages is only relative.

The young infant, it is surmised, is at first possessed of only rudimentary awareness alike of himself and his immediate environment as an undifferentiated totality. His first intellectual feat is to achieve consciousness of himself as an entity, this marking the dawn of the ego. The conventional pleasantry of referring to the little creature as "it" comports with the concept that he is mostly at this early stage merely a composite of "id" factors. His "libido," which is to say his emotional interest, is invested mostly in himself and especially in those parts of himself that have to do with alimentation, i.e., the oral and anal structures. This self-investment marks the "narcistic" stage of development. The first displacement of his libido is upon his mother, who is his primary source of nourishment and comfort. At an age the mention of which seems to most people to mark a preposterous exaggeration his libido becomes somewhat centered in his genital structures—a fact of which vulgar nursemaids, however, show awareness in their methods of pacifying restless babies. As development proceeds, emotional engagement with others takes primarily two courses. The little boy's love for the mother deepens and acquires more or less of a sexual coloring. The father becomes correspondingly the rival for the mother's interests. This marks a normal state of affairs for the early years. As the libido becomes further eroticized it is normally transferred to other young males, a fact that is evident to the parents when their son begins to "gang up" with other boys. This phenomenon marks the normal homosexual stage of development. The biological utility of this evolution would seem to be that it is a device whereby the libidinous attachment to the mother is normally broken. It is the failure to achieve such normal

emancipation that gives rise to the so-called Oedipus complex, a feature found almost routinely in the intimate personal histories of schizophrenic patients. Another psychological peril with which the boy is confronted in his juvenile years is that he may fail in the final transition from homosexuality to heterosexuality, success in which transition is marked by his first normal "love affair" outside the family. In actuality, as Kinsey and Beach have emphasized, both heterosexuality and homosexuality commonly persist into adulthood in both sexes and are often used interchangeably at the behest of circumstances. In a high proportion of schizophrenics partial or complete failure of the heterosexual transition is seen.

The foregoing account in terms applicable to males is likewise true, *mutatis mutandis,* to females.

One further aspect only of the reproductive pattern as seen in man will be mentioned. That is the prolonged period of childhood that is characteristic of our species. The biological advantage in this retarded developmental tempo is not immediately obvious, entailing, as it does, an unusually large proportion of relatively helpless members of the tribe to be supported and defended. Its survival value would seem to lie in the accentuated opportunity for the acquirement of the specialized skills and sophistications that mark the particular superiority of our species over our competitors.

CONCLUSION

To recapitulate, man is depicted as the culminating phenomenon in a long process of integrative evolution. The

panorama of existence embraces at one extreme the subatomic particles—the electrons, the neutrons, and the protons—and at the other the highest levels yet reached of social organization. The aggregated subatomic constituents are organized in a series of increasingly complex forms that include atoms, molecules, molecular crystals, proteins and other structural materials, protoplasm, cells, tissues, organs, organ systems, individual beings, and social groups. Emerging at the various levels are the properties of form and structure, metabolism, reproduction, life, heredity, awareness (consciousness), affect, drives and instincts, behavior patterns and empathy. These attributes in ensemble give rise to individual personalities and to social aggregates. As matter evolves into increasingly higher forms new levels of organization are imposed upon the constituent substrate units and there emerge new properties in each system thus derived. What were wholes at one level become parts at the next level. It is the peculiar new relationships of such parts that give rise to the new properties of structure and behavior. It is of especial moment to our thesis that the new emergence, at whatever level, reveals qualities that are unique and must be studied by methods appropriate to that level, though knowledge of the lower levels is necessary for the adequate understanding of the higher. This is the essence of the concept of *holism* as expounded in psychiatry by such writers as Meyer and Angyal.

We are all so familiar with the phenomenon as a matter of personal experience that we readily overlook the astounding tour de force that nature accomplished in evolving a unified personality out of so many discrete elements. The body is a seething laboratory in which hundreds of chemical

processes are going on simultaneously. It is thus a vast complex of activities at the molecular level. Each of the three thousand billion cells that make up the body carries on its own existence, assimilating its own food and oxygen, excreting its own wastes, and carrying out, in addition, its specialized functions. Thus at the cellular level also many kinds of activities are taking place. Similarly the different organs have a variety of separate functions and the organs in turn are associated in co-operating systems. The various sorts of controlling mechanisms—chemotactic, neural, hormonal, instinctual, and voluntary—come in further to complicate the picture. Yet out of this composite diversity is derived that unified totality, the individual personality.

The schizophrenic psychosis represents a failure or distortion somewhere in the course of the integrative series. Its explicit cause remains unknown. The malintegration could conceivably exist at any level from the atomic to the social. Whether the psychosis is singularly or multiply caused and the nature and level of operation of the etiological factor or factors remain for research to determine. Until such knowledge comes to hand attempts at prevention of the disorder will be mere trial and error and treatment will be empirical shooting in the dark.

The foregoing discussion of the biology of man represents, of course, a highly specialized selection from the observations and reflections of a personal lifetime as well as from some portion of a vast deal of relevant literature. Many of the topics discussed in individual paragraphs would afford scope, as they often actually have done, for entire books. The selection has been made throughout with the purpose of throwing light upon that most baffling breakdown of biolog-

ical adaptation, the schizophrenic psychosis. How the breakdown is manifested in "typical" schizophrenia and some of the particulars of the breakdown as our group have studied the psychosis at the Worcester State Hospital over the past 18 years will be the themes of succeeding sections.

SECTION TWO

THE PATTERN OF SCHIZOPHRENIA

THE SCHIZOPHRENIC psychosis has been intimately observed under one or another designation for centuries and a vast deal of detailed information about it has been accumulated. Systematized accounts of our knowledge have appeared in many terms, many times, and many places.

To one with even a cursory knowledge of the literature, it is obvious that the predilections of the observer play a considerable role in his estimate of the disorder. The internist sees in it evidences of the kinds of disease factors with which he is accustomed to deal. The psychologist is more impressed with various sorts of conditioning. The psychiatrist by his own declaration attempts to see the problem and the patient "as a whole," but his idea of the totality is likewise colored by preconceptions. The biologist is tempted to pride himself on an ability likewise to see the "problem as a whole," but his vision, too, may be distorted by the fact that he is wont to seek in any given human situation parallels with those demonstrable in the lower orders of creation and he may be unconsciously moved to argue ineptly from analogy. Being titularly concerned, however, with life in any of its manifestations he might entertain a hope of achieving something broader than a specialist's conditioned vision. He should be equally well prepared to find the solution at any level or levels of integration between that of the atom and that of a society. As biologist, however, he

might well be expected to lose at least a part of the advantage of his eclectic viewpoint because of his ignorance of many details known to specialists.

SCHIZOPHRENIA AS A BIOLOGICAL PROBLEM

To the biologist as such, schizophrenia like any other manifestation of life raises the primary question: what is the fundamental nature of the psychosis and what does it mean as a special manifestation in the order of living things? And these questions entail several others. What sort or sorts of people succumb to schizophrenia? How does the disorder begin, how is it essentially manifested, and how does it end? With what other manifestations of the life processes is it akin? What is its survival value, positive or negative, for the individual and for the species? Does it evoke compensatory reactions in the individual and, if so, what are the reactions? Wherein does it as a biological deviation take origin—is it in whole or in part a result of hereditary peculiarities or is it a purely acquired disorder? Is it a genuine disease due to structural defects or does it represent merely a functional disorganization of normal structures and mechanisms? If a disease, structurally determined, what can plausibly be postulated as to its causation and mechanism? Is it of single or multiple etiology? Is it a self-limited disorder? And, finally, how is the course of the psychosis modified by changes either in the subject or the impinging environment? These are some of the questions that must be answered before the psychosis can be adequately appraised as a biological phenomenon.

CURRENT STATUS OF THE SCHIZOPHRENIA PROBLEM

It will be recognized at once that many of these questions are precisely those that have been insistently raised by psychiatrists for many years and that any attempts to assemble the evidence bearing upon them must savor of hackneyed repetitiousness. In extenuation, I can only say that the schizophrenia problem in this year of grace presents a jigsaw puzzle that many of us have tried as yet in vain to solve. Indeed, numerous of the pieces necessary to the solution may not yet be on the table. I can only ask, then, of my readers that they will be patient as the old familiar pieces of the puzzle are once more arrayed. After I have presented an assemblage that seems to me most nearly to make biological sense it will be my purpose to bring forth a few newer and less shopworn pieces that my associates and I of the Worcester State Hospital have been able to extract from the arcanum. Perhaps some of my readers may derive entertainment if not profit in the fitting of these pieces into their own favored patterns of assemblage.

Now to return to some of the biologist's queries. Again, what is "schizophrenia"? Is it an entity or, mayhap, merely a semantic convention? Some psychiatrists, Ludlum among them, maintain that schizophrenia represents but an arbitrary segregation of a certain proportion of the human totality who fall in a continuum that includes normality, as well as such disturbances as neurosis, cyclothymic disorders, general paresis, and the senile psychoses, with intermediate zones in which the designation "schizophrenic" or "nonschizophrenic" is a matter of individual choice. Not infre-

quently the initial choice in such cases is wrong as shown by subsequent developments. On our Service we have had many occasions to revise the diagnosis "schizophrenia" that patients have brought to us from other hospitals and no doubt on occasion the same fate has befallen our diagnoses elsewhere. On occasion also what seemed in its early manifestations to be veritable schizophrenia has later proved to be some other disorder. Further suspicion of the biological identity of schizophrenia is aroused by the fact that the literature contains accounts of many instances in which that diagnosis has been applied to individuals suffering from such dissimilar misfortunes as brain injury or intracranial tumor, chronic low blood sugar, epilepsy, or hypothyroidism. And, according to Menninger, many sorts of toxic and infectious processes may be accompanied by what is, at the clinical descriptive level, indistinguishable from schizophrenia. Many of the individual symptoms that are commonly included in the schizophrenia picture can be paralleled in other disorders and especially in general paresis. Likewise reactions that are of definite "schizoid" order can be evoked by drugs such as mescaline, bulbocapnine, alcohol or morphine and by breathing air of restricted oxygen content. But of this more later.

Despite these various difficulties in actually defining and characterizing the psychosis the most enlightened psychiatric thought is gradually coming to an acceptance of the assumption that the psychosis is a genuine entity that consists of true "process" or "constitutional" schizophrenia and should be set aside from the various schizophreniform reactions that are frequently grouped with the true psychosis. Many believe with Lewis that these latter confusing

disorders differ fundamentally in their essential nature, pathogenesis, and prognosis. In the discourse to follow we shall commonly use the term schizophrenia in the sense of "process schizophrenia."

From the general biological point of view, however, it seems to me that the possibility must still be faced that "schizophrenia" may be an entity by fiat only, as are disorders in general that are delimited merely on a basis of symptoms. For all that we know explicitly to the contrary the psychosis may be stricty comparable to such diagnostic entities as "headache" or "hypertension," each of which has a common core manifestation but each of which may represent very dissimilar disorders. The first and most fundamental question of all, then, explicitly what is schizophrenia, must continue disconcertingly to face us throughout the remainder of this discussion.

SCHIZOPHRENIC BEHAVIOR

The psychosis presents a bizarre mélange of behavioral normality and abnormality. The core disturbance, the so-called process schizophrenia, is perhaps still best expressed in Kraepelin's definition of the psychosis as "a peculiar disorganization of the inward coherence of the psychic personality with predominating damage to the affective life and will." In other words, the patient cannot "think straight," "feel straight," or "will straight." His logic limps woefully. In his thinking processes he is a constant victim of the *non sequitur* fallacy and he frequently employs that old domestic stand-by the *ignoratio elenchi*. He often substitutes uncon-

scious punning for reasoning and to him argument from analogy is singularly convincing. Many of his mental processes represent sheer magic mongering—as, for example, one of our patients who, to improve his character, repeatedly wrote the golden rule on a slip of paper and swallowed it. It is these latter peculiarities that led Bleuler to ascribe primary importance to "disorders of the association processes." Memory and orientation are usually well preserved. The patient often shows little disturbance of apprehension. Despite frequent appearances to the contrary, he is usually rather well aware of what goes on about him. The fundamental disorder of the thinking processes leads ultimately to such deviations from normality as hallucinations, delusions, poor judgment, incongruity of emotions—often with apparent neutrality or indifference—incoherence in train of thought and displacement of normal volitional responses by automatic or impulsive reactions. These are the manifestations that strike the physiologist as most significant in the picture of schizophrenia as aberrant biology. The list of particulars is, of course, neither complete nor adequate, but it will serve for the immediate purposes of this discourse.

VULNERABLE PERSONALITY TYPES

In the biological appraisal we may now consider the question, what kind of people get schizophrenia? Many years ago Hoch pointed out that the shy, withdrawn type of individual is especially vulnerable and the observation has been frequently supported by others. But the studies of Bowman and his colleagues at the Boston Psychopathic Hospital, a few

years ago, emphasize the difficulties in recognizing constant or characteristic features in the heterogeneous phenomenology that the investigator encounters in field studies of this problem.

In a series of 173 cases studied by Boisen on our Service, the patients by and large were found to have shown early what the ordinary person would call simply "weakness of character." [1] Even allowing for the fact that the group had encountered more than their normal share of vicissitudes, they had failed almost to a man to have the inner hardihood to adjust to their life situations. Practically the entire group had proved themselves inadequate in one or another major field of self-expression. None had clearly attained to normal adult sex adjustment. Vocational maladjustments were evident in more than half and failures of social adjustment in more than two thirds. Indeed there was maladjustment in all three fields in over a third of the cases and in two fields in three fourths.

The second World War afforded us a sample schizophrenic population in which a better than usual opportunity was presented for an appraisal of the psychosis, in that several variables which operate in cases arising in civilian life were largely eliminated from the immediate picture. These variables include wide differences in physical condition, the nature of impinging stresses, home and community complications, sex, age, and diet. A study of 33 such cases arising in the armed forces has recently been reported from our Service by Malamud and Malamud. Even among the patients who had succeeded in making fair preinduction ad-

[1] In the use of this handy expression no moral judgment is implied. We are dealing here with symptoms, not sins.

justments, such long-standing personality characteristics as sensitiveness, serious-mindedness, shyness, and rigidity were found, while among those who had adapted to life poorly such traits were listed as "quiet," "passive," "timid," "seclusive," "insecure," "inferior feeling," "immature," and "sullen." Heterosexual adjustment in the group as a whole was notably poor and tendencies toward homosexuality were apparent in several. Some further insight into their character defects is derivable from a consideration of what features in the military situation had proved most disconcerting. These were loneliness (nostalgia), the complexity of army life, worry over relatives, a sense of being "picked on," regimentation, and disappointment with the army life as affording an anticipated escape mechanism.

In over-all view, then, and as a biological first approach, it can be said that the schizophrenic psychosis commonly arises in frustrated, inadequate people. And even in those individuals who, prior to their psychosis, have been of superior intellectual or artistic type, an element of lack of robustness of personality that would fit them for the stresses of social adaptation is discoverable.

And these considerations serve somewhat further to particularize the over-all problem that is presented. What is it that is fundamentally wrong—that renders the patient, to use the vernacular of the street, unable to "take it"? Or in Rosenzweig's terminology, what is it that has reduced his "frustration tolerance"? Is it something that he was born with, i.e., something "constitutional," or is it something that he has acquired? In the latter case, is it a product of faulty "education," i.e., a manifestation of malconditioning? Or are these early deviations actually a manifestation of the

psychosis itself in a prodromal form? The evidence so far cited permits no choice among these possibilities.

OBJECTIVE EARLY MANIFESTATIONS OF SCHIZOPHRENIA

The next question to be considered, then, is how does the psychosis arise—what phenomena are characteristic of its initial stages? When and how do deviations from the normal pattern of evolution of the personality appear? First of all, schizophrenic subjects when we first meet them as definitely psychotic are found to have failed to carry through the normal libidinal evolution. Difficulties of emancipation from the parents (Oedipus conflicts) are such common features in the intimate case histories as to be almost the usual. And perhaps even more common are failures to make the transition from the homosexual to the heterosexual pattern of adjustment. Indeed, Fenichel regards persistent homosexuality with narcism as an invariable feature of the psychosis. But it is not in terms of these underlying difficulties that the onset of schizophrenia is commonly apparent. What is revealed on the surface is a series of personality difficulties that superficially bear little or no relationship to the psychological developmental anomalies. These may first be discussed from the standpoint of an outside observer and with a view to further particularization of the problem.

Among the more recent studies of the early manifestations of schizophrenia and one that comports with other similar investigations is that carried out in our Service by Cameron, who surveyed the initial symptoms in 100 cases.

Two fairly well-defined trends were seen. One of these was the gradual development of the psychosis in an individual who had from childhood been odd and aloof and who, though sane, had shown many behavior problems such as persisting enuresis, tantrums, sulking, and emotional instability. The process was often of insidious onset, the subject becoming more and more peculiar until often the appearance of frank delusions marked him as unmistakably psychotic. In our earlier series of 173 cases, previously mentioned, 51 of the patients had shown an uneventful, gradual onset and in 68 cases the outbreak of the psychosis had been preceded by a fairly long period of withdrawal or of delusion building.

The second trend emphasized by Cameron is a fairly abrupt appearance of manneristic behavior which may take many forms such as stupor, states of ecstasy, suicidal attempts, or bizarre exhibitionism. This type of onset had been observed in 54 of our 173 earlier cases. Often considerable confusion and inability to concentrate are seen. Outstanding among the peculiarities are withdrawal, loss of adaptive capacity, emotional dulling, and the tendency toward misinterpretation.

The *withdrawal* phenomena follow a fairly consistent standard pattern. The patient frequently has maintained rather normal social relationships during his earlier years but gradually becomes less approachable. He spends more of his time at home and ceases to make new friends; old friendships are gradually dropped, and those that are kept up are marked by decreasing warmth as he becomes overwhelmed with gradual dullness. Increasingly he is found spending his

time in daydreams, often seeking solitude by way of facilitating such indulgence. Indifference and lack of spontaneity increasingly dominate the picture.

Closely associated with the increasing withdrawal is *emotional dulling*—real or apparent. Variants of this manifestation, such as moodiness or outbursts of irritability, are occasionally seen. In addition to loss of interest in the environment, an element of inscrutability or estrangement enters the picture. It becomes increasingly difficult for others to experience rapport with the patient. In Kretchmer's metaphor, it is as though a sheet of glass stood between him and the observer, and loss of empathy is experienced by both, a characteristic underscored by Southard in his diagnostic criterion, the "empathic index." As has often been emphasized, it is in affective relationships that schizophrenia is most fundamentally manifested, and these rather than disorders of mentation should be the primary concern of psychiatrists. The loss of empathy demands special emphasis.

Associated with the defects of empathy and of individual emotivity there appears a *loss of capacity* to get on effectively with everyday activities. The patient is likely to complain of inability to concentrate or to muster his former energy. Objectively he seems to have lost his ambition and his interest in life. Friends and family are likely to protest against his growing "indolence." Episodic exhibitions of poor judgment and inability to grasp situations may be seen.

Another early symptom is a *tendency toward misinterpretation.* The patient at first is likely to complain of passing feelings that people are looking at him or talking about him but he is able readily to correct his error. His growing suspiciousness may be manifested outside the sphere of imme-

diate personal relations, for example, in regard to the wholesomeness of his food, or he may fear contamination of his beverage.

In Cameron's series there were a few other less common but fairly characteristic early symptoms of the disorder. Among these were complaints of mental blankness, the intrusion of absurd and irritating thoughts, and feelings of unreality. A variety of physical disorders were also complained of. Most often these appeared as a general feeling of weakness or easy fatigability, but more specific hypochondriacal features also were recorded. Many sorts of *mixtures* of these various aberrations can be seen in any large group of patients.

Cameron divides the early "indeterminate" symptoms into two patterns, the "hyperactive" and the "hypoactive." In the hyperactive group he includes the nervousness, sleeplessness, worry, nightmares, hypochondriasis, moodiness, impatience, tantrums, faultfinding, and moralizing. Among those designated as "hypoactive" are the seclusiveness, daydreaming, preoccupation, loss of interest, of energy, and of concentration, weariness, and poor appetite. These indeterminate symptoms had persisted in Cameron's series from weeks to years before the psychosis was defined. The transition to diagnosable schizophrenia was marked by such ideational features as suspiciousness and fears, strange ideas such as those of disgrace or redemption, and "supporting hallucinations." Other behavioral items included dazes, dizziness, complaints of strangeness and of odd somatic experiences together with screaming or giggling spells, tantrums, and un-co-operativeness in everyday activities. These early manifestations sum up in total to a picture of inexplicable queer-

ness. It is at this stage that a failure of empathy becomes unmistakably and bafflingly evident.

So much, then, for the early manifestations of schizophrenia. It would seem that it is among these that the key to the fundamental nature of the psychosis might most profitably be sought. And that consideration poses another fundamental question: when does the psychosis actually become psychosis? In other words, how is one to interpret the meaning of the so-called early nonspecific symptoms? Are they really nonspecific or are they actually early manifestations of the psychosis itself? Most of the psychiatrists whom I know best and whose judgment I value most highly adhere to the belief that these earlier symptoms are genuinely nonspecific and that the onset of the true psychosis first appears as a mysterious intrusion among these other manifestations. In short, the latter are merely the marks of vulnerability.

The biologist's chief reactions are two. First of all, he reflects that in the phenomenology of living creatures things that are indistinguishably alike commonly prove to be actually the same thing. While the possibility must still be recognized that our inability to differentiate a specific element among the nonspecific manifestations reflects merely inadequate precision of the tools upon which we are dependent, the biologist remains skeptical. He continues to feel something less than respectful toward a diagnosis that can be made only in retrospect. He reflects further that humanity is addicted to wishful thinking and that even psychiatrists are not immune; hence he wonders if the wish is not father to the thought that schizophrenia is schizophrenia and neurosis, neurosis and that the twain shall not be allowed to meet.

Actually the crucial point is whether, on the one hand, the nature of the psychosis—true "process schizophrenia"—is a manifestation dependent upon the nature of human nature when subject to a particular overwhelming stress or constellation of stresses or whether, on the other hand, it acquires its uniqueness from a peculiarity of the disease process itself. Both alternatives must be considered.

On the supposition that schizophrenia represents a disorder of specific and definitive etiology two primary problems are presented: first, what is the nature of the actual etiology and, second, where does it operate or center? The fact that despite many researches by many competent men, no organic pathology—and I mean neuropathology—has as yet been discovered by no means closes the issue. In Section One it was hinted that a true specific pathology may yet be found in a study of the enzyme systems of the brain. As to where in the brain pathological process might most hopefully be sought, consideration may again be deferred.

We may also consider briefly the implication of the other alternative, namely, that the disorder is nonspecific in its etiology, that it actually represents merely a malignant neurosis. In that case we should be dealing with a situation that parallels rather closely what we observe in the cardiopathies. In heart disease the patient may carry on in approximately good health for years with the aid of compensation factors, but when these factors finally prove inadequate and the heart "decompensates" he begins to suffer from a disease that is at least as different from its earlier manifestations as is schizophrenia different from neurosis.

For the moment, then, I shall leave the question in this form: does schizophrenia represent actually "decompen-

sated" neurosis? If such should prove to be the case, the primary etiology of schizophrenia would have to be recognized as the same as that of neurosis—an etiology that, in the belief of many psychiatrists, is simply immaturity. The cause of the specificity of the psychosis might then be sought in the nature of the "decompensating" process. The problem would thus move onto ground that is quite familiar to the biologist and would resolve itself into this question: why do some organisms mature and others fail to mature? The motivation of wishful thinking is here obvious. These questions will be reconsidered when further evidence has been assembled.

WHAT THE PSYCHOSIS MEANS TO THE PATIENT

So much, then, for the early objective manifestations of schizophrenia. What appears in cold recital gives, however, but a vague indication of what the psychosis represents to the patient himself—how it feels to the one who experiences it. The literature on this aspect of the subject is not nearly so extensive as that on the objective manifestations. And in this regard schizophrenia stands in rather striking contrast to such disorders as alcoholism or manic-depressive psychosis, in which considerable informative autobiographical material is available.

One must, of course, be ever critical of subjective material, however derived, because of the human tendency both to rationalize and to project. No matter what the source, whether from the patients themselves, their mothers, wives, or any other witnesses who are affectively concerned, all testimony regarding the inner aspects of the psychosis is

suspect. And furthermore, in his synthesis of "the patient as a whole," the psychiatrist adds his own modicum of projective material. We must utilize such evidence, however, or remain in essential ignorance of the inner meaning of the psychotic experience and this, from the standpoint of the patient, is the essence of the psychosis.

The most comprehensive investigation of the subjective aspects of schizophrenia of which I am aware is that made by Boisen, who co-operated with us at the Worcester State Hospital in a study of the 173 patients previously alluded to. This observer brought to bear not only the critical attitude of a trained scientist and technical sophistication in psychology and sociology but also the insight that he had gained from having himself passed through an acute catatonic episode.

Boisen conceives the primary evil in this psychosis to exist in the field of social relationships and particularly in life situations that involve a profound sense of personal failure. The patients are "isolated from their fellows through a social judgment which either consciously or subconsciously they accept and pronounce upon themselves." From this condemnation arises an intolerable *loss of self-respect.* As pointed out in the introductory section of this work, a sense of self-esteem is an imperative biological necessity. Inability to attain and maintain this sense represents a fundamental failure of adaptation.

Boisen distinguishes three chief methods of reacting to the loss of self-esteem. In one group the patients offer little evidence of concern but *drift* into the psychosis without apparent effort to combat its onset. They accept easy modes of satisfaction and gradually withdraw into a world of fan-

tasy in which ultimately their dreams take the place of reality. All of the factors connoted in the normal person by the term "ambition" are lacking. It is as though they become psychotic because they do not care to take the trouble to remain sane. "Such persons seldom show any great emotional disturbance. They have no marked hallucinations and their ideation is not particularly bizarre. But they drift down toward dissolution and destruction."

In a second general group the difficulty is met primarily by *delusional misinterpretation*. Their chief concern is with "face-saving." They strive to escape a sense of failure or guilt by refusing to admit defeat or error and, with little resistance, they accept distortions or delusions. The delusions are many and varied but generally speaking they center in the relationship of the person and his environment. Although the end result is, in effect, to separate the individual from his group as unassimilably queer it does serve to keep him from complete wreckage and enable him to maintain a certain degree of integration and poise.

A third general reaction pattern is that of *panic*. The individual is likely, in Malamud's phrase, to become aware that he is tasting forbidden fruit and to sense the danger in which he stands and to become fearful of it. "In its extreme form this emotional disturbance may appear as that profound despair and hopelessness in which the sufferer loses all interest either in the external world or in himself and he feels himself to be as one dead." This type of reaction has been recognized by James, Boisen, and others to be somewhat akin to that of the profound religious conversion experience. The disturbance may take the form of either stuporousness or agitation.

These three general reaction patterns occur sometimes in easily recognizable, typical form but more often in combination.

To the patient himself, his ideas and emotions are, of course, the matters of primary significance rather than the manifold aberrations of behavior that impress the onlooker. To him they represent grim, terrifying, torturing, mocking, and fascinating reality. An initial feeling of strangeness is rather common. In the words of one patient, the subject is often beset by a "flood of mental pictures as though an album within were unfolding itself." Elements of the unconscious come into awareness and are interpreted as manifestations of the supernatural, often with devastating impact. In the new world into which the patient is thrust previous principles and standards seem irrelevant. "He sees strange meanings in everything about him and he is sure of only one thing, that things are not what they seem." His new ideas and mental pictures become so vivid as to constitute the voices and visions that a large proportion of the patients experience. "Very commonly it is as if the conscious self had descended to some lower region where it is no longer in control but is at the mercy of the terrifying ideas and imagery that throng in upon it. The eyes are opened so that one seems to see back to the beginning of creation. One seems to have lived perhaps in many previous existences." To the individual the new experiences are so vivid that they seem to represent profound, new revelations and the marked sense of mystery is often associated with the more profound types of disturbance, with characteristic archaic symbolism, bizarre ideation, and often deep religious concern.

In many of these patients the first experiences are followed

by an acute sense of peril and fear of death. They see things in a new light and believe that "the dawn of creation" has come. One of our subjects reported that he was living in a different world and was a much more important person than he had ever dreamed. He believed that in previous incarnations he had been Jonah, Christ, and St. Augustine. Many variants of this type of experience occur. The world is in imminent danger of falling to pieces and the patient himself is the world. Its fate depends upon him. If he dies the world is ruined. Other patients get revelations that the second coming of Christ is at hand and that they are to have a central role in the great event. Gods, devils, and heroes cross the stage in endless procession. One patient was alternately God and the devil and one announced belligerently that "little Charlie can lick God." Ideas of imminent death to be self-inflicted or accepted as inevitable can often be elicited or may be openly proclaimed. But more often such ideas are rather assiduously concealed. Boisen cites numerous instances of such ideas of importance, self-depreciation, danger, despair, and exultation. But despite this seething inner turmoil, to the visitor on the ward the patient is likely to appear as mute, stuporous, and inert. Alternatively or later, however, he may be freely communicative and overactive.

Rather generally, the patients who show acute disturbances of the order cited—cosmic identification, delusions of rebirth, sense of mission, and what not—are facing their problems and accepting responsibility for the sins of which they stand in their own minds convicted. It is perhaps this very persisting honesty and willingness to fight it out that accounts for the relatively good prognosis in such cases.

They are likely to fight through to more or less satisfying victory, but failing this, are likely to reach a state of unresolvable despair.

More commonly, however, as was true in 130 of our 173 cases, one form or another of *evading the issue*—of concealing the actual terms of the conflict from the individual himself—can be recognized. The most frequent concealment mechanism is what Boisen terms *externalization of conscience*. This was evident in 113 of the 130 cases. In 73 of this group the patient heard accusing voices that charged him with unacceptable behavior, or he detected that people were talking about him and deriding him. In 22 cases there were delusions that the mind was being read or thoughts recorded by one means or another. In 14 cases the patient believed that he was under surveillance by enemies, detectives, or spies. Ideas of being poisoned or drugged were found in 37 cases and of being killed in 29. "These ideas may all be regarded as indications of a resisted and uneasy conscience."

Ideas of being *under compulsion* and thus exonerated of blame were evident in 70 of the 130 cases. The patient conceives himself to be under the control of someone else, usually an enemy, through the agency of electric currents playing upon the body or upon different organs, the brain and the genital structures being favored sites. Various sorts of mystic influences such as telepathic or hypnotic control of the mind were postulated by 32 of the patients as explaining the unacceptable thoughts that came to them. Frustrations of their plans by other individuals or organized groups—and especially secret societies—were of fairly common report.

Another mechanism that was frequently encountered—

and one that is by no means restricted to psychotics—was the maintenance of a fictitious *sense of self-importance.* In 10 of the cases this was sufficiently potent to enable the patient to reach a delusional reconstruction that afforded him some considerable degree of comfort.

Another reaction and one that is also widely used by others than schizophrenics for escaping a sense of responsibility for personal failure is that of a *delusion of physical illness.* This was seen in 29 cases. "While unquestionably a concealment device which seeks to save the individual's self-respect, it differs from the preceding reactions in that it involves the recognition of difficulty and it locates that difficulty within the individual. It is, however, a confession of weakness and a bid for sympathy and attention."

As frequently mentioned, one of the outstanding difficulties among schizophrenics is that of coming to terms with sex. As mentioned before, only rarely—and according to some authorities never—has the individual succeeded in making a good *erotic adjustment.* Whether this fact fundamentally indicates predominance of sex cravings in the biological scheme of things or merely rigidity of social mores and taboos is a moot point, but in many cases the intimate history of the individual reveals what seems to him to be an attempt at preservation of his integrity against the disintegrating power of primitive cravings. Many patients speak frankly of "the fearful and disgusting, yet fascinating, imagery that swarms in upon them, supposedly at the behest of hostile forces." The patients are usually reluctant to discuss the matter but often will admit that the "voices" that they hear accuse them of unacceptable sex practices such as sodomy or incest. Of our entire group of 173 cases, 36 had so

far lost their self-respect as to indulge openly in sex practices. Fifty-six of the group showed no open eroticism but acknowledged that managing the sex drive had been a source of difficulty. In 81 of the cases so great was their reticence that no positive evidence regarding their sex difficulties could be secured.

The chief item of significance brought out in the consideration of the subjective aspects of the psychosis, in addition to those features emphasized in the preceding section on the objective aspects, is the further emphasis that is laid on the factor of depressed self-esteem. This element of the picture warrants consideration both as a possibly important etiologic factor and as especially significant in relation to psychotherapy.

THE ESTABLISHED PSYCHOSIS

So much, then, for the objective and subjective aspects of the onset of schizophrenia. Attention may now be turned to the sorts of clinical pictures that are seen after the psychosis becomes well established. Most of the mechanisms that have previously been discussed remain operative but the patients to some extent succeed in coming to terms with their difficulties. In addition to a certain element of resignation to their fate the picture often becomes somewhat stabilized by habituation to the hospital environment and by increasing personal familiarity with their own peculiar reactions. It is possible to set up paradigms of behavior around which the symptom constellations tend to group themselves, but as previously mentioned there is considerable overlapping as

from one group to another. In our own work we have found it convenient for descriptive purposes to utilize the Kraepelinian categories, though some of us share the conventional doubt as to whether these subclasses represent anything in the way of true nosological delimitation.

In our experience the most definitely characterized of the subgroups, psychologically and somatically, is the *paranoid.* These are the patients, of course, who present largely an exaggeration of the common human reaction of maintaining self-esteem by self-deceit. In a major proportion of the instances a passable degree of equanimity is thereby attained, but in some 15 per cent of our series a considerable amount of residual panic with attempts at concealment could be detected. Often the patient gradually succeeds in convincing himself that he really is an important and specially privileged person—hence his "delusions of grandeur." He may also escape a sense of responsibility by delusions of persecution. Either type of delusion may antedate the other. His delusions aside, he most nearly succeeds in maintaining psychosomatic normality.

Most of the patients who show the panic reaction as the primary mechanism fall in the group conventionally designated as *catatonic.* It is in this group that withdrawal from the environment is most clearly evident, the patient with apparent perversity refusing to respond to any stimulus, external or internal. In his detailed symptomatology he often reveals the underlying difficulty in his manifestations of "ambivalence." He is likely to be highly suggestible, either negatively or positively. There is much impulsive and stereotyped conduct, and commonly active hallucinosis can be recognized. Primarily his reaction seems to represent a

manful if misguided attempt to solve his inner problems. Of all schizophrenics he is the individual who is most obviously overwhelmed by failure of his own sense of self-esteem and most determined to regain it at a reality level rather than by the unrealistic, projective technique employed by the paranoid. In many cases the total picture gives the "feel" of a genuinely psychogenic disorder—a fact that is consonant with the relatively good prognosis.

Contrasted with that of the catatonic is the attitude of the *hebephrenic*—mostly what Boisen calls the drifter type—who early gives up the fight and lapses into psychosis, accepting "easy satisfactions" from whatever source they may come. He is likely to be a glutton and a masturbator whose residual sense of shame is betrayed by inappropriate silly grinning and ingratiating acquiescence in whatever may be offered to him. Often no convincing evidence can be secured of impressive psychogenic factors, hence in these cases a somatic origin seems more probable.

Finally, there is the somewhat less common *simple* type, the patient who goes through a relatively brief and usually rather uneventful schizophrenic episode then passively accepts the status of inferiority in his own eyes and drifts into a condition resembling that of ordinary simple-mindedness. This variety, too, impresses the biologist as probably of organic etiology.

We have found it convenient to recognize also a fifth variety, the *late indeterminate* in which the characterizing classificatory features have dropped out of the picture. This type will be discussed in later paragraphs.

Again, and especially for purposes of biological appraisal, it must be re-emphasized that much overlapping between

the various paradigmatic diagnostic categories occurs, a fact that strongly suggests that none of the differentiating characteristics is in itself fundamentally meaningful. More impressive is the common feature that is detectable in the members of all the groups, namely, a loss of the inner cohesion of the personality. Whether this be designated as "weakness of the ego," "intrapsychic ataxia," or what not, it is the breakup of the individuality into disjunctive fragments that is most striking. So long as the schizophrenic process continues in active form the individual drifts through his mental life with his attention directed now to this fragment, now to that, in a fashion that precludes logical thinking and effective action. Rather literally several warring persons exist in the same body and the patient is truly bewildered as to which one to accept as "I"—hence the fairly common symptom of "depersonalization." It is especially the repudiation of unacceptable fragments of his disintegrating personality that gives rise to delusions of "voices" and of foreign influence generally (Malamud). The central problem, then, in the biology of schizophrenia is what brings about and perpetuates the disintegration of the personality.

THE FINAL OUTCOME

We have considered the phenomenology of the onset of schizophrenia and that of the psychosis in its established forms. Brief attention may now be given to the final outcome of the disorder.

In a small proportion of the cases the patient may make

a complete recovery and in the process gain sufficient insight and sufficient stabilization of his personal and social values as perhaps to have been the better for the experience. A larger proportion of the patients succeed in making a fair adjustment to their psychosis and in taking their places in society, though with a residual modicum of "queerness." Often they have the wisdom themselves to seek a simple environment in which harassment of their weakened egos will be at a minimum. A third group succeed in coming to terms with their psychosis and, although they must remain in the hospital indefinitely, succeed in retaining a sufficient degree of integration of personality to get on with no great difficulty to themselves or the hospital personnel. These seem to be appropriately designated as instances of an arrest of the psychotic process—whatever it may be.

There is, however, another substantially large group in which such arrest fails to occur and the process goes on to a final stage of deterioration. This end stage is commonly regarded as offering relatively little scope for profitable detailed investigation. Arieti's recent study emphasizes that a gradual reduction of brain functioning occurs until little is left beyond that of the ancient primitive structures that we share with infants and lower animals. Most striking, perhaps, is the gradual cessation of activity—often to a point at which the patients no longer bother to eat unless coerced to do so. This inertia may or may not be followed by a terminal increase in impulsive motor activity which may give rise to senseless violence, destructiveness, or assaultiveness. These activities appear not to be associated with delusions or hallucinations but to represent merely uncontrolled motor responses to incidental stimuli.

At this last stage of motor excitability the activity tends to channel through long-used habit patterns. Thus in the dining room the patient becomes addicted to food grabbing and apparently voracious eating. Like children or decorticated monkeys they seize various available foods in the order of earlier preference, the dessert being regularly consumed first. At a later stage of deterioration any sort of food is gobbled, then, later, objects edible or otherwise are placed in the mouth at random. They may or may not be swallowed. Finally a stage of deterioration is reached at which the patients largely fail to react to any sort of stimuli at all—the notable and suggestive exception being the most ancient sense, that of smell, a sense that operates reflexly at the subthalamic level.

And thus when the schizophrenic process proceeds unchecked to its terminal phase the patient makes his exit from life as little more than a vegetative organism practically devoid of all that is human. And the question that is primarily posed is this: does the end stage represent merely something comparable in functional terms to atrophy from disuse—a sort of all-pervading ennui—or does it signify the active and long-persisting agency of some metabolic noxa? It is this terminal phase that seems most definitely to suggest that the psychosis represents an actual organic disease. Two lines of recent evidence, however, indicate that the deterioration is not quite such an obliterative phenomenon as is often supposed. The partial reversal that is seen in some cases of lobotomy indicates an active process rather than merely irreversible destruction. Also Kant's recent studies of the characteristics of very deteriorated, withdrawn, end-stage

patients—using sodium amytal to aid the explorations—also indicate the persistence of active processes. The extreme withdrawal, he finds, is always accompanied by extreme disorganization—in the psychiatric sense. Enough of the active process was still elicitable so that in 97 per cent of the cases the original basic subtypes could be clearly re-established.

THE SCHIZOPHRENIC IN COMPARISON WITH OTHER BIOLOGICAL PATTERNS

So much, then, for the panorama of schizophrenia. What does it represent as disordered biology? What resemblances can be seen between the psychosis and other biological phenomenology of a normal order? In short, what is revealed by a relatively simple naturalistic, as compared with a detailed analytic, approach? Are there to be discovered any over-all simplicities of the sort to which the solutions of biologic problems tend to reduce? Alternatively, what can a naturalistic approach contribute to a sharper delineation of the fundamental problems of schizophrenia?

The biologist can recognize in the picture little that he is familiar with in lower orders of creation. It has been stated that in a monkey colony occasionally one individual animal will become so browbeaten and abused by his companions as to reach a state suggestive of schizophrenic withdrawal. Within the year, too, I have seen a dog that carried the "beaten cur" behavior to a stage at which he would throw himself on his back with an ingratiating and silly ineptitude somewhat suggestive of the behavior of a hebephrenic

patient. These superficial analogies, however, go but a little way to contravene the general belief that schizophrenia is a strictly human disorder.

This consideration naturally raises the question: what are the characteristic human peculiarities that might render the subject vulnerable to the schizophrenic aberration? The two obvious ones are the prolonged childhood of the human race and the elaborate systems of symbolization in terms of which human life is largely lived. Obviously, the fact that immaturity exists so long implies that the forces that lead to maturity are relatively weak in man as compared with those of lower animals. Equally obvious is the fact that habituation to symbolism adds to the difficulties of reality testing. In an estimation of the nature of schizophrenia these points would seem to warrant consideration.

Of the various human patterns to which schizophrenia can be compared one thinks first of all of that of *normal childhood.* Among the obvious similarities between the patterns are, first of all, the general immaturity as manifested both in the thinking processes and especially in affective reactions. The child, like the schizophrenic, frequently uses autistic escape mechanisms. His thinking is concretistic and his competence in reality testing is inadequate. In general, the concept of "regression" in schizophrenia implies high degrees of similarity if not of identity in the two patterns.

As Shakow says, if one gives up the notion of regression as a systematic backtracking over the steps of the developmental process and considers it rather as a falling back on previous tendencies and forms of behavior when available forms of reaction become inadequate, then the evidence for the existence of similarities between schizophrenics and chil-

dren is impressive. The studies of Wegrocki, Cameron, Barker, Dembo, and Lewin, among others, supply evidence of mixtures of old and new forms of reaction to given stimulating situations. It would appear that there is more of this harking back to the past in the affective than in the non-affective sphere.

But a review of the field seems to indicate that whereas there are many similarities in the two patterns there are also significant differences. The schizophrenic has gone through numerous experiences that have been denied to the normal child, and even if schizophrenia represented literally a return to childhood the pattern would necessarily be colored by residues of the later experiences. In penetrating psychological explorations of the schizophrenia pattern—for example, by use of the Rorschach technique—many results of the later experiences are characteristically seen.

A distinction must be made between the problem that the patient faces and his manner of handling it. The schizophrenic seems a good part of the time to be concerned with a problem that harks back to his childhood and to be using techniques for solution that are a mixture of adult and inappropriate childhood patterns.

The appearance of so much of the immature in the schizophrenic reaction pattern again raises the question whether in the last analysis schizophrenia may represent fundamentally a failure in the maturation process. It would seem that even such maturity as may have been established is so weakly anchored that it can rather readily be lost. If this be the crucial aspect of the psychosis then the problem is almost automatically transferred from the mental hospital to the biology laboratories in which the factors promoting the

maturing processes can most penetratingly be studied.

Another pattern that forces itself upon one's attention as presenting similarities to that of schizophrenia is that of *dreams* and the reverie state. An adequate particularization of the likenesses would necessitate as long a discussion as that devoted to the schizophrenia pattern itself. Both patterns are characterized by elaborate symbolization, by condensations, displacements, and what not. In both, the raw material of thought consists much less of conceptual relationships than of sense imagery. Both patterns include mechanisms for escaping the vigilance of the superego. The resemblances between the two states have been commented upon by numerous psychiatrists. Jung's characterization of the schizophrenic as a dreaming man in a world awake is particularly apt. "Let the dreamer walk about and act like one awakened and we have the clinical picture of dementia praecox." Pelletier specifically compared the symbolism and thought sequences gathered verbatim from schizophrenic patients with those of dreams and, following Masselon, attributed the peculiarities of both to disturbances of attention. The physiologist is tempted to offer the alternative suggestion that the brain is functioning—quite possibly for organic reasons—in a state of reduced awareness. To list the eminent writers who have been most impressed with the resemblances and those who have emphasized the differences between the respective patterns would serve no useful purpose in this connection. The outstanding literature has recently been summarized by Cameron. It is perhaps literally true that the resemblance between the modal schizophrenic pattern and a normal dream is closer than the resemblance among many cases that would be unhesitat-

ingly accepted by all competent diagnosticians as representing genuine schizophrenia. The case seems to me to be as good, therefore, for assuming a fundamental identity between the two states as for assuming any sort of unity within the psychosis itself. It we understood adequately the mechanism of dreams we might well have the key to schizophrenia.

But there are about as many theories regarding dreams as regarding the psychosis. Among these are the theories of brain suboxidation, functional depression by metabolites, and induced states of spreading inhibition—theories that are actually equally applicable to schizophrenia. The latter theory draws one's attention to Vervorn's old concept of the nature of inhibition as representing merely repetitive subthreshold stimulations. Is the sleeping brain merely a brain with physiologically elevated thresholds? To the biologist, as to many psychiatrists, the outstanding deduction that the accepted facts compel is that a morphologic pathology is no more a logical necessity in the schizophrenia state than in the dream state, however probable on particular grounds such pathology may be. A further suggestion is that researches devoted to the mechanism of dreams might well prove to be as illuminating regarding the schizophrenia problem as researches devoted to the psychosis itself.

Of somewhat contrary tenor is the evidence bearing on resemblances between the schizophrenic psychosis and the results of *cerebral injury,* whether traumatic or syphilitic. In brain injury and in organic psychosis it is adequately established that the capacity to generalize, to form concepts, is markedly disturbed. Although a schizophrenic actually shows a decreased achievement in this type of task the question arises whether we are here dealing with an actual under-

lying capacity disturbance. An alternate possibility, and one that is supported by numerous of our studies at Worcester, is that the defect in schizophrenia is due fundamentally to an inability to "keep a set," to sustain a task—that is, to maintain control and contact—with the loss in generalizing capacity as a secondary resultant.

Goldstein's studies in this field are especially impressive. He compares results of cortical lesions with various manifestations of the schizophrenic psychosis. He emphasizes two fundamental similarities—concreteness and isolated functioning, i.e., inability to maintain adequate boundaries—to distinguish between "figure" and "ground." He notes also, however, certain differences between the two groups of manifestations. The disintegration following brain lesions is toward concreteness that is of a simplified form because of poverty of mental material, whereas that of the schizophrenic is a concreteness that is much richer because of its great personalization. The nature of the concreteness is modified in the schizophrenic by his personal ideation. The Rorschach findings in the two groups bear out this generalization.

According to Lindsley's recent summary the electroencephalograms of the two conditions differ significantly. The brain waves of the schizophrenics are stated to show a variety of abnormalities mainly of the low-amplitude, irregular, high-frequency rhythms. There are also some evidences of slow dysrhythmias and in some cases patterns of an epileptiform type. "The most common disturbance in brain trauma is excessive delta wave discharge, but the absence of alpha rhythm or variability of alpha rhythms with sudden sharp wave discharges or actual epileptiform activity may be the

chief indication of an acute or chronic disturbance following a brain injury." Our own earlier studies fail to support Lindsley's differentiation in so far as we failed to detect any consistent differences between the brain waves of normal and of schizophrenic subjects.

In view of the fact that cerebral trauma, as such, is a highly variable condition whereas the cytopathology of schizophrenia, if such exists, is presumably more specific, the resemblances in the manifest patterns of the two are perhaps more significant than the differences. So far as this evidence goes it seems to me to support the concept of an organ pathology for schizophrenia rather more than the concept that it is a functional disorder, but no such conclusion is actually compelled.

A final comparison may be drawn between the pattern of schizophrenia and that of *feral human beings*—the so-called wolf children. The outstanding facts as now known were summarized in the first section of this work. These creatures, it will be recalled, have commonly been found to deviate widely from normal persons of similar ages. They have shown few of the characteristics, body form aside, that mark a human being as different from animals. In particular they have been completely devoid of fellow feeling for members of their own race. That is to say, their faculty of empathy has been markedly deficient.

The interpretation of the phenomenology is difficult because of uncertainty as to what their mental endowment may have been prior to their severance from their kind. Granting that they may have had normal initial capacity, as their survival suggests, the evidence seems to throw into high light the importance of empathy as a necessary condi-

tion for normal development and functioning. It throws open the possibility that the primary defect in schizophrenia —a defect from which the remainder of the symptomatology stems—is inadequate empathy. In view of the fact that the normal development of empathy is dependent upon maturation, these data serve to suggest again that the fundamental pathology of schizophrenia is likewise a failure of maturation. And again we arrive at the suggestion that strategically the most advantageous place in which to study the psychosis might be in the laboratory of the biologist.

The force of the foregoing argument is obviously weakened, however, by the fact that, in addition to defective empathy, the feral beings have also shown a marked deficiency in their ability to make use of language. It could be assumed that it is the poverty of their lives at the symbolic level that is the important factor in their failure of personality development. On this assumption, the data would be immediately relevant to the schizophrenia problem only in so far as early defective symbolization might be thought of as contributing to the later evolution of the psychosis.

THE BIOLOGICAL MEANING OF SCHIZOPHRENIA

It may be reiterated that the primary purpose of this section of the work was to be an attempt to define the problem of schizophrenia in a biological frame of reference. To our first question, what is the fundamental nature of the psychosis and what does it mean as a special manifestation in the order of living things, a satisfying answer cannot yet be given. We have discussed the sorts of people who succumb

to schizophrenia and the pattern of the psychosis in its various phases. We have compared the manifestations of schizophrenia with various of the other biological patterns and find suggestions of both psychogenic and organogenic causation.

We now come to the question: is schizophrenia an adaptation or is it a disease? If the former, what is its survival value for the individual and for the species? The only adaptive value that I can see in the psychosis is that it might have some use as a mechanism to compensate for a sense of inferiority. The price of this benefit, however, is so high that one must doubt that nature ever chose to pay it for such a purpose, i.e., that any such method of control was ever evolved. Under jungle conditions in which our biological attributes mostly came to flower it would seem that the price of the psychosis would almost inevitably have been individual death rather than adaptation.

Alternatively, is the psychosis an adaptive device for the elimination of the unfit and thus of survival value not for the individual but for the race? This possibility cannot be gainsaid, but it fails of much appeal especially because of the elaborateness of the phenomenology. Nature, in her solicitude for the species, customarily employs much simpler methods of elimination.

Finally, the biologist would inquire whether the psychosis represents a mutation and thus arises on a particular genetic basis. He reflects that mutations most commonly have antisurvival effects and that they often lead to bizarre manifestations, criteria with which the schizophrenic psychosis accords. The chief deterrent to the acceptance of this concept is the difficulty of visualizing just what sort of genetic influ-

ence might lead to such proximate stereotypy in so elaborate a system. The difficulty is not, however, insurmountable. Neither is the reversibility of the psychosis a compelling counterargument, since gradations in the potency of the mutational factor could be postulated. The obvious affective reaction that we all feel to such a theory has, of course, no relevance to its truth or falsity.

The other questions that were posited at the beginning of this section need not now be reiterated. None of them, so far as I can see, can be answered satisfactorily in terms of knowledge at the naturalistic level. Some of our own attempts to secure further light on these various problems by a variety of investigational methods will afford the theme for the third section of this work.

SECTION THREE

PSYCHOSOMATIC ASPECTS OF SCHIZOPHRENIA

IN THE two preceding sections we were concerned primarily with the nature of normal man as related to the schizophrenic psychosis and to the over-all pattern of deviation from normality that constitutes the disorder as seen objectively and as reported subjectively. This pattern was compared with various other biological patterns. This naturalistic approach offered numerous suggestions regarding the fundamental nature of schizophrenia but no proof of their validity. This section of the discussion will be devoted mostly to an account of various attempts made during the past 18 years at the Worcester State Hospital further to elucidate the disorder. The material upon which I shall draw represents some hundreds of man-years of work; hence only a relatively small proportion of the total can be dealt with.

As a further limitation I shall confine attention largely to researches at the physiologic-metabolic level. This selection, of course, is not intended to cast any aspersions upon the work of my colleagues who have approached the problem from psychiatric and psychological points of view. Rather it is a concession to my own limitations. Finally I am constrained deliberately to set the picture somewhat out of focus, citing mostly our own work and quoting that of others only as necessary for the elucidation of particular points. This procedure implies no disparagement of prede-

cessors or contemporaries nor any implication that our successes have been of such order of significance as intrinsically to merit the relative overemphasis that will be accorded to them.

ENDOCRINE RELATIONSHIPS IN SCHIZOPHRENIA

In the first phase of our work at Worcester, beginning in 1927, attention was largely focused upon the endocrine aspects of the psychosis. A representative group of patients was put through a somewhat elaborate test schedule in an endeavor first to determine the incidence of endocrine disorders among them. Many of the same patients were subsequently treated with a variety of endocrine preparations in accordance with the indications that could be recognized. Although the scope of the undertaking was later extended in a variety of ways, the endocrine aspects have continued to engage our attention during all the intervening years and many therapeutic investigations have been carried out. These attacks have been motivated in part by a desire to ameliorate the lot of the patients and in part, by the use of endocrine tools, further to explore the nature of the psychosis. A large part of the therapeutic explorations have yielded either negative or equivocal results. These, in general, will not be explicitly mentioned.

Almost from its earliest entry into the field of science, endocrinology has suffered at the hands of its overenthusiastic devotees. The knowledge that the hormones figure as important influences upon all the physiological processes of the body burst upon the world almost overnight. In the vast deal

of theorizing that ensued regarding the meanings of the new insights—some profitable but many not so—psychiatry had its part. Various proponents have arisen to proclaim a conviction that schizophrenia is but a special variety of endocrine disorder and many others have confessed to a suspicion that such may be the case. The literature on this subject was reviewed by Cohen and myself in 1939. In this article numerous relevant publications mentioned below are cited.

That hormone factors may be of significance in the etiology or symptomatology of schizophrenia is suggested by such characteristics as abnormalities in the oxygen-consumption rate and sugar metabolism, disturbances throughout the domain of the autonomic nervous system, and especially aberrations in the sex field. Numerous writers have postulated that the psychosis may be due to an unknown toxin that selectively interferes with endocrine functions. Weigand, for example, regarded all the functional psychoses as dependent primarily upon an innate disposition involving especially the central and vegetative nervous systems and the endocrine glands, the latter disturbances being particularly significant in schizophrenia. Sicco implicated the hormones in a threefold way—as primarily influencing brain development, as regulating the functions of the nervous system, and as factors in affectivity. A representative formulation and one of the most persuasive that has been offered—it was based largely upon personal researches—is that of Langfeldt. He postulated that schizophrenia is largely determined by an underlying constitutional defect that depends upon what he called a "specific inferior endocrine formula." "The inferiorily constructed endocrine system," he explains, "besides resulting in the development of the special con-

stitutional type. also results in an inferior development of the brain. When, then, this inferior endocrine system at puberty, or through other accidental causes, is exposed to too great a strain, we get the acute disturbances which we have seen in acute phases." Many other students of the disorder have supported the thesis that endocrine factors play an important role in the psychosis.

In this attenuated form the theory of endocrine etiology of schizophrenia is still tenable, but that hormonal derangement is the primary factor is a claim to which few qualified students of the disorder would now subscribe. As has been pointed out upon numerous occasions by Notkin and others, full-fledged endocrinopathies are seldom encountered among schizophrenic patients nor are the victims of positively recognized glandular disorders particularly prone to schizophrenia as should be the case were endocrine factors the dominant immediate influences in the chain of causation. That is not to say, however, that such factors may not be important as intermediary links.

It is obviously necessary to consider the hormones in two categories of relationships, to wit, as predisposing factors and as precipitating factors. The possibility of the intervention of endocrine disorders as precipitating causes of schizophrenia rests especially on two sorts of manifestations. The first is the disfigurement that is characteristic of certain of the endocrinopathies such as acromegaly or genital infantilism of the obese type. Lurie, among others, emphasizes the distortions of personality frequently seen in such cases. The second possibility of etiological importance is that numerous of the endocrine disorders are accompanied by lack of energy and initiative—a lack that entails failure or medioc-

rity in accomplishments. This latter factor might well be of particular importance as determining the weakness and futility of personality and of the debasement of the sense of self-worth that stand as foreground elements in the earlier phases of the psychosis. The significance of endocrine factors in personality I have discussed at greater length elsewhere.

The case for presumptive intervention of hormone disabilities in the etiology of schizophrenia is strong; that for proved relationships is relatively weak. The case for the latter rests primarily upon the evidences of disturbed glandular function in the psychosis and the results of therapeutic tests. The evidences as regards these items can best be discussed in connection with the individual glands.

THE THYROID GLAND IN SCHIZOPHRENIA

Our most nearly satisfying data regarding endocrine disorders in schizophrenia are those relating to the thyroid gland—a structure that has been aptly characterized as the "vital speed regulator." Thyroxin acts as a catalyst on the oxidative and other metabolic functions throughout the body. It influences both the developmental processes of the organism and the operative efficiency of the finished structures. It goes without saying, therefore, that the thyroid hormone plays a part in the psychosis just as it does in all the normal functions of the individual. The crux of the problem is, of course, whether it plays a specialized, particular role.

Among the a priori evidences we may give brief attention to the effects of thyroid perturbations upon the personality

manifestations. Thyroid deficiency may give rise to either of two major deviations from normality. The better known is that seen in myxedema, in which general sluggishness of functions, mental and physical, predominates. But an underlying element of irritability and truculence can often be elicited even in these seemingly placid cases. In a second, less common, type of thyroid deficiency the patients are neither overweight nor sluggish and they are abnormally responsive to the annoyances of life. Thyroid deficiency, then, resembles the state of general fatigue in which either general relaxation or tenseness may be seen. It is to be noted also that the thyroid hormone promotes both anabolism and catabolism, one or the other effect predominating, depending upon circumstances and especially dosage. In this second aspect thyroid deficiency has been described by McLester as giving rise merely to a condition of "general poor health" and especially a lack of endurance—often designated "chronic nervous exhaustion"—an inability to endure physical or mental strain. Stoll's recent study of the personality in chronic hypothyroid invalidism brought out as characteristic, irritability, mendacity, suspiciousness, delusions, retarded cerebration, inability to concentrate, introversion, and failing memory. Bleuler has further stated that, rarely, thyroid deficiency is accompanied by a psychosis that at the clinical level is indistinguishable from true schizophrenia.

As to whether the thyroid gland is disordered in any consistent fashion in schizophrenia, the testimony of the pathologists is not concordant. The most exhaustive study that has come to my notice is that of Witte, who reported on a series of 815 schizophrenic cases with control material in

psychotic and nonpsychotic subjects who had died of the same terminal diseases as had his schizophrenic patients. He was unable to confirm the high incidence of thyroid atrophy reported by some observers but did note a characteristic tendency to accumulate colloid—a picture that commonly represents, functionally, low-grade hypothyroidism. Lewin noted thyroid fibrosis in 29 or 30 cases but no more marked in schizophrenic than in other psychotic subjects. Other pathologists have reported mostly normal conditions in the thyroids of schizophrenics. The evidence, on the whole, is not impressive, but so far as I know the problem has not been adequately studied by the use of modern cytological techniques, which alone might reveal characteristic finer structural modifications and especially disturbances in the enzyme system of the glands.

No more convincing is the evidence from therapeutic tests. That thyroid substance or thyroxin has been given to many thousands of patients can safely be assumed and the fact that, although positive results have sometimes been noted, no general success has been claimed is in itself significant. Such evidence is not conclusive, however, in that there is no certainty that the dosage has commonly been adequate in amount and carried out over a sufficiently prolonged period adequately to realize the potential benefits that might be derived.

Over the past 18 years we have administered thyroid treatment to some hundreds of patients, sometimes briefly by way of therapeutic exploration, and sometimes intensively and in high dosage for months in succession. Our earlier results were reported in 1930. Subsequent experiences have in general confirmed the earlier findings but have added to

them little of further significance. The fairly elaborate diagnostic and check procedures that were employed were reported in 1933. Suffice it here to say that we came to recognize a picture that we regarded as indicating functional thyroid deficiency and that was rather consistently validated by therapeutic tests. The picture includes all or a majority of the following features: scanty urine with downward trends in total solids and total nitrogen but with normal creatinine; subnormal oxygen-consumption rate; downward trend of body temperature, blood pressure, and pulse rate; subnormal red-cell count and elevated lymphocyte count; abnormal—and usually reduced—weight; decreased lung volume; and sluggish colon-emptying time. Of these abnormalities we now regard the triad, low oxygen-consumption rate, secondary anemia and scanty, nitrogen-low urine, as most significant. When these findings are present the patients, in our experience, seldom fail to respond in some degree favorably to thyroid medication.

To particularize briefly, the subjects were studied for a control period of about three months with psychiatric observations, psychological studies, and various tests of physiological functions. In the 1930 series of 130 cases the diagnoses included: pituitary deficiency, 13; thyroid deficiency, 18; and unspecified endocrine deficiency, 57. A belief was recorded at that time that the latter group included a considerable number suffering from "adrenal deficiency."

Treatment was then instituted in accordance with the diagnostic indications. As controls for the thyroid series we had a group from the "unclassified endocrine deficiency" category, in whom the thyroid could not be explicitly implicated, as well as a group showing no particular evidence

of endocrine involvement at all. Patients with initially good prognosis were systematically excluded from the therapy series—a fact that has obvious bearings upon proportional improvements that were recorded.

Desiccated thyroid—or less often, thyroxin—was given in ascending dosages with a view to determining the individual therapeutic optimum. This usually proved to be the point at which moderate symptoms of hyperthyroidism were induced, such as loss of weight, tachycardia, and hypermetabolism of moderate grade. The final dosage level varied from 3 or 4 to 50 grains of desiccated thyroid daily, continued for several weeks or, occasionally, several months. In a few instances 60 grains daily was given for shorter periods. All due precautions were taken, of course, to make sure that the tablets were actually swallowed. The thyroid was usually given for a period of about three months, alternating with control periods without medication. The laboratory tests were repeated at intervals throughout the study.

Of the 18 "hypothyroid" patients of the 1930 series, 16 received thyroid treatment. The prognosis had been recorded as bad or poor in 15 of these. In two instances no significant improvement was noted but in the other 14 results were "good" or "excellent," 5 of the patients becoming well enough to be dismissed on home visit which could be prolonged for weeks or months. In no case, however, was anything that we could conscientiously label a "cure" obtained, both psychological and physiological residuals persisting in even the most satisfying instances.

Among the 41 control patients only 14 registered significant improvement. It appeared, then, that of patients showing initial thyroid deficiency, 88 per cent responded favor-

ably, whereas in the "nonthyroid" group the proportion was but 34 per cent. At the end of the third year an analysis of the 171 cases then available confirmed the earlier findings. Altogether, as a result of these and subsequent experiences, I believed then as I do now that evidences of thyroid deficiency appear in about 10 per cent of adequately studied state-hospital cases of schizophrenia and that in such cases thyroid medication in adequate dosage and for a sufficiently prolonged period usually results in improvement. Contrariwise, however, little benefit is to be anticipated from such treatment in cases selected at random.

Having learned that thyroid in properly selected cases is good but not good enough when used alone we have for the most part employed it during the later years in combination with a variety of other medicaments, the rationale having been frankly to try to hit upon some combination or combinations that could be relied upon with a degree of regularity to bring about significant clinical improvements. As to results of these many studies, suffice it here to state that no sufficiently satisfying combination has yet been revealed to us.

The principal use of thyroid in most recent years has been in an attempt to "potentiate" the influence of other hormone preparations. This plan has envisioned two well-established mechanisms: the general stimulating effect of thyroid in body systems generally—including the other endocrine glands—and the augmentation of bodily reactivity. In such studies the thyroid material has seemed to be of some genuine value, and particularly in combination with androgen treatments, but not of enough utility to justify elaborate, evaluating researches.

THE ADRENAL GLANDS

From the beginning of our endocrine studies, we have been led to suspect the possibility that adrenal inadequacy may play a significant role in schizophrenia. This is suggested especially by the frequent occurrence of general lassitude, low blood pressure, reduced oxygen assimilation, mild anemia, and aberrations of sugar metabolism not otherwise accounted for. Researches of the past half-dozen years have served to indicate with increasing clarity that the adrenal glands have important relationships with adaptive reactions generally. Cannon's well-known "emergency theory" of the adrenal medulla comes to mind, but the newer work lays greater stress on the cortex of the gland. From this structure are derived more than a score of individual steroids. These include both male and female sex hormones as well as important regulators of water, salt, and carbohydrate metabolism. Albright has offered the interesting concept that the steroids in general array themselves in two functional groups, one of which, the *S* group, promote the breakdown of muscle tissue for the liberation of its glucose component, and a second, the *N* group, that build up muscle tissue.

That the adrenals may be especially related to the schizophrenic psychosis in which adaptation is notably defective is suggested by their part in what Selye calls the "general adaptation reaction." In numerous publications he has pointed out that almost any stressful condition leads to immediate overaction of the adrenal cortex, marked in the first stage by hypertrophy and followed, often, if the stress is continued, by secondary atrophy. Clinical studies by

Browne and others have shown that stresses such as burns or fractures lead to an outpouring of adrenal cortical hormones. Pincus and Hoagland have shown a similar reaction to stress in normal individuals such as aviators.

As to the relationships of the adrenals to human functions at the personality level, the evidence is rather fragmentary. In Addison's disease the patients tend to show a depression of affect, with apathy or anxiety; occasionally paranoid ideas are accompanying manifestations. A condition of subacute adrenal deficiency has often been described; fatigability and general ineffectiveness are emphasized as the chief manifestation. At the other extreme there has been described a "hyperactive-adrenal" type of individual who is characterized by intense psychomotor activity. Of somewhat definite relevance is the recent report of Aub regarding the psychological features of a case of Cushing's disease, a disorder in which oversecretion of the adrenal cortex is an important feature. The patient had been a well-adjusted, highly intelligent adolescent. With the onset of the disorder she slowed up mentally as well as physically and her schoolwork deteriorated markedly. With recovery she regained her earlier abilities and returned to the top rank in her classes. Another suggestive item from the literature is the well-known work of Liddell and Hartman in which adrenal-cortex extract was found to have a marked ameliorative influence on the manifestations of "experimental neurosis" in sheep. This work was well controlled and the findings were clearly evident objectively.

These various considerations suggest that adrenal dysfunction might well be an important factor in the schizophrenic psychosis. As to the actual condition of the glands

in that disorder, the evidence is rather inconsistent and unconvincing. Various pathologists have recorded such abnormalities as fibrosis and lymphocytic invasion. One of the most extensive studies is that of Witte, who found a notably high incidence of lipid depletion in a series of 650 well-controlled cases. In the light of current researches this is just what might have been expected. Various other observers, however, have failed to discover any very significant morphologic abnormalities.

In the earlier years of our work at Worcester we made many therapeutic tests with such adrenal preparations as were then available, and have subsequently made some use of the more potent, newer preparations. Suffice it to say that in none of these tests have we been able to satisfy ourselves that significant improvement in the psychosis was obtained, though occasional successes from the use of cortin have been reported by others. The possibility remains open that with larger and more frequent doses given over more prolonged periods better results might have been secured.

The one preparation that we have employed that has led to any sort of impressive results is a commercial glycerine extract that we investigated somewhat extensively. We were able to show repeatedly that this material when given by mouth resulted in sustained improvement of the blood pressure and nutrition of the patients. It also made them clearly more responsive in terms of circulatory reactions to environmental stimulation. Unfortunately, however, these improvements at the physiological level were not mirrored in any significant degree by improvements of the psychosis. The results were published in a series of articles by Freeman and myself from 1933 to 1935.

Recently the problem has been subjected to renewed attack by Pincus working with several other members of our group. Two general methods were employed, namely, analyses of the urine for its steroid content and determinations of the lymphocyte counts in the circulating blood. The latter procedure is based upon evidences now available from several sources that the proportional lymphocyte counts vary in inverse ratio with changes in output of hormones from the adrenal cortex. The latter phenomenon may be used, therefore, as a check on urine analyses.

In the case of the first method the procedure was to collect timed urine samples over three- or four-day periods. The fact that we had available methods that permitted reliable quantitative determinations in samples of as little as one hour's duration permitted the collections to be made in three periods: during the night, during the first period after awaking, during the remainder of the day and the evening preceding sleep. It was thus possible to plot diurnal variations in the steroid output. Of the total steroid, about 70 per cent is derived from the adrenal cortex, though the sex hormones fall into the same group. The latter were determined independently by biological tests.

In normal men under ordinary conditions of activity there is a characteristic diurnal rhythm of 17-ketosteroid output. The maximum titer occurs in the hours immediately following awakening, being from 50 to 80 per cent above the sleep level. The average awakening rise in our experience is 62 per cent. Another moiety, the nonketonic steroid, can be measured independently by Pincus's antimony trichloride reaction. This latter fraction shows a similar but somewhat smaller (about 40 per cent) morning rise.

A group of 28 schizophrenics in chronic stages of the disorder were studied in regard to the *steroid output.* They showed, on the average, less rise upon awakening than do normal subjects: the rise in 17-ketosteroids was about 40 per cent and in the nonketonic, about 5 per cent. The distributions, however, were not nearly so consistent as is true of normal men. Among the 28 patients, 8 showed not a rise but a morning drop in the 17-ketosteroids while 6 showed an actually exaggerated rise of 100 per cent or more. In general a similar pattern was seen in the nonketonic fraction. In a larger population (70 patients) additional data that have not yet been completely analyzed showed again an average flattening of the diurnal curve.

There are two possibilities of interpreting these data obtained from patients experiencing ordinary daily living routine. The diurnal rhythm, it now appears with sufficient clarity, expresses a response to everyday stresses, internal and external. Since the patients mostly fail to show a normal morning rise it would appear either that the adrenal cortex is not responding adequately to the stresses or that what would be "stress" to normal people is not actually stress to the schizophrenic—in short, that his adrenals share in the "schizophrenic-withdrawal" mechanism. In other words the flatness of the curve might be ascribed to the daytime persistence of the "dream state." A fact that Elmadjian of our staff has noted, however—that the lymphocyte response to injected cortical hormone is approximately normal in schizophrenics—suggests that the abnormality is actually one of failure of the cortex to respond to stress.

We have also studied the responses of normal subjects and of schizophrenic patients to *imposed stresses.* These in-

cluded exposure in a seminude state to a chilly atmosphere; trying exercises on "pursuitmeters"; trying interviews or experimental frustrations; exposure to a hot, humid atmosphere; and breathing air of reduced oxygen content.

Our first approach was the application of the cold stress, but this proved to be relatively mild, i.e., to evoke only a moderate response even in the normal subjects. In these tests the response of the schizophrenic patients was definitely less than normal.

In the psychomotor (pursuitmeter) tests, normal subjects showed an elevation of the 17-ketosteroid output, but the schizophrenic subjects seldom did. Following the stress, normal subjects commonly showed a sharp reduction in the ketosteroid output—as though the adrenals were resting—whereas the patients often showed a delayed rise, no change, or a moderate drop. In general the results in the psychological stresses were similar to those of the psychomotor stress, as were also those of the "anoxia" stress.

The effects of heat stress on ketosteroid output in the urine were somewhat ambiguous in that, as we have recently discovered, a part of the material is disposed of in the sweat. Our data, so far as they have yet been analyzed, suggest that when the urine output and sweat output are combined, the results fall in line with those of other stresses.

Generally speaking, the changes in the lymphocyte counts in normal subjects and in schizophrenics confirmed the findings on the urine assays in indicating a diurnal rhythm of the adrenal cortex. In case of both heat stress and psychomotor stress, the results were more impressive than were those of the assays. In normal subjects the stresses were followed by clean-cut drops in the lymphocyte count, with

gradual restoration to normal values during subsequent rest. The patients, however, commonly failed to show this drop and, indeed, usually showed an increase in the counts. These latter findings suggest that the adrenal-cortex hormones are not secreted with normal promptitude and, indeed, often not at all by the patients.

In over-all perspective, then, it appears that the schizophrenic patient is handicapped in most cases by a failure of his adrenals to respond adaptively to the changing needs of the body. It is this characteristic, rather than any marked failure of secretion, that is impressive. By analogy, it is as though one were to attempt to drive an automobile through congested city streets with the throttle set at approximately a standard level and not subject to prompt modification of the gasoline in-put in relation to the exigencies of traffic. In retrospect, it would seem that our failure to obtain therapeutic benefit from the earlier use of glycerine extracts of the adrenal may have been due to this peculiarity. To continue the metaphor, we merely opened the throttle somewhat further but without adding anything to adaptive control.

THE SEX GLANDS

Of all the endocrine glands those that have the best warrant for intensive consideration in relation to schizophrenia are the gonads. Whatever may be the underlying cause, it is an undisputed fact that maladjustments in the psychosexual sphere are among the most frequent manifestations of the disorder. It would be impracticable to attempt even a cursory review of the voluminous, relevant background litera-

ture. The subject of psychosexuality in schizophrenia was discussed at some length elsewhere in 1943. It will be merely emphasized now that sexuality in the adult is determined in part by a variety of social factors, in part by various physiological factors, and in part by the operation of the sex hormones themselves. The sex hormones are important agents in the development of the reproductive structures as well as inciting factors for subsequent sexual behavior. In the developmental aspects the sex hormones are specific but, as inciters, the androgens and estrogens are largely interchangeable.

As to whether functional defects in the gonads, considered as endocrine organs, form a consistent part of the picture of schizophrenia the earlier evidence is somewhat inconclusive. Numerous observers have reported that atrophy of the ovaries and disturbances in the menstrual function—which might reflect ovarian abnormalities—are common. Mott and various other investigators have reported atrophy and fibrosis as characteristic findings in the testes also. The recent work of Hemphill and Reiss, using biopsy specimens, seems finally to have determined the matter in the affirmative. Their evidence is convincing that in males, at least, the psychosis is characterized by gonadal atrophy and the degree of deterioration correlates with the severity of psychosis rather than with the age or nutritional status of the patients. From the fact, however, that the atrophy is largely confined to the seminiferous tubules these investigators suggest that what is primarily at fault is probably a deficiency of a gonadotropic factor from the anterior lobe of the pituitary. In the case of both sexes it must be presumed that gonadal defects are of fairly late onset because, generally speak-

ing, enough of the hormones have been present in the earlier years of the individuals to insure rather adequate development of the secondary sex structures.

In addition to such morphological studies the problem can be approached also on a basis of therapeutic tests. During the past several years we have made numerous attempts to appraise the value of androgens and, to a minor extent, of estrogens in the treatment of schizophrenia. Our earlier studies in men with various sorts of extracts then available gave completely negative results. When synthetic androgen—testosterone—became available we were encouraged to continue with the investigations. The first publication was by Rosenzweig and myself in 1941. This was in the nature of an exploratory study in which a male schizophrenic, for 35 years an enthusiastic homosexual, gave completely negative results. Our hopes were revived, however, by a control study made by Freeman in a case of impotence and neuroticism in an otherwise apparently normal man who was successfully treated with a combination of testosterone and gonadotropin, though neither agent had been individually effective.

Our next approach to the problem was also made with a gonadotropin-androgen combination. This was a "blind test" in a group of 20 subjects, 10 of whom received the medication and 10 placebos that were especially prepared so as to be indistinguishable in appearance from the potent preparations. The patients were observed psychologically by Rosenzweig and psychiatrically by Freeman, neither of whom knew which materials the various patients were getting. Their pooled observations permitted correct appraisal in a high proportion of the cases as to which subjects had had

the placebos and which the active agents. Being thus assured that something more than wishful thinking was involved in the results, we turned to more elaborate studies. The most successful outcome in the series was obtained in the case of a eunuchoid schizophrenic whose case was reported by Sutherland and me. Preliminary treatment with thyroid had proved quite ineffective but when to this was added methyl testosterone by mouth and a testosterone implant, he made a rapid and striking improvement and was discharged from the hospital in apparently complete restitution.

We then instituted a somewhat elaborate study in which a group of 40 patients were put through a searching test routine that included physical, metabolic, psychological, and psychiatric observations. After an orientation period, each was given testosterone-in-oil intramuscularly in 25 mg. doses, three times weekly, for a period of six weeks. This was followed by another control period, after which the test routine was repeated.

The results may be briefly recapitulated. In well over half the cases the patients showed encouraging improvement in their clinical status, becoming more alert, approachable, and warm in their personal relationships. Although in some instances increased frequency of erections and an occasional nocturnal emission were reported, in general little evidence of increased sexual concern was noted. Indeed, in some instances the patients seemed to be more placid in this regard. In no instance except that of the eunuchoid previously mentioned, however, did the improvement carry through to a really impressive degree.

The studies were continued in the case of this test group

by the use of methyl testosterone by mouth in dosages ranging from 10 mg. to 30 mg. per day. In addition, some of the patients received testosterone implants of 150 mg., sometimes singly and occasionally several times repeated at monthly intervals. Thyroid was frequently added in an attempt to "potentiate" the effects of the androgens. The results in these cases were quite similar to those in which the intramuscular injections of testosterone-in-oil were given. In several instances the patients became well enough to go home on visit and some have remained out for more than a year, making fairly satisfactory social and economic adjustments. Searching psychological explorations in these latter cases have revealed, however, the same sorts of residuals that were noted in the thyroid series. Generally speaking, the patients retained their psychotic mechanisms but had them under materially better control. For a more adequate discussion of this point the 1945 paper of Shakow, Rodnick, and Lebeaux may be consulted.

The work has not yet progressed far enough to permit an appraisal of the precise value of the androgen therapy. Some of the patients fared better under the treatment than their initial prognoses indicated as probable. It is well known, however, that similar improvements are often seen in hospitalized schizophrenics irrespective of therapeutic measures. It is my over-all impression that the sex hormones are worth-while adjunctive therapeutic measures but that, by themselves, and in the time periods and the dosages that we have used, they offer little hope of bringing about genuine cures.

It is to be noted, however, that the time span of the influence of sex hormones is normally a long one. For example,

as Aub recently emphasized, it takes about seven years for estrogen to bring a girl into a state of sexual maturity. In view of the fact that schizophrenia is marked by many evidences of immaturity, it is quite possible that prolonged administration might lead to more significant results than we have seen.

It is to be noted, too, that in large measure androgens are self-antidoting agents. The human being is so adjusted as to carry on under the influence of both gonadotropins and androgens. If, however, the androgen titer is increased very much it serves to inhibit the anterior pituitary in its production of gonadotropin, whence the actual effect of androgen within the moderate dosage range is almost nil. It is possible, however, to go into a still higher range in which augmented end effects of the androgen may be secured despite the existence of a paralyzed anterior pituitary. We have not as yet carried our studies into this higher-dosage range.

Heller has recently reported that in the treatment of clinical hypogonadism testosterone implants were highly efficacious, whereas methyl testosterone in fairly high dosage was useless. The hormone is absorbed from implants in the amount of 1 or 2 mg. a day, only—an amount that is seemingly below the threshold of the pituitary-paralyzing effect. In further investigation of the utility of androgen, therefore, it is planned to utilize implants repeated at monthly intervals over a relatively long period. There is some hope that a maturing effect can thereby be induced which will be translated into more substantial clinical gain for the patients.

Brief mention may finally be made of some recent at-

tempts that we have made to determine the androgen and the estrogen output of schizophrenic men. Numerous of the urine samples that were collected in the course of the adrenal-cortex studies previously mentioned were assayed also for their content of sex hormones. For the androgen determinations the comb-growth reactions of "baby" chicks was employed and for the estrogens, the standard Allen-Doisy technique. The data so far available indicate that the average output of androgen in subjects that have reached a chronic stage of the psychosis is less than normal but that estrogens are not depressed. It is obvious that this research should be continued to conclusive length. It is important to know how early in the psychosis and how consistently depression of androgen production takes place.

THE PITUITARY

As is well known, the master gland in the endocrine hierarchy is the anterior lobe of the pituitary. Through its regulatory relationships it largely determines the levels of functional activity of at least the thyroid, the adrenals, and the gonads, and perhaps of some of the other glands. Thus it is theoretically possible that many if not all the functional perturbations in schizophrenia that hinge upon hormone deficits may actually have their origin in the pituitary rather than in the outlying glands themselves. A temptation to assume that such is actually the case is found in Cushing's emphasis upon the close interrelationship of the hypothalamus and the pituitary. While in this presentation I have avoided neurologizing, it may not be amiss to point out

that many elements in the schizophrenia picture are such as could be evoked by disturbances in this region of the brain. As a single instance Brookhart has shown that hypothalamic puncture can completely abolish sexual behavior in animals in which the sex glands remain structurally intact.

The literature bearing upon the immediate probabilities of a causal relationship between pituitary dysfunctions and the pattern of schizophrenia is rather vague and unconvincing. Several investigators have reported a high incidence of pituitary disturbance in delinquent human beings, but the evidence upon which the glandular diagnoses was based is not compelling. Mayers and Welton, who have made a special study of the personality of acromegalics, believe that the terminal phase of that disorder, in which pituitary deficiency is marked, is characterized by a gradual loss of initiative and other evidences of weakening of the personality, but I do not know of any studies in which appropriate, modern, psychological techniques have been brought to bear.

So far as I am aware no adequate cytological study of the pituitary glands of schizophrenics has ever been made. Cushing has published the statement that in an examination of 70 pituitary glands from state-hospital patients—I have heard that the glands were obtained from the Worcester State Hospital—not a single normal organ was seen. Several pathologists' reports are available, including those of Frank, Morse, Mott, and Robertson, and more recently, Lewin. The trend of this evidence is that the pituitaries show various signs of exhaustion or fibrotic degeneration, but such gross observations regarding an organ so complex in its func-

tional cytology as is the pituitary carry relatively little weight.

No less unconvincing are the diagnostic and therapeutic studies that have been made. In our own 1930 series of 130 cases pituitary dysfunction was diagnosed in 13, but the diagnostic criteria that were employed we now regard as inadequate. In an occasional instance over the years we have detected in the X-ray plates of the skulls of schizophrenics evidences of hyperpneumatization and sclerosis of the cranial tables that indicate rather definitely the existence of early and prolonged pituitary dysfunction. But these have not occurred with sufficient regularity to justify the assumption that the hypophysis is selectively involved in the psychosis. Likewise, I am not aware of any convincing therapeutic studies in the literature.

We have administered numerous sorts of pituitary preparations, including desiccated gland substance in large amounts and a variety of commercial and special extracts. Suffice it to say that none of these explorations has yielded sufficiently promising results to justify detailed presentation of them. We have not, however, made adequate trial of the currently available multipotent preparations. Again the possibility remains open that in properly selected cases and with adequate dosage for a sufficiently long period significant results might accrue.

What is especially needed in further researches in this part of the field is an accurate determination of the titers of the various pituitary tropins of an adequately large group of patients. We have made a beginning of such studies, assaying the urine for its content of gonadotropin. The results so

far suggest that the output of this hormone is normal, but the data are as yet by no means conclusive.

OTHER GLANDS

Very little is known regarding the possible relationship of the parathyroid glands to the schizophrenic psychosis. In view of the marked influence of the parathyroid hormone in allaying neuromuscular irritability it might be suspected that the agitated, belligerent type of schizophrenic might be suffering in part from parathyroid deficiency. In the hands of Bowman, however, as well as of our group, a few attempts at alleviating agitation by parathyroid extracts have been rather unsuccessful.

Whether the results of insulin treatment of schizophrenia should be considered as relevant to the endocrinology of the disorder is doubtful in that the dosages used are so grossly unphysiological as to afford little evidence regarding possible interposition of the islands of Langerhans in the mechanism of the psychosis. Suffice it in this connection to remark that in our researches directed toward an elucidation of the mechanism of the beneficial effect of insulin shocks we have seen some indication that those patients who respond favorably give evidence of an improvement in adrenal functions, whereas those not responding fail to do so.

In summary, then, it appears that various of the functional disturbances seen among schizophrenic patients are quite similar in kind to those resulting from various sorts of glandular deficiencies. Furthermore, the various endocrine glands have been frequently reported to show struc-

tural alterations suggestive of functional inadequacy. Of the various endocrine preparations that have been used in the treatment of the disorder, thyroid and the androgens appear to have given the best results. In a larger proportion of the cases than would have been expected by random chance or as a result of increased personal attention, the patients have improved coincident with such medication. In our experience, at least, however, no single gland preparation nor combination of gland preparations has sufficed to bring about complete restitution of the patients—the one exception having been a eunuchoid who seemed to be really cured by androgen.

While such data definitely throw the burden of proof upon proponents of endocrine therapy, they by no means close the issue. It is quite possible that were appropriate and potent preparations selected and were these given for sufficiently prolonged periods, materially better and, conceivably, even completely adequate results might be secured.

Another possibility remains open, namely, that the numerous evidences of functional glandular inadequacy that are seen in schizophrenia may be due not to deficits of the individual hormones but to *inadequate responsivity* to them. The high tolerance often manifested by schizophrenics to thyroid points in that direction. We have noted also that schizophrenics generally respond in less than normal degree to injections of adrenalin and insulin. Whether the same is true of other hormones should be determined. In the event that depressed reactivity to hormones should prove to be a consistent characteristic of the psychosis, then therapeutic attempts should be addressed primarily to nor-

malizing responsivity. How or whether this could be done remains a matter for empirical determination.

OXYGEN METABOLISM IN SCHIZOPHRENIA

Of the intimate relationship between human behavior and oxygen assimilation there can be no question. Oxygen is literaliy the breath of life and the multifarious combustive reactions of the body a large part of "life" itself. Since enough oxygen is a necessity to existence but too much is essentially inconsequential, the problem of oxygen metabolism in relation to schizophrenia resolves itself mostly into two questions: first, does the schizophrenic in actuality show a deficiency of oxygen uptake, and, second, are the results of oxygen deficiency as seen in normal individuals phenomena of a schizophrenic order? The second question may be discussed first.

Many observations beginning with the classic studies of Paul Bert on the effects of breathing rarefied air have been recorded. Of recent years, Barcroft and McFarland have written extensively on the subject and it is to be presumed that when the results of wartime researches in aviation physiology come to publication numerous additional data will be disclosed. That the results of deficient oxygen assimilation are at least of the general order of the symptoms of schizophrenia seems sufficiently obvious. These include limitation in the field of attention; perseveration; apathy; depression of spirits; inappropriateness of affect with silly laughter; poor judgment, often with a high opinion of mediocre performances; obliviousness to danger; loss of self-

control; anxiety; excitement without apparent cause; uncontrollable emotional outbursts with laughing, shouting, singing, weeping, and violence; insidious loss of the power of decision and unwillingness to bear responsibility; tangentiality of associations; and gradual failure of sane judgment and a sense of the fitness of things. In short, as McFarland has emphasized, such manifestations evidence a general loss of intrapersonal integration. Schizophrenia might also be appropriately described by exactly the same phrase.

Furthermore the many resemblances between the dream state and the psychosis demand consideration in this connection. Suboxidation in the brain may be the fundamental cause of the dream state.

At first thought one might conclude that the possibility that oxygen deficiency is a major cause of the psychosis is negated by the fact that dwellers in high altitudes in actuality do not show any particular predilection for the development of schizophrenia. The obvious answer, of course, is that the normal individual under such circumstances has at his command a variety of compensatory mechanisms by which he soon becomes acclimated to oxygen deficiency in the inspired air. To adapt this phenomenology to a theory of schizophrenia it would have to be postulated that there is not only a chronic deficiency in oxygen uptake but also an inability to compensate for the defect. A chief deficit of our knowledge and one that detracts from security in postulating a suboxidation factor as important in the psychosis is that we do not know that prolonged exposure to lesser degrees of a lack of oxygen would have the same sort of effects as has acute deficiency over a shorter period.

In our own work at Worcester we were interested from

the beginning in the problem of oxygen consumption both because of the fact that reduction in the basal metabolic rate is a chief indicator of endocrine deficiency and because of the relation of the problem to metabolic manifestations generally. Our publications of 1929 and 1932 still represent our matured convictions upon this point and from them I shall quote rather freely.

In the early days when basal metabolic-rate determinations were first introduced into medicine, Benedict warned that in actual practice they would probably be as often misleading as instructive. In researches on the schizophrenic psychosis, Benedict's warning seems to have been fairly commonly ignored. "Basal rates" are freely recorded in numerous articles with a carefree abandon that betrays an astonishing unconcern as to the meaning of basality. The basal rate actually mirrors the oxygen cost of the mere business of staying alive. To obtain a true basal rate in most schizophrenic subjects is difficult if not impossible. Only careful and patient attention to technical details can insure even a fair working approximation to that goal. Unless the patient has been habituated to the test procedure, the rate as recorded mirrors both the basal oxygen uptake and that undetermined addition that results from psychomotor tension. And this is true even though the patient contributes an apparently satisfactory degree of co-operation to the undertaking. Any deviation from basality is necessarily in the upper direction. For this reason the lowest rate that is obtainable in any given subject—technical errors being excluded—the most nearly represents the true basal rate of that individual. In ordinary experimentation special selec-

tion of the data is likely to vitiate the results. In basal-rate work a failure to make such special selection is equally precarious.

Our own published studies have been based on determinations made mostly on patients habituated to testing. That of 1932 included results in 214 patients. Standard methods of determining the oxygen-consumption rate were employed throughout. Special care was taken to avoid leakage around the mouthpiece, the apparatus was tested daily for leaks, and we systematically avoided the use of spent soda lime—the three conditions that are capable of giving a speciously low "consumption rate." If the patients showed other than minor activity before the tests or overt evidence of tension, they were excluded. It was found by experience that if several test runs were made at a given session, the first or second was most often the lowest, with the rate gradually rising; the patients seemed to be "fed up" with the procedure. Hence in the tabulated results, the lower of two consecutive runs was used, except in an occasional instance in which only a single technically satisfactory test was secured. Usually in the series reported, several test runs were made on each patient. The average rate was found to be 88 per cent of the standard textbook normal. In individual cases from 1 to 15 pairs of readings were obtained. In such pairs, considerable degrees of variation between consecutive readings were often seen, the *average difference* being 6.2 points and the first or second being higher in approximately equal numbers. The average difference between the highest and lowest "acceptable" readings obtained in each patient in the total series was 21.6 per cent, the actual range being from 2

to 70 per cent. The average lowest reading obtained in each patient, and this probably most nearly represents the true basal rate, was 81 per cent of standard prediction.

Altogether, then, we were and are convinced that one of the most characteristic features of the psychosis appearing at the metabolic level is deficiency in the uptake of oxygen. This is fairly easily demonstrated under laboratory test conditions and it is probably even more true of patients living at their habitual, "slumped" vital level. It is to be noted, however, that in the oxygen-consumption rate, as in numerous other physiological processes, the patients are able under special stimulation and episodically to rise to normal or approximately normal levels of physiological performance.

As to how the lowering of oxygen assimilation is brought about, more information is needed—and it is conceivable that an answer to this problem might actually reveal the essential mechanism of schizophrenia. A pregnant suggestion was made by Golla in 1928 in his report that a few subjects that he studied were less than normally reactive to the carbon dioxide of the blood as it reached the respiration center in the brain. Freeman made an elaborate study of this possibility, comparing a group of normal controls and a group of schizophrenic patients in their responses to changes in the concentration of carbon dioxide in the inspired air. Both the depth and frequency of respiratory excursions were recorded. In brief, it was found that the patients were quite as responsive as the controls. Hence whatever may be the explanation for the reduced oxygen consumption in schizophrenia, it is not due to "laziness" of the respiration center.

There are two other major possibilities of explanation for the reduced oxygen consumption. One is that the blood

of the patients might leave the lungs in an undersaturated condition and the other that the tissues might fail to abstract an adequate amount of oxygen offered to them in normal supply. McFarland has stated that with careful attention to the techniques of obtaining arterial samples, thus avoiding stimulation of the patients, emotionally or otherwise, a significant lowering of the oxygen content of the arterial blood can be demonstrated in some schizophrenic subjects. In the studies that we have made the arterial oxygen has been found consistently to lie within normal limits.

It is obvious, however, that a defective degree of oxygen transport might arise even though the arterial blood contained a normal proportion of oxygen. This might be due either to a diminution of the *volume* of the blood in actual circulation or to a sluggishness in the *circulation rate.* Looney and Freeman of our group have shown that the total blood volume when referred to surface area averages significantly less in schizophrenics than in normal subjects. Such a measured total, however, might well include a considerable amount of inactive blood that is usually stagnant in the splanchnic reservoirs and hence not afford a true index of the circulating volume. That the rate of flow is diminished in schizophrenia will be brought out in a discussion of the circulation in paragraphs to follow.

Altogether it seems more probable that the important cause or causes of the defective oxygen assimilation may be found in the tissues of the body—and that means their enzyme systems—rather more than in defects of oxygen supply. This conclusion follows from the fact, among others, that although the oxygenated blood is longer exposed to the reducing action of the tissues in schizophrenic than in nor-

mal persons they succeed in abstracting no more oxygen from it despite this advantage.

One evidence of inadequacy of the oxidative mechanisms in the psychosis is a relatively greater accumulation of unoxidized *lactic acid* in the blood of schizophrenics than in that of normal subjects when graded exercise is imposed. Looney found in 35 control subjects that 10 minutes of running up and down stairs led to an average production of lactic acid of 0.065 mg. per kg. per meter per minute, while in the patients the production was half again greater, namely, 0.097 mg. In this case the cards were stacked against the investigator in that the normal subjects actually pushed themselves harder than did the patients.

Another indication of defective oxygen-assimilative mechanisms is seen in the relationship between the *glutathione* and the lactic acid content of the blood. In tissue respiration, glutathione serves as one of the intermediary bodies whereby the assimilation of oxygen is promoted. That the normal individual is not in any major way dependent upon this mechanism is indicated by the fact shown in our laboratories that the glutathione and the lactate levels in the blood —hence in the tissues—vary quite independently. In the schizophrenic group, however, a statistical relationship between the two substances was shown. In cases in which lactate had accumulated, elevating the titer of that material, the glutathione was found to be low, a fact that suggests that it was being utilized in excess as an adaptive means to facilitate oxygen assimilation. It would seem, then, that the schizophrenic person is forced even during rest to utilize an accessory mechanism upon which the normal subject is not dependent.

Another indication of tissue sluggishness in oxygen intake is the high tolerance for thyroid, previously discussed. Were the tissues normally responsive to so powerful an oxidative catalyst as thyroid, 50 grains a day of the desiccated substance or 5 mg. of intravenous thyroxin which Cohen employed should have rather promptly brought the patients to a deep state of hypermetabolism. In the same connection it may be mentioned that Freeman found schizophrenic subjects to be less than normally responsive to dinitrophenol, which is another powerful oxidative stimulant. As previously remarked, similar deficiencies in responsivity to adrenin and insulin in most schizophrenics are easily demonstrated.

Final mention may be made of still one other indicator that tissue assimilation is defective. As is well known, the very consumption of food, and especially protein food, sets off a mechanism for its increased oxidation within the cells. I am referring to the well-known *specific dynamic action* of food. It should follow from this principle of specific dynamic action that the more nitrogen that appears in the urine—hence the more protein material catabolized—the higher should be the basal metabolic rate. We were able to test this hypothesis by determining the degree of correlation in a rather large body of data on medical students supplied to us by the late Allan Winter Rowe of the Evans Memorial Hospital. In the case of these data, a definite positive correlation was found. In the case of our own data on schizophrenic subjects, however, the relationship seemed to be purely random, hence their tissues not adequately responsive to products of protein digestion. Fischer has confirmed this deduction by direct studies. He reported that the spe-

cific dynamic action begins to decrease with the onset of the disorder, persists at a reduced level as long as the psychosis is active, increases with clinical improvement of the patient, and becomes normal when full remission is attained. He ascribed a high etiological significance to the defect. We made some attempts to check on Fischer's findings but, in the face of the wide "spontaneous variability" in the oxygen-consumption rate of the patients, did not succeed in obtaining convincing results either positive or negative.

Altogether the aforementioned evidence seems to indicate with considerable clarity that a trend toward defective oxygen metabolism is a significant feature in the schizophrenic psychosis. Inadequate oxygen assimilation would necessarily be influential in cutting down available energy and in handicapping the patient in making adaptive adjustments.

The oxygen metabolism of the body represents a complex series of interactions in which energy food (mostly dextrose) is oxidized in a linked series of reactions passing successively through several organic-acid stages to the final end products of the series, namely, carbon dioxide and water. The defective oxidation in schizophrenia might occur at any stage of the oxidation cycle and might be due to lack of either an enzyme or a co-enzyme specific to each stage. One of the obvious needs in this sector of the field is to bring to bear the modern techniques for a study of the tissue-enzyme systems and especially those of the brain. Such studies have been on our agenda for several years but circumstances have not yet rendered it possible to carry them out to any significant extent. Hoagland's method, based on thermodynamic considerations, can be expected to yield significant data.

CARBOHYDRATE METABOLISM

That the level of carbohydrate in the blood may have an important influence upon mental processes has long been known. It is a matter of record that cases of simple hypoglycemia due to overactivity of the islands of Langerhans have been diagnosed as "epilepsy" and as "schizophrenia," and Romano and Coon have recently reported a careful case study showing that hypoglycemia can result in delirium.

In a review of the older literature by William Freeman of our group in 1933, reports were found on fasting blood-sugar determinations in 620 patients. In 76 per cent, the findings were within normal limits; in 9 per cent, below normal (80 mg. per cent or less); and in 15 per cent, above normal (120 mg. per cent or more). At that time records were available in our series on 59 patients who had undergone fasting blood-sugar determinations, mostly six times each at intervals, giving a total of 347 samples. In that series, 95 per cent of the determinations fell within the conventional limits of normality, the average being 96.6 mg. per cent as compared with a similar average of 95.4 mg. per cent in 31 normal control subjects studied by the same technique. Of the 16 deviations from normality, 8 were in the hypoglycemic and 8 in the hyperglycemic range. Thus it appeared that in the fasting-resting state the schizophrenic finds himself in a normal degree of metabolic equilibrium so far as this factor is concerned.

Many studies of carbohydrate metabolism in the psychosis have been made by administering the sugar in various ways and noting the succeeding effects on the blood-sugar titers.

The results from the *intravenous administration* of glucose have been variously reported. In a recent group of 46 patients (military subjects) Freeman found a suggestion that the mechanisms for dealing with such sudden insults of the carbohydrate-controlling mechanisms were less than normally efficient as indicated by the fact that the blood sugar rose higher than has been reported in normal individuals. Colonel J. M. Looney, however, made a parallel study, using identical techniques in 20 normal soldiers. His findings were closely similar to those in our patients. It would seem, then, that so far as an ability to displace excessive carbohydrate out of the blood stream is concerned, the schizophrenic is rather a normal individual.

It is quite possible that the phenomenology involved here is primarily a matter of transudation into the tissue-fluid reservoirs. More interest attaches, therefore, to studies in which the carbohydrate-controlling processes proper are involved. After considerable experimenting with various sorts of *carbohydrate-ingestion* techniques we have of late years utilized almost exclusively the Exton-Rose method in which 100 grams of glucose is given in two equal portions at intervals of a half hour. In the normal individual the first, provocative dose serves to mobilize the metabolic mechanisms in such fashion that the second dose is promptly dealt with and no further significant rise of the blood-sugar titer results. This fact we have confirmed in most of our own normal subjects. In most of 38 schizophrenics, however, the sugar curve continued to rise after the second dose. In individual instances the value reached as high as 180 mg. per cent. Such findings have been repeatedly confirmed. Many attempts have been made to account for this abnormal re-

sponse. It might conceivably be due to a failure of secretion of insulin or to reduced response to that hormone. And, indeed, in the patients as a group compared with controls as a group, the insulin reaction proved to be materially less; in 45 per cent of the patients the response was less than the lowest response recorded in any of the controls. No significant correlation was found, however, in individual schizophrenics between the reactivity to insulin and the aberration of the Exton-Rose sugar curve.

The possibility was considered that the undue elevation of the blood sugar might have been due to an oversecretion of adrenin. Since, however, the high carbohydrate values were not accompanied by corresponding increases in the blood pressure and the pulse rate this hypothesis was not supported.

Despite many attempts to elucidate the relationship the only correlation that has appeared with any consistency is between degrees of *tension* and the abnormal glucose response. Thus it was found that numerous subjects, who gave normal findings, when put through a trying "pursuitmeter" test shifted from the normal to the abnormal type of response to the ingested sugar. The results as they stand somewhat controvert Gellhorn's conclusion that states of excitement in schizophrenics evoke more than the normal discharge of insulin.

The topic would lend itself to elaborate theorizing, and especially to a consideration of the recent work of Meduna and of Gellhorn but this would hardly be profitable in the current state of our ignorance of the actual mechanisms involved. For the moment, then, the aberrant reaction to ingested glucose may be dismissed as one evidence that schizo-

phrenics, at least in the earlier stages of their psychosis, show evidences of tension. It is probable that the abnormality has deeper meanings.

CIRCULATORY CONDITIONS IN SCHIZOPHRENIA

In an earlier section it was emphasized that one of the important factors involved in levels of oxygen assimilation is that of transport between the lungs and the tissues. This raises the question of circulatory efficiency in schizophrenics as compared with that of normal individuals. This problem we have investigated with considerable thoroughness. We have long been aware of the fact, as remarked before, that episodically and in response to stimulating situations the schizophrenic is able to rise to a deceptive degree of normality in numerous of his physiological manifestations. Thus if patients are selected at random and subjected immediately and without habituation to test procedures, both their systolic and diastolic blood pressures are found to be approximately normal. We were especially interested, however, in the sort of performance that is to be expected from the patients when brought into as nearly as possible a genuinely basal state.

Our first study of the problem was made on 180 patients in chronic stages of the psychosis as compared with results obtained on 323 medical students of Boston University. In this series the *systolic pressure* in the patients averaged 104.5 mm. Hg. and in the students 115.7. The average *diastolic pressure* in the patients was 54.5 and in the students 71.2. Thus numerous older reports were confirmed to the

effect that one of the characteristics of schizophrenic patients is a fairly marked tendency to hypotension. Some of the patients included in the first series were subsequently utilized in an elaborate research program; they had accordingly become thoroughly habituated to being studied and correspondingly indifferent to the test procedures. When 50 of these patients were retested after such habituation, it was found that the average systolic pressure was further reduced to 100.3 mm. This latter finding, among others, indicates that even in chronic schizophrenics, in whom the withdrawal mechanism is a prominent feature, enough contact with the environment persists to affect the blood pressure even under conventional basal conditions.

Comparative studies in 50 schizophrenic as compared to 25 normal subjects by Krinsky and Gottlieb of our group showed that the venous blood pressure was not significantly different in the two groups.

The schizophrenic subject in the basal state commonly shows also a less than normal frequency of the *heart rate.* With the heart delivering at reduced stroke frequency and at reduced systolic tension, it is an interesting question what the actual *circulation rate* of the blood through the tissues might be. Here again results vary with the degree of excitement in the patients. In 73 trained subjects studied under basal conditions and using the sodium-cyanide technique, Freeman found the arm-to-carotid circulation time to have a mean value of 25.5 seconds. When 52 of these patients had become further habituated to the testing a few weeks later the basal circulation time had been further slowed to 27.9 seconds. In 26 normal subjects under basal conditions the circulation time was about a fourth faster, namely 21.9 sec-

onds. The patients in this test were in a chronic phase of the disorder. In another study made under similar conditions on patients in a more acute phase, the mean circulation time was 23.2 seconds in one series and in another series of tests a month later it was 24.1 seconds. This series was controlled by studies on a group of 29 normal subjects who lived for a considerable period in the hospital, underwent the same degrees of activity, took the same tests, and ate the same type of food as the patients. In this group the difference from the patients was again significant, the circulation rate again being about 20 per cent slower in the patients. We, at any rate, are convinced that among his other handicaps the schizophrenic patient labors under a considerable tendency to circulatory sluggishness.

Of probably still greater significance is the fact that he is much less efficient than normal in making *adaptive adjustments* to local and passing demands upon the circulatory mechanism. In a purely mechanical "circulation scheme," such as the device commonly used in teaching laboratories of physiology, the dependence of the diastolic pressure upon the systolic is immediate and the correlation between the two is correspondingly high. By this same token the more nearly a human being approached a robot condition the higher would be the correlation between his systolic and diastolic pressures. Conversely, the more that the simple hydrostatic laws were modified by interpolated and episodic activities of the controlling nervous mechanisms, the lower the correlation would fall. Thus a determination of the *systolic-diastolic r* should afford a particularly meaningful indicator of the adaptive efficiency of the individual. We were fortunate in having adequately large and well-con-

trolled samples of blood-pressure determinations, together with competent biometric collaboration, to utilize this method with unusual confidence in the validity and meaningfulness of the results. For the application of the method as well as the statistical procedures that were involved we are indebted to a former colleague, E. M. Jellinek.

For control material, we had a sample of 323 determinations made under basal conditions at Boston University and 1,398 determinations made under nonbasal conditions at the Iowa State University. The correlation coefficient in the basal group was .43, whereas that in the nonbasal group was statistically the same, namely .45. Similar determinations were made on two different schizophrenic populations both under basal conditions, the groups consisting respectively of 180 and 100 individuals. In both samples the correlation coefficient was identical, namely .62.

In view of the fact that changes in the relationship between the systolic and diastolic pressure are largely determined by degrees of excitement it was confidently surmised that the sympathetic components of the controlling mechanism would prove to be most concerned. When this supposition was tested by injections of adrenin in a slightly better integrated group of schizophrenics having a correlation coefficient of .52, the correlation dropped to .18, indicating that the immediate interdependence between the two pressures had been almost totally disrupted. As is well known, thyroid hormone causes relative overactivity of the sympathetic nervous system—a fact that is made use of in the well-known "Goetsch test" for clinical hyperthyroidism. To another group of schizophrenics having an initial systolic-diastolic correlation coefficient of .61, thyroid medication

was administered. This was followed by a drop in the coefficient to .42. It is clearly evident from such observations that the schizophrenic shows a well-marked sluggishness in sympathetic responsivity. As evidence that the phenomena under discussion are characteristic of schizophrenia as such it may be mentioned that 72 subjects of dementia paralytica gave a systolic-diastolic correlation coefficient of .48, essentially the same as that of normal individuals. The various findings were rigorously tested statistically for significance of the differences of the r's; all those cited are meaningful.

TEMPERATURE REGULATION IN SCHIZOPHRENIA

Another obvious group of phenomena that could be studied in the hope of obtaining insight regarding adaptive efficiency are those involved in temperature regulation. Thanks to the generosity of the Rockefeller Foundation we were enabled to install a well-insulated laboratory in which the temperature, the humidity, and the internal air velocity could be accurately and independently controlled. In addition, the laboratory was equipped with a large "silk scale" upon which a man could be weighed with an accuracy of 2 mg. By the use of an electromagnetic damper the oscillations of the scale were reduced practically to zero without significant sacrifice of sensitivity. A recording stylus affixed to the weight end of the balance permitted continuous kymographic records of the displacement of the weight arm as the tests proceeded. It was thus possible by use of a calibration scale to read off directly and accurately the changes of weight of the subject over intervals as short as one min-

ute. The installation of a Jones metabolimeter on the couch arm of the balance permitted simultaneous determinations of weight changes and of oxygen-consumption rates. By the use of these devices we were able to make numerous accurate studies of the insensible perspiration rate, as well as other factors concerned in temperature control. These studies are cited in the bibliography at the end of this book but will not now be recounted in detail. Suffice it to state that for the most part the schizophrenics whom we studied behaved as regards heat control in approximately a normal fashion. The two chief differences that we were able to detect were (1) less than normal reactivity to the oxidative stimulant dinitrophenol and (2) a less than normal ability to maintain an oral-rectal temperature differential. The average difference between these sites in the controls was 0.95° F., whereas in the patients it was only 0.54°. The correlation coefficient of the oral *versus* the rectal temperature in the controls was 0.56, whereas in the patients it was 0.73, this difference again seeming to mark an approach to a robot condition. Thus it appeared that although the schizophrenic can manage well enough the over-all sort of adjustments for maintaining the heat of the total body mass—albeit somewhat sluggishly—those arrangements for setting up local and presumably adaptive differentials are inefficient.

EQUILIBRIUM REACTIONS IN SCHIZOPHRENIA

Occasion will be taken for mention of only one further group of researches that we have carried out. The general

plan underlying the investigations of the psychosis from a psychological point of view involved a study of reactive efficiency at the various levels of function, from that of the simple reflex to that of the higher mental activities. Here I shall mention only studies at the reflex level. In the case of the *knee jerk,* results in schizophrenic patients were closely similar to those in normal controls. In studies of *reaction time* with choice and especially the influence of *set* on reaction times, a difference between patients and the controls became clearly apparent, the patients being notably less efficient. Attention will be directed more particularly, however, to a group of studies on the *equilibrium mechanism*—a more complex reflex function. The first of these studies was published by Angyal and Blackman in 1940. Results in 58 patients were compared with those in 20 normal persons. *Nystagmus* was induced either by irrigating the external auditory meatus with water at 20° C. or by rotation in a Bárány chair (10 revolutions). Both the absolute number and the frequency per second of the nystagmic beats were recorded. Following rotation, the average frequency of beats per second was greater in the controls than in the patients in a ratio of 1.67 to 1.32. The total number of beats was also greater in the controls, the proportion being 61 to 45. In response to caloric stimulation the difference between the patients and the normal controls was even greater, the mean number of beats being 60 and 116 respectively and the frequencies 0.82 and 1.34 respectively.

In a subsequent study, 36 schizophrenics and 20 normal persons were again subjected to caloric stimulation, and the influence of alcohol, hyperpnea, and CO_2 inhalations on the nystagmic reaction was determined. Under these conditions

a rather astonishing, paradoxical phenomenon was seen. Both hyperpnea and alcohol caused an *increase* in the nystagmic reaction in the normal subjects and a *decrease* in the patients. Contrariwise, whereas in the controls the carbon dioxide caused a decrease in the reaction, in 40 per cent of the patients it caused an increase; in 45 per cent the reaction was uninfluenced and 15 per cent of the patients behaved somewhat similarly to the normal subjects. In discussing the presentation of this work Paul Schilder affirmed that the experiments offered conclusive evidence that there is an organic change in the vestibular apparatus in schizophrenia, a conclusion that coincided with our own deduction.

The study was further extended by Freeman and Rodnick. The effect of rotation on *muscle tonus* was investigated in 30 normal persons and 30 schizophrenics. The procedure consisted essentially of determining the steadiness with which the subjects were able to stand before and after rotation. The steadiness was measured graphically with styluses writing on a kymograph that summated frequency of anteroposterior and of lateral movements. The optical component in the stimulating situation was eliminated by the use of dark glasses. A record of the steadiness having been obtained, the rotation was imposed at rapidly increasing speed and maintained for two minutes. The rotation was then stopped abruptly and the subject quickly attached to the recording apparatus. The recording began as soon as the subject could stand unaided. Without summarizing the results in quantitative detail, suffice it to say that the patients manifested less than half as much unsteadiness following rotation as did the controls.

Finally, Angyal and Sherman studied the equilibrium reaction in 20 patients and 20 control subjects, each being blindfolded and instructed to stand in one place marking time. In this experimental setup the subjects unwittingly carried through a *rotation* about the vertical axis of the body (the "lost-in-the-woods" phenomenon). The test was first administered without vestibular stimulation in order to determine the amount and direction of rotation. The external auditory meatus in each case was then irrigated with 10 cc. of water over a period of 10 seconds, the temperature being 25° C. in two sessions and 28° in two others. The mean total vestibular reaction measured in degrees of rotation was less than half in the case of the patients than in that of the normal subjects. The total duration of the reaction as well as the degree of rotation per time unit were found to be materially less in the patients.

Altogether, then, the evidence is excellent that the schizophrenic is substantially less than normally reactive in regard to his equilibrium functions. It is difficult to escape the conclusion that the deficit here is centrally determined and is based on an organ defect. In view of the important role that is played by equilibrium reactions in everyday activity the defect would seem to impose a very considerable handicap, the compensation for which would add to the difficulties of adaptation. This difficulty might be one potent source of the chronic fatigue that has often been postulated as an important etiological factor in the psychosis.

The foregoing observations were selected for report largely because of their implicit bearing upon the problem of homeostasis. That topic may now be considered somewhat more explicitly.

HOMEOSTASIS IN SCHIZOPHRENIA

As Cannon has emphasized, one of the most important adaptive characteristics of higher species that have won in the race for survival is an ability to maintain a steady state —homeostasis—within the individual despite the stresses that constantly impinge upon it from the environment, external and internal. The existence of such a steady state is the more remarkable in that the organism is made up mostly of materials that are notable for their instability. It is only by the operation of a large number of mechanisms that come promptly into play to correct modifying influences of stresses that homeostasis is preserved.

As regards the schizophrenia problem, homeostasis presents two important aspects. First, are there systematic differences between schizophrenics and normal persons as regards the *levels* at which different functions are "set"? Second, to what extent is the "steady state" actually *steady?* A correlated problem is, how *promptly* is a given imposed distortion corrected in the one type of individual as compared with the other? Mere lack of promptitude in achieving adjustment might prove, in action, a formidable handicap even though ultimate restoration to normality were achieved. It is to be noted that the adaptive value of homeostasis would not be best served by an invariable pattern. Some functions would best meet the needs of the organism when held rather rigidly at standard optimal levels despite environmental stresses, whereas others would serve best if capable of facile variations to meet sudden new needs. This

last-mentioned feature of homeostasis has not been much emphasized.

As to resting *functional levels* the patients and the control subjects in our studies have proved in many respects to give essentially identical values. Attention will be directed at this juncture only to a brief recapitulation of our findings in cases in which systematic deviations have been noted.

As to the nutritional status, 55 per cent of the patients showed underweight, the mean level of the total population studied being 16 per cent below prediction from height and age. That deficiency in the dietaries was not the significant factor is indicated both by the fact that some patients achieved overweight on it and that the hospital employees had no difficulty maintaining normal nutrition. The underlying cause of the weight deficiency is presumably an abnormal attitude toward food consumption rather than either relative overactivity of the individual or inefficiency of his digestive system. But that inefficiency of tissue assimilation may be a significant factor is suggested by the fact that, according to our recent studies, the titers of several of the blood vitamins are usually much lower in the patients than is reported for normal individuals. The relationships between vitamins and nutrition, however, are complex and our findings have not yet been sufficiently analyzed to justify more than passing mention.

The *oxygen-consumption rate* as previously emphasized is commonly displaced in a downward direction, the mean of the lowest reliable determinations in a large group of patients being 81 per cent of prediction. The rate of *blood flow* also averaged 27 per cent lower in the patients than in

normal subjects, a fact that correlates with the 15 per cent lowering of the basal systolic blood pressure and pulse rate. We noted also considerable sluggishness of the *colon,* the emptying time being 50 per cent greater than normal. This sluggishness proved to be in part correlated with levels of bodily activity but was only partially corrected by an imposed regimen of physical exercise. The absence of indican reactions in the urine suggests that the defect is not of any great importance. The only other variation from standard levels that will now be mentioned is that of *urine output*—a level that we found to be nearly twice that of control subjects living in the same environment and eating the same food. This finding, of course, suggested a defect in the diencephalic-pituitary controlling mechanism. By the use of salt-and-water-retention tests, however, Sleeper was able to show that the difficulty lay elsewhere, and Miller found it to be due chiefly to the patients' attitudes toward water drinking. It is interesting that these two instances have appeared in which the homeostatic equilibria were seemingly determined by *attitudes,* a factor that has not hitherto had emphasis.

Another aspect of the homeostasis problem has already been discussed in connection with other topics, namely, *defective reactivity to stimulating agents.* Thus, to particularize an earlier statement, Freeman and Carmichael made a study of 72 schizophrenic patients as compared with 24 normal controls, tested under basal conditions, to whom a cubic centimeter of diluted adrenalin solution (0.05 mg.) was given intravenously. For the controls the maximal rise of systolic blood pressure averaged 56 mm. as against 44 mm. in the patients. Similarly the pulse rates increased 16.3 and

18.6 beats respectively. The depressed response has subsequently been confirmed in many other patients. Sleeper's and my studies, as well as those of Cohen and Fierman showing depressed reactivity to thyroid substance, have been previously noted. In the latter study eight schizophrenic patients were treated for several months with desiccated thyroid in daily dosages of 15 to 18 grains each. The oxygen-consumption rate was increased only moderately—from 95 to 141 per cent of prediction; the pulse rate also reached a level of 110 but subsequently diminished. No ill effects from the large doses were observed; no excessive perspiration, tremor, or gastrointestinal disturbances were noted and the psychiatric clinical changes observed during the period were slight. Again to particularize, Freeman also studied the influence of dinitrophenol in 20 schizophrenic patients as compared with 20 controls. The response in cutaneous temperature, insensible perspiration rate, and oxygen-consumption rate was materially less in the patients. Another striking example of depressed reactivity among schizophrenics was shown by Freeman and Rodnick. These investigators imposed experimentally a rather severe stress situation by having the subjects breathe warm, moist oxygen, thus blocking the loss of heat from the lungs, the skin remaining exposed to room temperature and humidity. The response in blood pressure, heart rate, and respiratory volume was markedly less in schizophrenic patients than in normal subjects. The reaction to this stress situation was so alarming in more than a fourth of the normal controls that the experiment could not be completed, while the patients gave little sign of any discomfort. A part of the reactions of the control subjects were apparently due, however,

to subjective factors. The findings in the various studies of the equilibrium reactions above mentioned are also relevant. Our own findings and those of Fischer showing a depression of the specific dynamic action of protein of course fall in line with the other instances cited. In further support can be quoted the studies of Meco, who reported the reactions to various thermogenic agents, mainly foreign proteins and other chemical stimulants. He found the rise in temperature in the schizophrenic group to be far less than that in the control groups and the whole "thermic shock" pattern to be much diminished in the schizophrenics.

We have elsewhere pointed out (1940) that lack of responsivity to such a variety of stimulating agents might well be regarded as an indication of "schizophrenic withdrawal" at the somatic level. Whatever may be the significance of this relationship, the facts seem to warrant the conclusion that schizophrenics as a group are less than normally reactive to a variety of stimulating agents and are thus significantly handicapped in their adaptive capacities. The defects were noted both in levels reached and in promptitude of reactions.

Perhaps even more striking is the evidence that the schizophrenic patient is less than normally competent in *holding to the steady state* under ordinary conditions of existence. At one period during the Worcester activities attention was centered for two years in a study of variability of schizophrenics as compared with that of normal subjects. To set forth the findings in detail would go beyond the scope of this work. Only a few of the numerous observations will be cited.

One of the convenient ways of expressing variability is

by the "standard deviations of the means." The standard deviations of some of the functions in the patients as compared with those of control subjects were the following:

	Patients	Controls
Blood sugar	8.6	5.8
Blood nonprotein nitrogen	3.3	2.2
Blood creatine	0.12	0.06
Arterial oxygen	2.64	1.50
Venous oxygen	3.06	1.80
Arterial CO_2	4.3	1.2
Oxygen consumption	12.0	9.0
Systolic pressure	14.7	9.9
Diastolic pressure	12.4	8.7
Urine volume	1702	629

Numerous other examples could be cited to indicate that in the various metabolic functions, the average variability in schizophrenics ranges from about one and a half more to twice that in normal persons of similar ages. Only occasionally, as for example in the case of blood cholesterol, has such a difference failed to appear.

These are examples indicating a reduced ability of the patients to maintain metabolic steadiness under conditions in which such steadiness would be regarded as a mark of psychosomatic stability. In many studies that have been made by Shakow and others of our group the variability in psychological functions has proved to be about four times as high as in normal subjects.

As previously noted, we have observed two well-marked instances in which the ability to maintain differential levels

within the organism is also defective, that is, conditions in which the schizophrenic approaches a robot state. One of these is the oral-rectal temperature differential in the maintenance of which the normal is about twice as efficient as the schizophrenic subject. The other is in regard to the systolic-diastolic relationship, previously discussed, in which the correlation coefficient for the patients was .62 as compared with .43 for the controls.

These various evidences sum up, then, to the generalization that the schizophrenic psychosis is marked by numerous defects of adaptive efficiency, leading to inadequate and uneconomical organic responses to changing stimuli. This conception may serve to account for the general picture of total inefficiency in the face of an ability, previously remarked upon, under conditions of special stimulation to achieve passing normality in many of the individual functions. Obviously, in the human mechanism failure of integration might be due to functional imbalance arising in a variety of ways—including conditioning in the broadest sense of the term. As Jellinek and I have suggested before, it is perhaps in considerable measure the physiological clumsiness thus arising—rendering the subject intolerant to stress—that serves as the "decompensation factor" postulated in Section Two. It would seem that the prodigality of effort required for organic adaptation leaves the patient with but inadequate energy for successful adaptation in the social field.

SECTION FOUR

A BIOLOGICAL APPRAISAL OF SCHIZOPHRENIA

As EMPHASIZED in the first lecture of this series, man is a highly complex organism who is made up, as is all the rest of creation, of electric particles organized in a hierarchy of systems ranging in complexity from that of the atom to that of a society. The schizophrenic psychosis is marked primarily by a failure of integration of the individual—as the name itself implies. On a priori grounds the failure of integration might be looked for at any level from the lowest to the highest. The failures of integration at the higher levels might be due to those at the lower levels or might appear for the first time at any intermediate level from the lowest to the highest. In actuality, failures of integration in the psychosis can readily be demonstrated at several different emergent levels. Which defects are most fundamental in the long chain of causal sequences is as yet unknown. Neither can it be stated with any degree of assurance what are the relative potencies of the various etiological factors that can be postulated. In conclusion, then, I should like in retrospect again to view the organism in evolutionary perspective and recapitulate briefly the chief possibilities of causality that are evident at the various levels.

So far as I am aware no one has ever detected any difference in the *atomic constitution* of the schizophrenic subject and that of the normal man. The sodium in each seems to be the same sodium and the chlorine as well.

At the *molecular level,* however, several deviations have been found. For example, Walter Freeman has reported evidence of a relative deficiency of catalytic iron in the brains of schizophrenics. In view of the various evidences of deficient oxygen uptake in the psychosis this report seems especially pregnant and affords a lead that should be followed up extensively. And not only catalytic iron but the *catalytic systems* of the body throughout demand attention. In Section One emphasis was laid upon the great potential importance of the enzymic regulators of the body in determining levels and directions of chemical changes. Almost any symptomatology might be accounted for by defects in the enzyme systems. Adequately to particularize these possibilities would require a large volume. I wish especially to re-emphasize the possibility that adequate studies of the enzymes might disclose a genuine pathology for the psychosis. Many researches by many able investigators have failed to bring forth evidence that either the brain as a whole or any of its parts show on the microscopic slide any deviations from normality that are characteristic of the psychosis. It is quite possible, however, that abnormalities of the enzyme systems might exist and lead to profound functional defects without disclosing themselves in any way in tissues stained by conventional methods.

Another deviation at the molecular level that may be of fundamental importance in the psychosis is *vitamin deficiency* of the individual. Previous mention was made of our own incomplete studies, which point toward rather marked deficits in the tissue vitamin stores. These have been seen not only in our own patients after long residence in the hospital where adequacy of the dietaries might be ques-

tioned but also in patients freshly transferred from military hospitals where the dietaries have presumably been under adequate control. There is a suggestion in these findings that the fundamental metabolism may be at fault and either the food vitamins not adequately assimilated or abnormal demands for such vitamins not met. In view of the important role that is played by the vitamins in the enzyme systems of the body, disturbances of this sort are potentially capable of exerting profound influences at the metabolic and thus at all the higher levels.

Another possibility of etiological factors existing at the molecular level lies in the influence of the various *amino acids* on cell processes and functions. Thus certain of the amino acids are necessary to growth, others to maintenance, and still others to processes of maturation and differentiation. Not much seems to be known regarding these latter factors in man and the higher animals but in some of the lower organisms the maturing processes and those leading to cell specialization are determined by *d*-glutamic acid and *l*-proline. According to Hammett, proline has exhibited a promoting effect on cell specialization in plants and animals in all species in which it has been tried. Previous emphasis was laid upon the evidences of immaturity as an outstanding characteristic of schizophrenia. Adequately to cite the evidence would be to recapitulate the entire doctrine of "regression" in the psychosis. The only point to be underscored in this immediate connection is that the defective homeostasis of the schizophrenic might also prove to be only a special phase of immaturity. From this point of view the psychosis might be regarded, then, as a functional disintegration of the personality due to an inability to meet the

demands of maturity with the resources of the immature. It is within the realm of possibility that the immaturity and hence the psychosis itself might ultimately prove to be fundamentally due to an aberration of amino acid metabolism.

And finally, as another possibility of etiology operating at the molecular level may be mentioned the evidences of *endocrine deficiencies* in the psychosis. Earlier in the discussion attention was called to the apparent paradox that although well-marked endocrinopathies and psychosis are seldom seen in the same patient many schizophrenics show deviations from normality that are suggestive of less severe endocrine disorders. The possibility was discussed that the defect is not necessarily one of levels of hormone production but might be due to inadequate reactivity to the hormones. Furthermore, defects in either hormone production or reactivity to hormones might likewise be basic to the immaturity of the schizophrenic. There is available in the literature much evidence that thyroid deficiency can hold an organism at an immature stage of development for long periods, the prevention of metamorphosis of the tadpole being a case in point. It is likewise adequately demonstrated in lower forms—again the tadpole lending itself well to such determinations—that early deprivation of the pituitary prevents maturation. And finally the recent work of Berg showing the important influence of sex hormone in the maturation of an adult behavior pattern in puppies demands mention. This observation is supported by recent clinical work on the maturing effect of androgen in children —for example, in the treatment of enuresis. The possibility still remains open, then, that further studies of the endocrinology of maturation might throw important light on

the etiology of schizophrenia and might conceivably reveal the primary mechanism of its causation.

So much, then, for causal possibilities at the molecular level. Those discussed might equally well have been designated "disturbances at the *cellular level.*" Another low-level emergence that demands consideration is that of *heredity.* Of the long-standing debate regarding the relative potency of "nature and nurture" in the causation of schizophrenia little will be said. How much potency is to be ascribed to hereditary tainting still remains a moot point but the well-known findings in regard to the double incidence of schizophrenia in monozygotic twins as contrasted with that in dizygotic twins throws the burden of proof upon the "nurture" school. The conventional counterplea that identical twins lead greatly more similar lives than do the other variety smacks of oversophistication and largely begs the question by arousing the query, what but organic factors lead to such similarity of "reaction patterning"? The only specific citation to be made at this juncture is the work of my colleague, Kant, whose studies indicate that the outcome in cases of schizophrenia in which the "tainting" was manic-depressive psychosis was manyfold more favorable than that in which schizophrenia itself was the tainting factor. Heredity could operate, of course, at any level from the molecular to the social-behavioral.

Another emergence that demands special consideration in relation to schizophrenia is that of awareness or *consciousness.* Here we have to consider the remarkable parallelisms between the pattern of schizophrenia and the dream state. Whatever may be the explanation of dreaming, one characteristic feature of it seems to be the operation of men-

tal faculties at a level of reduced awareness. It is perhaps conceivable that such might be the sole important factor in dreams and in schizophrenia as well. A further suggestion that the very factor of awareness may be important in relation to the psychosis is the characteristic inefficiency of the schizophrenic in reality testing. In view of the intrinsic limitation, however, on our possibilities of understanding the nature of consciousness it would not seem to be profitable to pursue this speculation any further.

We are, however, on safer and more profitable ground, I think, when we come to the emergent, social awareness or *empathy*. Perhaps as fundamentally characteristic as anything about the psychosis is the failure of the subject either to achieve or to retain an adequate breadth and depth of empathy. Whatever else he may be, the schizophrenic is an egregious egoist. Much evidence is available that defective empathy may exert profound influences on the individual—weakening the ego and preventing evolution of the personality. One interpretation of the wolf-child phenomenology would ascribe to this factor sufficient potency to account for the characteristic defects in adaptation at the social level and even for the final deterioration of the unhalted schizophrenic process. The available facts serve fairly well to support a hypothesis that defective empathy is but a special aspect of immaturity: the egocentricity of young children is proverbial.

The foregoing are the over-all aspects of the disorder that impress this physiologist as most meaningful when viewed in a biological frame of reference. For what the concept is worth, then, I would propose that the schizophrenic psychosis represents an end result of a generalized failure of

adaptation that arises from defective evolution of the maturing processes. The failure is manifested in an intricate variety of ways but especially in defective homeostasis—somatic and psychic—defective empathy, and final over-all disintegration of the personality. The accessory symptomatology of the psychosis can be regarded as constituting secondary adaptations to the difficulties arising out of the primary defect.

An obvious alternative to the "immaturity" concept of schizophrenia is that the psychosis may be due to a specific pathology, a pathology that leads to the "decompensation" that was discussed in Section Two. The possibility has been mentioned that such a specific pathology might exist in abnormalities of one or more enzyme systems in the brain. It is, of course, quite possible that the postulated immaturity might have its fundamental origin in such a specific pathology. I shall eschew any amateur attempt at neurologizing in relation to this possibility but will merely quote from a letter, received from the late Stephen Walter Ranson shortly before his death, expressing a belief that the best place to seek a solution of the schizophrenia problem is in the hypothalamus. I shall cite in support only a single item from the relevant physiological literature, namely, the work from Ranson's Institute, previously mentioned—that of Brookhart and his collaborators—who showed that by so simple a means as hypothalamic puncture it was possible to eliminate sexual behavior, hence reproductive capacity, from guinea pigs of both sexes. What is especially pertinent is that the reproductive apparatus, endocrine and otherwise, remained, so far as microscopic study could determine,

entirely normal. It is quite possible that many of the disturbances of homeostasis that were discussed in Section Three might similarly be results merely of defects in the hypothalamic region. And, parenthetically, if one chooses to regard the psychosis as, in the last analysis, merely a functional disorder due to malconditioning in the broad sense, it is quite possible that it is via the hypothalamus that the disorder is chiefly mediated.

RESEARCH APPROACHES

The two chief functions of any theory are to give mental comfort to the theorizer and to point out possibilities for research. Perhaps in the current stage of our baffling ignorance neither the foregoing nor any other formulation can be really gratifying but it does offer, I think, some potentially profitable suggestions for investigative strategy. These may be brought together in final recapitulation.

First of all, if the psychosis represents primarily failure of maturity, then the fundamental problem becomes one of the biology of the maturing processes. That implies, among other things, that the next and most fundamental research in schizophrenia should be made not in the mental hospitals but in the biology laboratories. The work of the comparative biologists on maturation in the lower marine forms and the lower vertebrates should be extended to the higher mammalian forms. As previously indicated, such studies might be addressed to the influences of the various amino acids and especially glutamic acid and proline. More work

is needed also on the endocrine factors in maturation with regard both to early hormone production and the factors that determine reactivity to the hormones. In such studies when carried out at the patient-treatment level, periods of years rather than of days or weeks, as are commonly now employed, should be planned for.

On general principles the vitamins should be included in such studies both because of their potential influences on the metabolic processes and because of their possible influences upon the endocrine mechanisms. Searching attention should also be paid to the various enzyme systems of the body in relation to the maturation processes. I may again call attention to Henderson's emphasis on the far-reaching potentialities of selective direction among chemical complexes by enzyme factors.

Quite aside from the immaturity hypothesis, however, many more studies are needed of enzyme relationships not only in the brain but in the psychotic patient "as a whole." My former colleague, Looney, has frequently emphasized what he regards as a high probability that the deviations from normality at the somatic level that are so common in schizophrenia may mostly or entirely have their immediate origin in enzyme abnormality.

The special need for further investigations of the psychosis in its incipient stage and in children showing premonitory suggestions of the approaching psychosis would seem to be sufficiently obvious. Further to particularize such researches would be merely to list all of the methods that have been productively used or might be so used in investigations of the evolved psychosis.

It is possible that from researches of the order suggested there may emerge a solution of the schizophrenia problem that will guide us to success in both prevention and treatment. In the meanwhile, however, an exigent need remains for *palliative methods.*

First of all we should have an adequate appraisal of the value of the various therapeutic modalities that are now in vogue. Aside from a certain amount of inadequate evidence regarding the value of the shock therapies, we know practically nothing in a decently quantitative way as to the value of any. Indeed, we do not even know how good psychiatry is for psychotics. And while faith is an admirable human attribute it is not an adequate basis for therapy.

Among the patients whom I have seen leave our hospital in a state of remission I have been more impressed with the improvement of their empathic capacity than with any other changes. I would suggest as a valuable type of research a systematic study of techniques for the promotion of empathy rather than continuation of the haphazard exploitation of this factor that is in current vogue—and especially in recent studies of group psychotherapy. In such studies attention should center in the patient's system of conditionings and especially his affective conditioning. For instance, as Erickson and I have pointed out, one fairly potent source of motivation is the conditioning that the patient has derived from his school experiences. In many cases, more sophisticated use could be made of the patient's religious conditioning. It is my observation that psychotherapy as usually carried out is lacking in the "uplift" element that is successfully employed by religious technologists and by

the group called Alcoholics Anonymous. In view of the necessarily allegorical quality of all formulations the squeamishness of psychiatrists in the use of theological concepts and terminology seems inept. In so difficult a job as treating a schizophrenic any good tool should be used. In short, the individual should be addressed in the language that he best understands.

The simpler procedures that can be brought to bear in practical psychotherapy I have discussed at greater length in another connection "the psychological treatment of the menopause." It was emphasized that an additional aim of the therapist is enhancement of the self-esteem of the patient. In this endeavor another leaf can profitably be taken from the book of the clerical practitioner, namely, an emphasis on the potency of service as a means to the promotion of self-satisfaction (and of improved empathy). The patient should be led as much as possible to give of himself to others, rather than be compelled to be the recipient of pampering or pauperization.

I would suggest that the shock therapies be further studied to determine whether they amount to anything more than coercive empathy or whether they, like the current leucotomy method, amount to a selective type of partial decerebration. In any case, we should seek to learn as expeditiously and as explicitly as may be just how the benefit from such procedures is mediated.

And may a physiologist offer, as his final suggestion, increased attention to, and more adequate prosecution of, researches along the lines herein discussed rather than further pursuit of that will-o'-the-wisp, that semiprojective synthetic artefact, "the patient as a whole."

CONCLUSION

A series of three lectures presented but inadequate opportunity for the discussion of so intricate a subject as the schizophrenic psychosis, involving, as it does, every aspect of human nature—physical, mental, and social. All that could be attempted was a hilltop view in which the major features of the terrain could be contemplated.

In conclusion, may it again be emphasized that this disorder is, numerically, at least, the most important with which medicine—nay, society itself—is confronted. It is doubtful that any other mishap of existence causes in total so much human distress or entails so much unproductive expense. A study in Massachusetts some years ago showed that 10 cents of every State-tax dollar went for the care of schizophrenics; the proportion is now somewhat less but is still high. The stark fact remains that one fifth of all hospitalized patients in this country are victims of schizophrenia. But no other important disorder has remained for so long so inadequately studied.

Several reasons serve to account for this remarkable state of affairs. Despite the fact that more than half of all symptoms that bring patients to doctors are of psychogenic origin and that more than half of all hospitalized patients in this country are suffering from nervous and mental disorders, less than 2 per cent of medical graduates go into the field of psychiatry. The total number of psychiatrists in the entire United States is only about 3,500. Upon this small group devolves all the work of administration and of treatment in the mental hospitals, as well as the private care of

psychoneurotic patients who are able to command such attention.

Another factor is the unrealistic attitude of the medical faculties. Until recently the shabby neglect of psychiatry in medical curricula was a standing reproach in nearly all. Academic style in this respect is now in process of changing for the better but much distance remains still. Improvement in both the quantity and the content of courses is needed.

Another major difficulty has been graphically portrayed by Gregg. This is the historical setting in which psychiatry is still operating. "The three most powerful traditions or historical heritages of psychiatry," he has written, "are still, as they have been from time immemorial, the horror which mental disease inspires, the power and subtlety with which psychiatric symptoms influence human relations, and the tendency of man to think of spirit as not only separable but already separate from the body. These are the inherent, the inveterate, the inevitable handicaps of psychiatry."

Where lies the blame, then, that progress toward the solution of the schizophrenia problem has been so slow? It would be the height of ungraciousness to blame psychiatrists as a class for dilatoriousness in the face of the insurmountable difficulties with which they have been and are confronted. It is unfortunate, however, that psychiatrists have been so long inarticulate in making known their needs.

No easy resolution of the difficulty is possible. The next steps that should be taken, however, are obvious. The first is to get on with the very difficult task of enlightening the citizenry to the fact that schizophrenia is a disease and not

a sin or a disgrace. Were this fact adequately appreciated the social pressure for the solution of the problem would no doubt become irresistible. Another necessity is more adequate recruitment of workers in the field. Not only should a much larger *number* of medical students be attracted to the field of psychiatry but a larger *proportion* of the soundly trained, research-minded young physicians should be secured. The responsibility for these reforms rests primarily with the medical profession. A share of the responsibility rests also, however, with professional biologists, who might well exert their influence to induce a larger proportion of their most competent students to seek in the field of the mental illnesses opportunities for satisfying careers.

The final and heaviest responsibility lies, of course, upon society itself. The law of supply and demand is operative in this as in all other fields of human endeavor. Society will get approximately what it demands and is willing to pay for. Up to the present time only a fraction of a per cent of the total funds devoted to medical research has been assigned to this, the greatest problem of all. While money alone will not solve the problem, none of the actual solutions are possible without it.

The problem is before us. Many promising leads for further research are obvious. Every baby born this year must take his chance of spending the best years of his life as a schizophrenic in a mental hospital. Society owes him a better defense.

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THE THOMAS WILLIAM SALMON MEMORIAL LECTURES

The Salmon Lectures of the New York Academy of Medicine were established in 1931, as a memorial to Thomas William Salmon, M.D., and for the advancement of the objects to which his professional career had been wholly devoted.

Dr. Salmon died in 1927, at the age of 51, after a career of extraordinary service in psychiatric practice and education, and in the development of a world-wide movement for the better treatment and prevention of mental disorders, and for the promotion of mental health.

Following his death, a group of his many friends organized a committee for the purpose of establishing one or more memorials that might serve to preserve and pass on to future generations some of the spirit and purpose of his supremely noble and useful life. Five hundred and ninety-six subscriptions were received, three hundred and nineteen from physicians.

Of the amount thus obtained, $100,000 was, on January 10, 1931, given to the New York Academy of Medicine, as a fund to provide an income for the support of an annual series of lectures and for other projects for the advancement of psychiatry and mental hygiene. For the purpose of giving lasting quality to the lectures as a memorial to Dr. Salmon, and of extending their usefulness, it was stipulated that each series should be published in a bound volume of which this volume is one.

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