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THE CHEMICAL BASIS OF CLINICAL PSYCHIATRY

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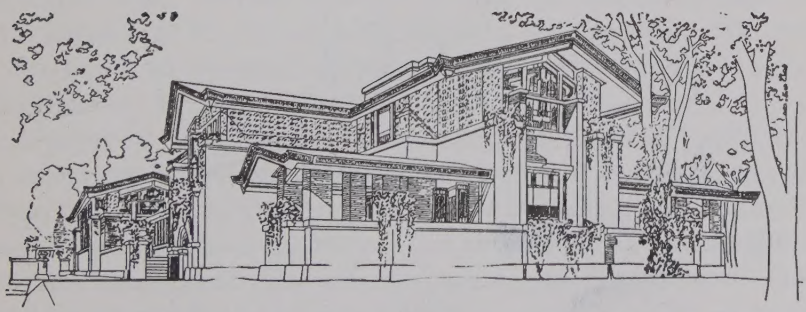
THE CHEMICAL BASIS OF CLINICAL PSYCHIATRY

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FOREWORD

Our Living Chemistry Series was conceived by Editor and Publisher to advance our newer knowledge of chemical medicine in the cause of clinical practice. The interdependence of chemistry and medicine is so great that physicians are turning to chemistry, and chemists to medicine in order to understand the underlying basis of life processes in health and disease. Once chemical truths, proofs and convictions become sound foundations for clinical phenomena, key hybrid investigators clarify the bewildering panorama of biochemical progress for application in everyday practice, stimulation of experimental research and extension of postgraduate instruction. Each of our monographs thus unravels the chemical mechanisms and clinical management of many diseases that have remained relatively static in the minds of medical men for Three Thousand Years. Our new Series is charged with the nisus elan of chemical wisdom, supreme in choice of international authors, optimal in standards of chemical scholarship, provocative in imagination for experimental research, comprehensive in discussions of scientific medicine, and authoritative in chemical perspectives of human disorders.

Dr. Hoffer and Dr. Osmond of Saskatchewan reveal clinical psychiatry in the light of chemical hypotheses. The inferences based on newer clinical and chemical knowledge, correlate established facts, integrate hybrid fields and perceive the oneness of mind and body. Mental disorders become the specific symbols in consciousness of the automatic changes in the organism. Anxiety is attributed to hormone imbalance; depression, to epinephrine insufficiency; model psychoses and psychedelic experiences, to psychotomimetic compounds; schizophrenia, to taraxein formation; all based on experimental studies of hormonal and drug metabolism, and its neural control through the hypothalamus, and indirectly other centers of the brain. The authors employ many of the newer techniques and especially the most common instrument of all reasoned experimental science—the balanced alternation of guiding hypothesis and experimental test.

I. Newton Kugelmass, M.D., Ph.D., Sc.D., Editor

INTRODUCTION

A cross section of psychiatric investigation reveals at least four current trends: namely (1) emphasis on the early recognition and care of persons with mental disorder; (2) the pharmacological methods of therapy that, apparently, have been successful enough to effect an increase in the discharge rate of patients from mental hospitals; (3) an accelerated swing of research interests into pharmacological, neurophysiological, and neurochemical fields with the concomitant attraction of more interested, adequately prepared, promising young scientists to these areas, and (4) the mobilization of more liberal financial support for psychiatric research by private foundations and federal and state sources.

Every successful search uncovers new unexplored areas and problems. However, there are two principal goals toward which a worker usually aims. One is to attempt the discovery of etiological factors, to thus allow a direct attack on prevention and cure of mental disorders. The other is to determine the capacity of the individual to withstand the mental stress inherent in the problems of living in society, and to find ways of reinforcing this capacity.

In pursuit of these general goals there are "frontiers" where the workers attempt the expansion of knowledge. Some of these are concerned with (1) hereditary and other constitutional factors, (2) neurophysiology, (3) neurochemistry and allied biochemistry, (4) experimental psychiatry, including the production of "model" psychoses by means of various substances, which may reveal clues to the origin, of some of the spontaneously developed symptom syndromes, and also including experimental therapy, and (5) attempts to place "social psychiatry" on a sound basis. Obviously some of these studies are devoted to the fundamental problems of behavior functions in terms of "structure-function" such as those in chemistry and physiology, while others focus on forms of social structure most likely to yield information on ways and means to improve mental quality and strength and to reduce, if possible, the

incidence of addictions, juvenile delinquency and other socio-pathological phenomena.

The fact that research in mental health has to recognize and deal with a combination of organismal pathology, constitutional pathology, and the pathology produced by social forces, as well, emphasizes a complexity of considerable magnitude which renders it the number one health problem of the world, and in which the only hope for solution lies in continuous research.

One of the most basic problems is the nature of the chemical composition of the organ of mind, the brain. In what characteristics do the brains of the psychotic compare among the mental reaction types and with normal persons? The natural objective of chemistry of the nervous system is, in association with neurophysiology and pathology, to understand the phenomena of structure of nervous tissue, and its behavior in the integration of the cerebral mechanisms and the "master" integration called the "mind," as well as the mental disorders which have been, at least, partially differentiated into types, by clinical experience.

Unfortunately in the past, active investigative interest in chemistry of the brain has lagged far behind that devoted to anatomy, physiology and pathology of its parts, and certainly far behind chemical investigation and knowledge of the other organs and organ systems of the body.

The main task is to attempt, by objective inquiry, to discover the properties of the living mechanisms that determine and execute behavior including that which is modified by both intelligence and the emotions. The laws of chemical action and those of psychological phenomena are not, as yet, directly comparable for no common units of measurement have been discovered. But this is obviously a challenge to those who have been, and still are pioneering in this field. Highly trained specialists must carry out these studies, and several skilled biochemists are now interested in this long neglected aspect of their profession. New methods of greater precision are being devised to detect the concentrations and activity of the numerous substances in the principal anatomic divisions of the brain, and in those bodily organs, including the blood, that support the brain.

Here the investigators in the light of their discoveries are faced with the decision whether a phenomenon is a "cause" (a) in terms of heredity; (b) is due to a metabolic upset in organ function, or is (c) the result of some outside social force that has altered the emotional situation. Is one dealing mainly with a predisposition product, a pathogenic one, or a pathoplastic one? Such questions constantly confront and complicate the interpretation of results.

The authors of this book have presented the historical development of scientific thinking, approaches and methods of investigation in this field, and discuss and critically evaluate the results so far obtained. They analyze, particularly the hypotheses which have been offered to account for anxiety, depression, schizophrenia, and other various disorders of mood. They review modern research methods, findings, and their possible significance, including their own extensive researches. They and their co-workers are active participants in the search for the chemical basis of psychiatric disorders, including the experimental psychoses, and are therefore well qualified to present this informative text bringing the subject, well documented, up to date.

NOLAN D. C. LEWIS, M.D.
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CONTENTS

Page

Foreword by I. Newton Kugelmass v

Introduction vii

Chapter

1. Research, The Scientific Approach and Methodology . 3
   - Introduction 3
   - The Good Hypothesis 7
   - Science and Psychiatry 9
   - What We Plan to Do 15
2. The Historical Background 17
3. Mood and Its Disorders 29
   - Introduction 29
4. Relationship of Mood to Catechol Amines 31
   - Psychological 32
   - Physiological 32
   - Biochemistry 33
   - Role of Isopropylnorepinephrine 37
   - Relationship of Mood to Indoles 38
   - Adrenochrome 39
   - Adrenolutin 42
   - Adrenochrome Metabolism and Tension 46
   - 5,6-Dihydroxy-N-Methylindole 48
     - Reactions of Normal Individuals (Not Patients) . . . 50
       - Good Response 50
       - No Response 51
     - Reactions of Depressed Subjects 51
     - Response of Schizophrenic Patients 59
   - 5,6-Diacetoxy-N-Isopropylindole (DIN) 60
     - Reaction A (One-third of Subjects) 60
     - Reaction B (One-third of Subjects) 62
     - Reaction C 63

Synthesis 63
A. Excess Production of Epinephrine 64
B. Normal Production of Epinephrine 66
C. Insufficient Epinephrine 67
5. Chemical Treatment of Depression and Anxiety . . . 75
Anergic Depressions 76
A. Epinephrine-like Compounds 76
1. The Sympathomimetic Amines 76
2. The Piperidines 76
3. Tofranil 76
4. Benzoquinolizines 77
B. Substances Which Inhibit Enzymes Which Act on Epinephrine 77
1. Marsilid 77
2. Cocaine 82
Mode of Action 84
C. Acetylcholine-like Substances 84
1. Arecoline 84
2. Deaner 85
D. Inhibitors of Acetycholine Esterase 86
Anxiety Depressions 86
A. Indoles 86
1. Reserpine 87
2. Indolylethylpyridines 91
B. Substances Which Reduce Reactivity of Receptors to Epinephrine 91
C. Substances Which Decrease Epinephrine Production 92
6. The Model 97
Objection One 98
Objection Two 100
Objection Three 101
Psychotomimesis 104
Psychedelics 106
7. Psychotomimetics Similar in Structure to Epinephrine . 111
A. Mescaline 111

Mode of Action 112
1. Direct 112
Electroencephalogram 113
2. Indirect Action 114
B. Mescaline Analogues 115
C. Adrenergic Compounds 116
D. Substances Which May Be Derived from Dihydroxy Phenylalanine 117
8. Psychotomimetics Which Interfere With the Function of Acetylcholine 122
A. Acetylcholine Esterase Inhibitors 124
B. Acetylcholine Antagonists 124
Atropine 125
Benactyzine 125
Piperidyl Benzilates 126
9. Psychotomimetics Related to Adrenochrome 128
A. Ergot Psychotomimetics 129
Mode of Action 130
1. Direct Action 130
2. Indirect Action 135
B. Other Psychotomimetics 141
1. Psilocybin 141
2. Dimethyl and Diethyl Tryptamine 141
3. Bufotenine 141
4. Harmine 142
5. Ibogaine 143
10. Adrenochrome and Adrenolutin 147
A. Synthesis 147
B. Properties of Adrenochrome and Adrenolutin . . . 148
1. Chemical Properties 149
2. Biochemical Properties 149
a. Carbohydrate Metabolism 149
b. Adrenochrome and Brain Inhibitor Factor . 150
c. Adrenochrome and Amino Acids 151
d. Adrenochrome and Iron Metabolism . . . 151

e. Adrenochrome and Melanin Pigmentation . 152
f. Adrenochrome and Oxygen Toxicity . . . 152
g. Adrenochrome and Allergies 153
3. Neurophysiological Properties 154
a. Effect on Electroencephalogram 154
b. Hypothermia 157
c. Adrenochrome and Diuresis 158
C. Adrenochrome, A Natural Metabolite of Epinephrine . 159
1. Assay Method 159
2. Does the Body Produce Sufficient Epinephrine for the Adrenochrome? 160
a. Evidence from Concentration of Epinephrine in Plasma 160
b. Evidence from Injection Intravenously of Epinephrine 161
c. Evidence of Rates of Secretion from Adrenal Glands 163
d. Evidence from Quantity of Epinephrine in Urine 164
3. Is Adrenochrome Present in the Body? 165
4. Oxidation of Epinephrine to Adrenochrome . . 166
5. Epinephrine Oxidase 167
6. Metabolism of Adrenochrome 168
D. Psychological Properties of Adrenochrome and Adrenolutin 169
a. Animal Response to Adrenochrome . . . 170
b. Psychological Activity of Adrenochrome in Humans 173
c. Potentiation of Adrenochrome Experience . 179
11. The Taraxein Hypothesis (Substances Related to Epinephrine Enzymes) 192
Extraction of Taraxein 192
12. How Do Psychotomimetics Work? 199

13. The Adrenochrome Model and Schizophrenia 203
A. Biochemical Differentiation of Schizophrenic Fluids from Non-schizophrenic Fluids 204
1. Introduction 204
2. Biological Assays 205
3. Adrenochrome Levels and Schizophrenia . . . 208
4. Adrenochrome Tolerance 209
5. Conversion of Adrenochrome to Adrenolutin . . 210
6. Discussion 211
7. Conclusion 212
B. Similarity of the Adrenochrome Induced Experience and Schizophrenia 212
C. The Similarity Between Experimental Psychoses and Schizophrenia 213
1. Introduction 213
2. Psychotomimetic Antagonists and Schizophrenic Therapeutic Agents 214
3. Psychotomimetic Potentiators 215
4. Autonomic Changes 215
5. Biochemical Changes 216
6. Conclusion 218
D. Treatment of Schizophrenia 218
1. Reduction in Production of Adrenaline 218
2. Decreasing Production in Adrenochrome Ascorbic Acid 219
3. Neutralizing Adrenolutin 220
4. Destroying Adrenochrome 223
E. Some Physiological Correlates of Schizophrenia Which Follows from the Adrenochrome Hypothesis . . 225
1. Antihistaminic 225
2. Formation of Pigments 228
3. Antithyroid 231
4. Diuresis 231
5. Indole Excretion 231
6. Effect on GABA 232

7. Oxidation of Ascorbic Acid 232
8. Phosphorylation 232
9. Relation to Iron and Copper 235
10. Diurnal Rhythm 237
11. Relationship of Schizophrenia to Diabetes Mellitus 238
14. The Way Ahead 249
Index 257

THE CHEMICAL BASIS OF CLINICAL PSYCHIATRY

Chapter 1

RESEARCH, THE SCIENTIFIC APPROACH AND METHODOLOGY

INTRODUCTION

It may seem presumptuous to start so small a book with discussions of science and the way it works. But research generally and psychiatric research in particular still suffers from not making full use of that great instrument which has been Europe's unique contribution to mankind, the scientific approach. Indeed, men may one day hold that this and perhaps this alone justifies the depredations which Europeans have committed.

Both in Europe and the United States there are now suggestions that while science which is "deductive, hypothetical and selective by way of falsification" Popper (1957), has been brilliantly successful in "simple" matters such as physics and chemistry, some great change is needed for the "more complicated human sciences." If this were so the first task of those who like ourselves are attempting to relate a "simple" science such as biochemistry to a "more complicated" one such as psychiatry, would be to explore and describe this new method.

Several disciplines converge in psychiatric research and it is unlikely that there will be much success in dealing with its great illnesses unless they work together cooperatively. It is perhaps this which has made psychiatrists and their colleagues increasingly preoccupied with methodology. Much less attention seems to have been given to the way in which scientific discoveries are actually made. Indeed the distinction between these discoveries, which we shall call the scientific approach, and the specialized use of logical techniques known as scientific methodology is rarely discussed in psychiatry or indeed in other fields of enquiry.

Herbert Dingle (1952) defines methodology in these terms, "This is a discipline conducted for the most part by logicians unac-

quainted with the practice of science and it consists mainly of a set of principles by which accepted conclusions can be reached by those who already know them! When we compare these principles with the steps by which discoveries were actually made we find scarcely a single instance in which there is the slightest resemblance. If experience is to be any guide to us at all—and what scientist can think otherwise?—we must conclude there is only one scientific method: produce a genius and let him do what he likes. We are not yet able to practice this method and the best we can do is learn how to spot the natural genius at as early an age as possible and protect it, by fiery dragons if need be, from the god of planning. I am not arguing that scientific methodology is a useless subject . . . but I would plead for it to be given its proper function which is that of assessing the significance of scientific knowledge for philosophy as a whole and I would argue that it be given a more appropriate title which does not suggest that it bears any relation to the processes by which scientific knowledge is acquired."

What Dingle is asking is that methodology should remain the handmaiden of scientific discovery and should not attempt to become its taskmistress. Researchers, especially those who have made some of the greatest discoveries, have recognized this. Among the earliest comments on this topic are those of Galileo, Cohen (1957), when he was engaged in a battle with the Aristotelian logicians of his day, he pointed out, "It may be possible that an artist may be excellent in making organs, but unlearned in playing on them. Thus he might be a great logician, but inexpert in making use of logic; like as we have many that theoretically understand the whole art of poetry, and yet are unfortunate in composing but mere four verses, others enjoy all the precepts of Cinci, and yet know not how to paint a stoole. The playing on the organs is not taught by them who know how to make organs, but by them who know how to play them."

Dingle shows that the scientific and logical viewpoints are different and should not be confused, "From a purely logical point of view scientific cosmology would appear to have no justification, to be a gigantic impertinence. It is saved from this by the frank recognition by scientists of what it is and what its limitations are.

The work of three centuries has shown that the scientific approach is on unassailable grounds when it declares itself to be the best prescription yet devised for obtaining knowledge of the relations between phenomena. Whether or not its generalizations have any right to be regarded as the *truth,* they lead to further knowledge—which so far as we can see, would be quite unobtainable otherwise. But they do this only on the condition that we abandon them the moment we see that they cease to hold. They originate in phenomena and they are at the mercy of phenomena. The Aristotelian general principles on the other hand were conceived a priori, independently of phenomena, and phenomena were distorted at liberty so as to exemplify them. The problem was to 'save the phenomena.' The basic principles themselves could not be threatened; it was the phenomena that stood in need of salvation. . . . We are prepared to revise our principles to fit observation because man's whole experience in seeking knowledge has taught us that nature is far more likely to follow in the large the laws we observe her to follow in the small than to behave according to our intuitive ideas of decorum."

The traveller who is expert in finding his way by means of maps will not necessarily survive when exploring unmapped country. It is a mistake to let researchers believe that they can depend on the "maps" of the methodologists, when their task is to go where there are no maps. There is a danger that those giving monies for research may become so preoccupied with the need for "sound research design" that they forget there is a world of difference between demonstrating what is known already and exploring the unknown.

What then is science and how does it commonly proceed? Dingle's definition has rarely been bettered, "By its very nature science consists of the rational ordering of the facts of experience." It seems that this rational ordering can be seen as a series of simple steps, although we do not suggest that such steps are easily made, indeed a very small step forward in science may take half a lifetime. The first step, as Claude Bernard, Green (1957), long ago insisted, is "the idea." He writes—"Facts are necessary materials, but their working up by experimental reasoning, i.e., by theory, is what estab-

lishes and really builds up science. Ideas given form by facts embodies science. A scientific hypothesis is merely a scientific idea controlled by experiment. Reasoning merely gives a form to our ideas so that everything, first and last, leads back to an idea. The idea is what establishes, as we shall see the starting point, or the primum movens of all scientific reasoning, and is also the goal in the mind's aspiration towards the unknown."

The way in which ideas develop is mysterious. Hanson (1958) notes, "the paradigm observer is not the man who sees and reports what all normal observers see and report, but the man who sees in familiar objects what no one else has seen before." Galileo spent years brooding over his own ideas and those of other astronomers of his day before he formulated his great hypothesis. Newton, Andrade (1954), seems to have developed some of his greatest ideas in that extraordinary eighteen months in about 1665 when in solitude on the family farm at Woolsthorpe he revolutionized mathematics, celestial mechanics and physical optics. He himself described this period later in these words: "All this was in the two plague years of 1665 and 1666 for in those days I was in the prime of my age for invention and minded mathematics and philosophy (science) more than at any time since." During that fateful period he lacked any discussion of mathematics and science with learned men, neither did he correspond with them. When asked much later how he made his discoveries, he said, "By always thinking unto them." On another occasion he was a bit more expansive, "I keep the subject constantly before me and wait until the first dawnings open little by little into the full light." Darwin, Eiseley (1958), gestated his theory of evolution while in retreat with his family at Down, seeing very few scientists but corresponding with those whom he wished to know. Wallace, Eiseley (1958), who reached the same conclusion by a different route seems to have recognized the central ideas of the theory in a brief period while gravely ill with fever in the far East. However, he too had devoted years of work in the field of biology. Kekule's, in McKellar (1957), discovery of the carbon ring seems to have been much influenced by a vivid dream. Bragg quoted by Hanson gives an account of a modern crystallographer wrestling with a problem, "The analyst has before

him the separate bits of jigsaw puzzle and he has to fit them together . . . In making guesses at possible arrangements he draws on a wealth of experience . . . I can well remember the intense concentration. One lived with the structure. I am tempted to say that one ate, slept and shaved with it. Finally after six months or longer, and if one were fortunate, everything suddenly clicked into place . . . The successful analysis of one structure often leads to a quite new understanding of a whole range of forms . . . It is all the more important that really key structures should be chosen for examination as likely ventures in which it is justifiable to sink one's capital."

It is notable that these great masters of science tell us very little of discussion with others and very much about deep concentration and persistent contemplation of the problem on which they have focused their attention. Popper is a little testy about this,, "But this intuition is his private affair. Science is interested only in the hypothesis which his intuitions may have inspired, and then only if these are rich in consequences and if they can be properly tested." We feel that this dodges this issue but we are still very ignorant of these wellsprings from which we draw ideas of great consequence. We know, however, that without such ideas there would be no science. Perhaps an idea resembles the sculptor's vision of his completed statue, which must still be hewn from the hard rock of obdurate facts. Yet the sculptor often "sees" the finished statue in the still lumpish stone, and indeed it is only this that holds him to his heavy task. An hypothesis is the means by which an idea is made suitable for testing. Newton once said, "hypothesis non fingo" meaning that he did not indulge in speculation only. Yet how can one distinguish a good hypothesis from a mere speculation or a bald assertion? We believe that there are certain features which allow it to be recognized.

THE GOOD HYPOTHESIS

What hypotheses should commend themselves to the scientist? Claude Bernard gives excellent advice: "We must be bold and free in setting forth our ideas. We must follow our feeling and must on no account linger too long in the childish fear of contradicting

theories. If we are thoroughly steeped in the experimental method we have nothing to fear; for so long as the idea is correct we go on developing it; when it is wrong experimentation is there to set it right. We must be able then to attack questions even at the risk of going wrong. We do science a better service, as has been said, by mistakes than by confusion, which means that we must fearlessly push our ideas to their full development, provided that we regulate them and are always prepared to judge them by experiment." This and our next quotation echo the sonorous phrase from Bacon's essay "Of Despatch" which should be a slogan for the scientist reminding him always of his right, indeed his duty to risk being wrong, "for that negative, though it be wholly rejected, is more pregnant of direction than an indefinite, as ashes are more generative than dust." Pierce, in Buchler (1955), too is explicit on this point and since we have been frequently reproved for the "rashness" of our speculations by those who should know better, we believe, perhaps wrongly, that many medical men and others are unaware that science can only advance by calculated risks. Pierce writes, "A hypothesis is something that looks as if it might be true and were true and which is capable of verification or refutation by comparison with facts. The best hypothesis is one that can be most readily refuted if it is false. This far outweighs the trifling merit of being likely. For after all, what is a likely hypothesis. It is one which falls in with our preconceived ideas but these may be wrong. Their errors are just what the scientific man is gunning for more particularly. But if a hypothesis can quickly and easily be cleared away so as to go toward leaving the field free for the main struggle, it is an immense advantage."

In recent years there has been much emphasis on refined statistical techniques, remarkable instruments and other ways of reducing or eliminating the bias of the investigator. But without a good hypothesis experimental design however ingenious is useless and may prove misleading because it diverts attention from the source of failure, lack of ideas. We suggest the following criteria for such a hypothesis:

First: It must account both inclusively and economically for what is known already: an hypothesis which fails to do this would

be automatically disqualified. Second: It must do this better than any previous hypothesis. Third: It must be testable in a way which will readily lead to its refutation should it be false, using methods available to the science under scrutiny. An hypothesis which depends for testing upon methods or principles not yet developed, while not absolutely inadmissible, would be less useful than one which can be tested immediately.

Is there any reason why psychiatry should require anything different from the rest of science?

SCIENCE AND PSYCHIATRY

Psychiatry was one of the first specialties to emerge and be clearly differentiated after medicine and surgery. By the mid-nineteenth century its learned journals were published in Europe and on both sides of the Atlantic. At that time it was well advanced and had many able and some eminent practitioners. Alienists as they were often called had played a notable part in reforming the care of the mentally ill and had developed methods of treatment which compare favorably with those existing today. Psychiatry had little to fear in comparison with the surgery and medicine of that age. By the end of the 19th century Kraepelin had made a classification of mental disease which has stood unchanged except in detail for over sixty years. Yet the great revolution, that had been sweeping through medicine and which had driven a very conservative profession to exertions which had never been seen before, had less impact on psychiatry than elsewhere. There have been various explanations for this. In his famous address to the American Psychiatric Association, S. Weir Mitchell, in 1892, suggested that the trouble was due to the segregation of psychiatrists in mental hospitals. He urged them to leave and some apparently did so. The conditions of the mentally ill do not seem to have been bettered by Weir Mitchell's advice. Perhaps the ailment lay deeper than he supposed. Psychiatry seems to have been afflicted with two different sorts of difficulties whose effects one hopes a historian will one day sort out, for they are still with us at least in some degree. The first due to influences outside psychiatry may have been unavoidable.

When Claude Bernard was dying in 1878 he and many others would have predicted that the great medical advances of the next generation or two would come through the flourishing science of physiology. But in fact the next half century or more was dominated by bacteriology which was unknown before the 1860's. This was due to Louis Pasteur whose genius founded a new branch of science which attracted the finest medical minds of the day. It was applied bacteriology which allowed Lister to expand the range of surgery so much more than had been possible with the use of anesthesia alone. Anesthesia had only reduced the terrors of operation, it had not reduced the danger of sepsis at all. Syphilis apart, bacteriology had had only a small impact upon psychiatry. Physiology and its associated sciences, such as pharmacology which might have had a much larger bearing developed less quickly. The social sciences advanced very slowly and they too have much influence in psychiatry.

The second sort of difficulties arose from influence inside psychiatry which have many parallels in the history of medicine. Freud's researches in the 1880's laid the foundation of psychoanalysis. It was not until World War I had shattered the crust of custom which had formed during the comparatively peaceful 19th century that psychoanalysis had much effect upon psychiatry. A little before the start of the 20th century Adolph Meyer began to develop his psychobiological theories, whose chief distinction is that they advocate a holistic approach to psychiatry. For many years these two systems were more or less hostile, thus emulating the tradition of those 18th cenutry medical systems which split the profession amid vigorous vituperation. However, in the United States from about the mid-1930's they more or less fused to become what is now called dynamic psychiatry. This combination has been unspectacular in research and it would have been surprising had it been otherwise.

The Freudian system has never been subjected to scientific enquiry. At the start those who disagreed with the founder were usually expelled from or encouraged to leave the movement. In more recent years many of the older practitioners had or have a passionate loyalty to Freud's doctrines which have been interpreted

as immutable principles rather than as hypotheses to be tested and discarded if faulty. (It would be unfair if we did not add that Freud himself, although not practicing what he preached, constantly emphasized the tentative nature of psychoanalysis.) One suspects, perhaps unworthily, that as in many metaphysical systems its supporters are more concerned with "saving the principles of psychoanalysis" than in "saving the phenomena." Psychoanalysts have never to our knowledge described the crucial experiment which would allow their hypothesis to be refuted, and until they do this their system must be open to the criticism which Popper has put so well, "But this is merely one of the many instances of metaphysical theories seemingly confirmed by facts—facts which examined more closely, turn out to be selected in the light of the many theories they are supposed to test." Psychoanalysts have so far devoted laudable energy to refining their theory but almost no effort has been made to test it. This may be accounted for at least in part by the fact that many clinicians seem unaware that what they are discussing are hypotheses or theories—many mistake these theoretical models for concrete things. The ego, the id, the superego, resistance, projection, introjection, complexes, etc., are models constructed to explain certain sorts of experience and observed behavior. Yet these are regularly discussed as if they were things. The newer derivatives of psychoanalysis such as the existentialist and phenomenologist psychiatrists carry this deplorable tendency further and are becoming even more obscure than their predecessors.

The Meyerian system claimed that without a holistic approach it was impossible to explore an organism so complicated as man in his social setting. If such a claim is to be useful it should suggest experiments which would demonstrate the superiority of the holistic to the more atomistic way of science. In sixty years no such experiments have been forthcoming. Furthermore so far holism has had no successes in any branch of science, and until this happens it would seem rather rash to introduce it into psychiatry.

Psychiatric research has for the main part been uninfluenced by either Freud or Meyer and possibly in opposition to them has used "a down to earth practical approach." This is empiricism and

has to be criticized quite as severely though quite differently from the metaphysical and holistic systems. The astounding rise of scientific technology gives the empiricist opportunity to become lost in mazes of correlations. Believing that it is possible to use the inductive method he attempts to subdue them with electronic instruments, failing to recognize that these make an already hopeless task even more hopeless. A vivid description of a modern and distinguished exponent of the empirical approach illustrates this without distorting it. He writes, "It has been mentioned from time to time that we need more integration, more thought behind research. I believe that what we need most of all is more facts and *I believe that when we have enough facts the thoughts will take care of themselves.* That is not a thing which we should primarily worry about. The ignorance about the fundamental problems in psychiatry is so great that there is enough to do for all types of research workers and though at present the facts may seem like a jigsaw puzzle, when we have enough of them they will fall into place" (Tanner, 1953). Surely this is idolatry. This able man could not have chosen a metaphor which illustrates the weakness of what he advocates better. Indefinite multiplication of the pieces of a jigsaw puzzle does not help in solving it but simply increases the size of the jumbled heap. There is something nightmarish in the thought of the scientist ceaselessly gathering facts and hoping that they are falling into place when in reality they are begetting confusion. Gjessing's (1939) fascinating and scholarly observations on recurrent catatonia show the inherent limitations of even the most admirable and painstaking work in this style. In our view it is self defeating. This does not mean that we should not honor those who have attempted so huge a task. But long ago Bernard emphasized the difficulties that must arise in empirical research "by simply noting facts we can never succeed in establishing science. Pile up facts or observations as we may, we shall be none the wiser. To learn we must necessarily reason about what we have observed, compare the facts and judge them by other facts used as controls . . . a fact is nothing in itself, it has value only in the idea connected with it or through the proof which it supplies. We have said elsewhere that when one calls a fact a new discovery the fact itself

is not the discovery but rather the new idea derived from it; in the same way when a fact proves anything it does not give the proof but only the rational relationship which it establishes between the phenomenon and its cause. This relationship is the scientific truth. . . ."

It would be improper here to omit certain exceptions to this general rule, which are as notable as they are rare—oases in a great desert. The work of Franz Kallman (1953) and Eliot Slater (1953) have forced even the most rabid environmentalists to give some pause. Their studies of identical twins will play a part in medicine far outside psychiatry. William Sheldon's (1954) extremely sophisticated development of the German school of constitutional medicine has found much more favor among physicians than psychiatrists, many of whom seem to have condemned it without reading it. The subtlety of Sheldon's schemata and their many applications both inside and outside psychiatry have still to be developed. Sherwood's (1957) bold use of a remarkable technique to develop hypotheses which still need far more exploration indicates how much the scientific approach can do in far from favorable circumstances. These and other studies which we shall discuss later suggest that psychiatry is no less suitable to the scientific approach than any other aspect of medicine.

Unfortunately there is much psychiatric research which would not meet Claude Bernard's rigorous standards. Psychiatrists seem to use either speculative systems which are hard to test or empirical systems which are devoid of hypotheses. One wonders why this should be so. Possibly science is still foreign to medicine as a whole. Medicine is a profession in which open acknowledgement of fault or ignorance has been unrewarded from the earliest times. Few patients are benefitted by a doctor's candor regarding his mistakes. Yet science depends upon a calculated determination to risk being wrong. The system builder and the empiricist alike need never be wrong, by their caution they ensure against ever being right. That is the invisible penalty.

At present there is much talk about "multi-level-cross disciplinary research." It seems that some of our colleagues believe that this will either provide new ideas or may be a substitute for develop-

ing new hypotheses. While one would never discourage those with different scientific skills from meeting and talking together, particularly when they are engaged in a similar field of enquiry, we would like some evidence that this has in fact made contributions to knowledge which could not be made in some other way. We believe that cooperative action between different disciplines only becomes fertile when there is already an hypothesis upon which their attention and interest can be focused. We are not convinced that the "multi-disciplinary approach" has yet produced an idea which has developed into a useful hypothesis. However much the holistic goal is pursued more disciplines will always be excluded from any particular research than can be included in it. It seems pertinent to ask how the researchers will decide who should be excluded. Every empiricist, however determined he may be, always has an implied hypothesis, for without this he would not be able to select data.

Far removed from such grandiose conceptions come numerous notions or hunches which may be biological, psychological or social in origin. These range from statements claiming that psychoses arise from "the strains of modern life" or are "really only suppressed fear" to those who put forward equally simple biochemical ideas of which the serotonin suggestion is an example. This sort of notion makes no attempt to account for many aspects of mental illnesses which are disregarded completely. For instance, the serotonin idea, when examined as a hypothesis, i.e., as a question or proposition to be answered either yes or no, seems to amount to little more than a statement that serotonin plays some part in brain function. This has been refined to include the possibility that too much or too little serotonin in some unspecified parts of the brain might result in psychosocial disturbances resembling those found in schizophrenia or other psychoses. We do not suggest that such a proposition is necessarily untrue, but we have never read an article by those who subscribe to this notion which indicated that they realized that they were making an hypothesis to account for a great and complicated illness. They were therefore obliged to show how the biochemical changes which they envisage might produce the signs and symptoms of this great illness, and account for at least a little

of what is already known about it. Biochemists may be excused for such crudities—it is a pity that psychiatrists have encouraged them in this.

WHAT WE PLAN TO DO

In the pages that follow we plan to review some of the hypotheses which are being or have been used to account for anxiety, depression, the characteristic picture of schizophrenia and the model psychoses. We shall discuss the evidence of these hypotheses and the relationship between chemical, psychological and social changes insofar as these are known, or as the authors indicate such a relationship. We shall then discuss the way in which work of this sort might develop. It should be understood that while an hypothesis may be simple, elegant and even useful, it does not become even a candidate for recognition as a theory until it has been tested with extreme rigor. We shall, for the present at least, assume that while the scientific approach may have disadvantages, it is better than any other that we have.

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Chapter 2

THE HISTORICAL BACKGROUND

History is only admissible in a small work if it helps to avoid mistakes that have been made already. Bismarck once said, "Fools say they learn by experience. I prefer to learn by other people's experience." History is other people's experience. We are seldom grateful to our predecessors for their errors which allow us to act differently from them. Yet such is the relative nature of scientific truth that in the long run even the greatest scientist has no legacy for posterity more precious than his mistakes.

Thudichum (1884), the father of brain chemistry, would have been surprised by the way in which opinion has veered since he wrote his great book. There he states, "Many forms of insanity are unquestionably external manifestations of the effects upon the brain substance of poisons fermented within the body. . . . These poisons we shall, I have no doubt, be able to isolate after we know the normal chemistry to its uttermost detail. And then will come in their turn the crowning discoveries to which our efforts must ultimately be directed, the discovery of the antidotes to poisons and to the fermenting causes and processes which produce them."

When Thudichum published, Sigmund Freud (Jones, 1953), a young neurologist, was experimenting with the effects of cocaine on the psychology of mood. It was a misfortune that Freud's only excursion into psychopharmacology proved disastrous and this may well have made him inclined to shy away from this subject in the future. At this same time he was working with an older colleague, Joseph Bruer, using hypnosis in hysterical patients. Years later this work with Bruer culminated in psychoanalysis, part therapy, part science, part cult, which has developed a theory of psychotic illnesses (insanity) almost completely independent of brain chemistry. Yet Thudichum and the age of clinical exuberance of which he was a brilliant part, had left an indelible mark on psychiatry, for

those three great contemporaries, Kraepelin, Freud and Bleuler* were all at one time or another to a greater or lesser degree, believers in the chemical basis of dementia praecox which was later renamed by Bleuler "schizophrenia." According to Percival Bailey (1956), Freud may have been the most enthusiastic of the trio, at least from the content of his postcard to Schilder in the early 1920's, when he feared that chemistry might soon make dementia praecox as rare as the Red Indian, one might infer this. The exaggerated hopes for brain chemistry which occurred towards the end of the 19th century were followed by exaggerated disappointment and disillusion. Thudichum's prediction has not been fulfilled and so far the chemistry of the brain has given us only the slenderest clues towards "the poisons and fermenting processes" and none at all to developing antidotes for them. The greatest advances in psychiatry have come about in quite different ways.

It was the development of the Wasserman Test (immunology) and the discovery of the spirochaeta pallida (bacteriology) which jointly paved the way for Ehrlich's extraordinary foray into chemotherapy culminating in the discovery of Salvarsan-606. While the recognition and determination of those accessory food factors which we now call vitamins has lead to the elimination of pellagra and its associated psychosis. The use of bromides, barbiturates, anticonvulsants, insulin, ECT, CO_2 therapy, the new tranquilizers and energisers, while all emphasizing the importance of the chemistry of the mind, owe nothing to Thudichum's prescription. Indeed the failure of that prescription may be a lesson to those of us who attempt to apply a variety of sciences to medicine. So far almost exactly the reverse has proved far more profitable. Medical research is usually spurred on by the suffering of patients so that we work from sickness to health, from the pathological to the normal. Although Thudichum's method will doubtless be used in psychiatry one day as its analogues have been used in other branches of medicine, we should not forget how the great majority of medical triumphs have in fact come about—by an intimate, sustained and passionate study of the grossly abnormal.

*Due to some odd quirk few psychiatrists seem to be aware that these three remarkable members of our profession were born within about a year of each other. Kraepelin and Freud in 1856, Bleuler in 1857.

At this same time, when Kraepelin, Freud and Bleuler were on the threshold of their careers, another young man was beginning to distinguish himself. It is curious that in 1885 Louis Lewin (1931) was one of the first to point out the dangers inherent in Freud's use of cocaine to relieve morphine addiction. In 1886 he discovered the cactus Anhalonium Lewinii which still bears his name although the species is also known as Lophophora Williamsii—but this does not alter his great contribution to our understanding of that extraordinary plant known to the Indians of the South West as Peyote. Lewin, as any reader of his marvellous book, Phantastica, soon realizes, is the father of psychopharmacology. His enormous grasp of the subject, his humor, his humanity and above all his huge imagination mark him out as being far ahead of his time.

In 1906 Carl Jung, then just in his thirties, on the basis of clinical observations of dementia praecox made in patients while he was working at the Burgholzli under Eugene Bleuler, suggested that although the psychological mechanisms of this illness resembled hysteria, they were, like hysteria, developing in the setting of a poisoned brain. To account for this he postulated a toxine—X, a nerve or brain poison generated by the conflict of emotions. Just how far ahead his thinking was will be understood when we remember that Cannon did not publish his book on the Role of Adrenaline and Emotion until 1929. When Bleuler (1950) first published his book on schizophrenia in 1911 he emphasized how different this illness was from any known toxic condition. By this time Lewin had been discussing the strange effect of the cactus, Peyote, and its chief alkaloid, mescaline, for many years. He stated repeatedly that it did not produce a delirium and its effects were unlike that of most other substances. Lewin was specific about this. There seems to be no particular reason why Jung and Lewin should not have joined their ideas but they did not, and it was over forty years before anyone attempted to do so.

Before devoting our attention to schizophrenia, we shall dispose quickly of the chemical theories dealing with the other great group of functional mental illnesses, the mood swing or manic depressive psychoses. While there has been much study of euphoriant substances from cocaine to amphetamine and its many deriva-

tives (this latter substance has indeed in recent years become a major addictive particularly in the Orient) we know of no hypothesis connecting them with the natural control of mood. Yet amphetamine is not unlike epinephrine in chemical structure while ephedrine which produces euphoria in some of those who take it was thought, until recently, to act by blocking an enzyme which destroys epinephrine. Campbell (1953) in his extensive and scholarly review of the aetiology of manic depressive illness, repeatedly emphasizes the importance of the autonomic nervous system, but he and the authors whom he quotes do not suggest anything very specific. It is curious that there seems to be an absence of biochemical hypotheses in this regard in spite of much evidence that many authors by implication believe in such hypotheses. Indeed, none would seem less adventurous and more in accord with common observation than that the hormone thought to be concerned with anxiety and tension also determines the control of mood in a more general way. At a recent international gathering the following statements were made by a competent psychiatrist, Sargant (1959), "It seemed to me to be particularly valuable as a statement (referring to Lehman's paper) of the very unfortunate present position in which we now find ourselves trying to classify and to form concepts about a group of diseases of which we have as yet absolutely no real knowledge as to their fundamental causation." Yet mood as changeable as the sky and as varied must surely be related to a biochemical mechanism which can produce its changes just as quickly as the events it mirrors change.

To return to schizophrenia—what is it? Why is it so important? There is still no generally accepted definition of the illness which is, useful, descriptive and accords with what is known. We have therefore developed our own which is:

"Schizophrenia is an illness or group of illnesses characterized by changes in affect (mood tone and empathy), perception and thinking and sometimes bodily posture occurring separately or in concert usually without loss of awareness, memory or disorientation for space or time. Insight and congruity of affect may or may not be preserved but their evaluation depends so much upon the observer's preconceptions as to make them less useful guides. The onset of the illness may be catastrophic but is usually insidious. The

course and development is markedly influenced by the sociocultural setting and by the personal endowment of the sick person. All races and classes are thought to be affected. The illness is seen most frequently between the ages of 20 and 40. The sex distribution is roughly equal but with some differences in the age on onset. The overt illness can last from a few days to most of a lifetime. The longer it persists the less hopeful are the chances of remission. There is much evidence that inheritance plays a part. Most authorities agree that about 1% of the human race suffers from schizophrenia. Some put the figure higher. At least one hospital bed out of every five in the world is filled by a schizophrenic—this incudes both general and mental hospitals. Since it attacks young adults in their prime and cripples without greatly altering their expectation of life, provided there is no very gross neglect, the social consequences are as serious as almost any other illness and the unhappiness which it produces is incalculable."

This alone would be enough to make schizophrenia the greatest challenge to psychiatrists; but, in addition, when it afflicts great artists, poets, philosophers and scientists, which is not infrequent, it seems to play a part in some of the special qualities of their more astonishing productions. Schizophrenia, then, is a great and protean illness and if we can deepen our understanding of it, we would have a better grasp of other psychiatric illnesses including the manic depressive group, alcoholism, and other intoxications and possibly some of the afflictions of old age.

For many centuries there has been a sustained disagreement between those who tend to ascribe illness and with it unusual behavior to demonic influence or divine affliction, and those who ascribed the same happenings to physical happenings in the body. Hippocrates of Cos was one of the first whose writings emphasized a natural rather than a supernatural cause for mental illnesses. Throughout the centuries medical opinion fluctuated, its act of faith being sometimes Hippocratic and sometimes otherwise. For in those days opinions about the causes of any illness could be based on no more than acute observation and a predisposition to believe that phenomena are, even if not wholly reasonable, at least comprehensible by means of reason. The great humoral theory helped psychiatry no more than it did general medicine. It is one of those

monuments to both the need for and the dangers inhering in a system of classification. Mentally ill people probably suffered no more than the physically ill who were bled, purged or vomitted to death in thousands.

By the 19th century, as we have already noted, a chemical basis for mental illness was becoming acceptable. At this time psychiatrists, or alienists as they were called, were one of the more advanced and better organized medical specialties—a fact that has been overlooked in recent years. In the 1850's, for instance, Thomas Kirkbride (1880), a founding member of the American Psychiatric Association, wrote, "The young should therefore be taught in their schools sound physiological doctrines about the brain as the organ of mind, and its liability to disease like other portions of the body."

Early in the 20th century chemical hypotheses had what seemed to be their first experimental support, when Berger (1903) reported that the blood of catatonic schizophrenics contained a specific substance which had a stimulating effect upon the cortical motor centers of dogs. Berger's findings were received cautiously. He was among the first to pursue what has proved to be one of the most elusive, bewildering and often heartbreaking trails in medicine. His was early evidence of a toxic substance which has proved astonishingly evasive.

Quite early in their history chemical theories about schizophrenia became divided between those who envisaged a toxin produced by invading organisms of one sort or another (Exotoxins) and those who thought that the toxin was produced in and by the body itself as a result of faulty metabolism (Endotoxins). Exogenous hypotheses are presently out of fashion but they have been very popular as the work of Cotton(1921), Bruce (1906) and Devine (1929) suggests. For many years Papez (1949) reported that schizophrenia was produced by a specific organism which was found only in schizophrenics where it presumably elaborated a toxin to do its damage. Lowenstein (1944) continued until recently to find tubercle bacilli in schizophrenic patients. While Rosenow (1955) believes that a specific streptococcus plays a part in inducing some sort of allergic response of the central nervous system. These views get very little support now, but it is impossible not to admire the

energy, single-mindedness and devotion of their originators in the face of discouragement and scepticism. Buscaino (1952) occupies an intermediate position for he envisages poisons of an indolic sort elaborated in the bowels, possibly due to some aberration of the gut flora. These produce liver damage and further metabolic disturbances which finally produce the typical psychological changes. This is allied to some of the theories of autointoxication which led to massive removal of the colon early in this century when surgical expertise outran medical sense for a short time.

There are two subdivisions to the endotoxic hypothesis whose merits are rarely argued. Some consider that the balance of a substance or substances already present in the body is altered, while others think that during the course of the illness some new substance not normally there is elaborated. It may be difficult to decide whether a toxic substance, once isolated, is the cause or result of some change in the normal body chemistry.

Those who require a concise review of the pursuit of toxine—X in body fluids should consult the McGeers' (1959) useful paper. Like many writings about psychiatry by those without clinical knowledge it shows little sympathy for the many difficulties which faced the seekers.

The period between 1920 and 1950 is dominated by the courageous efforts of the late Hermann de Jong (1945) who with his still surviving colleague, Henry Baruk (1958), attempted to use bulbocapnine as a model for the endotoxin of schizophrenia. Other workers including the veteran Buscaino who, with his son is still in the chase, continued to find evidence of a toxic substance. There were several obstacles which gradually reduced the momentum of these varied and long sustained assaults upon the great psychosis.

To us the fundamental difficulty, though not the most obvious, sprang from a failure to construct a model of schizophrenia which related to clinical phenomena and the reports of patients. Generally the patients' own accounts of their illness have been either disregarded or have only been accepted as the raw stuff for extensive and often fanciful elaborations by doctrinaire interpreters. De Jong came very close to devising a suitable model but unfortunately he made catatonia one of his criteria and failed to recognize that only reversible catatonia would be at all analogous to the clinical

illness. It was here perhaps that he lost his way for his choice of bulbocapnine was almost prophetically apt. Other investigators, learning from him, can now understand why the natural history of the illness schizophrenia must be aligned with the psychopharmacological models. Tayleur Stockings (1940), another pioneer, showed how closely the mescaline experience could resemble schizophrenia. Not long before him Lindeman (1935) had noted that mescaline and epinephrine were chemically similar. But once again the opportunity to develop this model at this time was not taken.

As long ago as 1938 Stoll and Hoffmann synthesized d-lysergic acid diethylamide and some years later accidentally discovered its astonishing potency as a hallucinogen. Greatly to his credit he and his colleagues made full use of the initial accident. We have still to grasp the possibilities of this new tool for psychiatric research. Later on we shall show that there has been unnecessary confusion about the use of mescaline and LSD-25 as models for schizophrenia, some believing that not a model but an identity was being sought. This slovenly thinking has hindered psychiatric research by wasting energy in a useless sort of controversy which could have been easily resolved by a clear definition of terms.

Any reader of the McGeers' survey must be struck by the amount of evidence suggesting that a toxin was present and also by an uneasy feeling that none of it was wholly conclusive.

Apart from the failure to construct a model which would form the basis of hypotheses at least two other factors hindered chemical research into schizophrenia. We have mentioned the first in the preceding chapter—the extraordinary influence upon psychiatric thinking of the holistic preoccupation of Adolph Meyer (1906) and his disciples—expressed in his school of psychobiology. Meyer was, it seems, a more persuasive teacher than writer, for it is hard to discover in his rather diffuse works much to account for the reverence in which his opinions were held, especially in the United States. The notion that all factors must be taken into account and that illnesses may result from deviations of habit was apparently once seductive. It has proved scientifically of little use. To many it appeared to contain a kernel of self evident truth—but we never found anyone who could explain what this kernel was and what might be done with it. The holistic approach was not particularly

favorable to a toxic hypothesis for it tended to lay emphasis on all possible variables rather than on any one in particular. The supporters of toxic hypotheses, in contrast, seemed narrow, fanatical and one-eyed, compared with this much broader view. Unfortunately advances in clinical medicine have almost always developed from break throughs on what seemed to be very narrow fronts. From the mid 1930's on the rising influence of psychoanalytic schools began to displace or merge with psychobiology particularly in the United States. These people have often gone far beyond Freud in ascribing what seems to be a psychological autonomy to the great psychoses or later considering them to be manifestations of social disharmony in the family or larger society. It is strange that in an age when pharmacological chemistry applied to many and diverse human ills has been extremely successful, it is often thought pessimistic to subscribe to a toxic hypothesis. Only a little thought is needed to convince one that our expertise in this direction is greater than in psychological and social matters, however much it may flatter us to think otherwise. There is a least amount of support and encouragement without which ideas of any sort cannot flourish. By the start of the 1950's some observers were relegating the toxic hypothesis to the scrap heap. The clearest and most unequivocal statement about this came from M. Bleuler (1955), son of E. Bleuler, and at that time Director of the Burgholzli in his father's place. He wrote, "Looking over these and other works into the pathological physiology of schizophrenia, one is forced to make this negative statement. These works have failed to bring us even one step closer to the possibility of finding behind the psychological psychosis of schizophrenia a definable, specific, pathological, somatic schizophrenia. We have no evidence of any disturbance which would neatly differentiate it from other psychoses, somatic disorders or from the norm. It is possible that as a consequence of these negative results the search for a specific somatic basis for schizophrenia will be given up for a long time to come if not permanently." Bleuler's positive suggestions are not encouraging. They amount to an endorsement of phenomenolgy, psychoanalysis, psychobiology and in addition to this existentialism, as being likely to increase our understanding of the great psychosis and lead to their alleviation. For about half a century these approaches have

been barren and stereotyped enough to lessen one's confidence in their future performance. Almost a decade later another surveyor, Kety (1959) whose competence differs greatly from the foregoing, writing in a context which has changed considerably, struck an equally pessimistic note. Caution can always be justified on the grounds of not sticking one's neck out. It is true that if one is sufficiently cautious one will never be wrong—but as we have suggested earlier the first duty of a scientist is to be wrong in a correctable manner. He writes, "These possibilities are mentioned only to indicate how large is the haystack in which we are searching for the needle; one cannot avoid a feeling of humility when one realizes how slight the chance is that anyone of us has already found it or will find it in a relatively short time."

Perhaps this very metaphor shows that he has not grasped the essential difficulty involved in the hunt for toxine—X. An immense amount of clinical evidence strongly suggests that we are dealing with a highly specific, often reversible chemical process. Looking for a needle in a haystack is an elementary piece of detection—any metal detector will solve that. What we are trying to do is to locate a particular needle in a very large pile of rather similar needles. There is only one way of doing this, to learn how to distinguish one needle from another. This may indeed be extremely difficult but if our analogy, our model, our hypothesis is correct, it is at least possible to succeed—where the haystack analogy must lead to failure. In subsequent chapters we shall discuss how we and others have attempted to identify a particular needle from its fellows.

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Chapter 3

MOOD AND ITS DISORDERS

INTRODUCTION

Anxiety is the most common cause of distress for psychiatric patients. If prolonged, it may lead to depression, to schizophrenia or into a vast group of major neurosis and psychopathic states which affect so many people. Conversely, the realization that there is a disturbance in thinking or feeling which often follows these illnesses will cause much anxiety. Inappropriate responses due to such disturbances will add to the discomfort. Anxiety is thus both cause and effect and tends to perpetuate the illness. Anxiety or tension can result in such anguish and mental pain that its unhappy victims will leave nothing undone in order to obtain partial or complete relief, including even death by suicide. It is therefore strange that it has received comparatively little attention from physiologists and biochemists.

Perhaps Cannon did his work too well. Few have followed him into the breach which he made. Possibly biochemists have persuaded themselves that anxiety is purely psychological when they should have recognized that it has both psychological and physiological aspects which can only be understood together. This neglect has resulted in psychological explanations for anxiety many of which do not seem to have been related to any physiological mechanisms. It is not always recognized that feelings of anxiety are a response to a variety of events which may be biochemical, physiological or psychological in origin. These events must have a final common path in an electric disturbance in the brain. This electrical disturbance with its accompanying feeling of anxiety may not be related causally to any event outside the body. Although it is evident that after the feeling of anxiety has been experienced, it is usually possible, and indeed for psychological comfort often essential, to find some explanatory event to which it can be attached.

The biochemist has been so little concerned with these matters that in a recent monograph on anxiety (1950) edited by Hoch and Zubin out of 247 pages 8 are given in a rather apologetic manner to its biochemistry. Even physiology only accounted for 13 pages.

Psychiatrists have assumed that a formulation which purports to explain why particular events occur is the equivalent of knowing how it occurs. In our opinion these are very different orders of explanation which are not necessarily related. The majority of psychological explanations deal with the reasons why anxiety occurs.

We do not see that one can have any thought, feeling or perception without its biochemical component. Anxiety, like other aspects of experience, must have both psychological and biochemical elements. If this is so, then to evoke anxiety, we require (1) a stimulus which may be psychological or biochemical, (2) suitable chemical mediators which will, in response to this stimulus, affect other brain centres resulting in a series of changes eventually experienced in anxiety.

The psychiatrist must appreciate this particularly in the frequent dealings with those suffering from anxiety which seem to be out of the ordinary either in intensity or duration. All around us, all the time, are "reasons" for anxiety. Most prolonged anxiety reactions undoubtedly develop from the sufferers relationship with his family, friends, enemies and society generally. Yet while this may be true for the vast amount of anxiety experienced by those who do not become ill, it does not follow that those who suffer from anxiety neuroses can be accounted for in exactly the same way. It is possible that anxiety which was at one time a response to psychosocial disruption can become autonomous. The biochemical processes which mediate anxiety may maintain this anxiety independent of the psychosocial trigger.

Chapter 4

RELATIONSHIP OF MOOD TO CATECHOL AMINES

It is often assumed that a chemical mediator of anxiety exists. Cannon (1953) and others suggested that this mediator might be epinephrine. It is easier to make such a suggestion than to demonstrate the nature of this mediator and to show how it works. There are many clues scattered throughout the literature which, when assembled, provide a substantial body of evidence pointing towards the sympathetic nervous system as Cannon believed. It may well be that feelings of anxiety depend upon the relationship between sympatheticomimetic amines such as epinephrine and isopropylnorepinephrine.

This is the evidence which supports the view that epinephrine is one of the mediators of anxiety:

1. When the secretion of epinephrine increases and its level in the plasma rises, experimental subjects look as if they are anxious and claim to experience anxiety.

2. Chemicals which decrease epinephrine levels or which change (usually reduce) the peripheral response to epinephrine, are often used to allay anxiety. These include various sedatives, barbiturates, etc.

3. Many substances whose chemical structure more or less closely resembles that of epinephrine have been used to treat psychiatric conditions characterized by apathy, anergia and listlessness. It has also been observed that if these are given in excess or if they are prescribed for already anxious people, then anxiety may increase. Occasionally psychotic states of brief duration have been reported after single large or repeated smaller doses.

4. Those substances which inhibit enzymes that destroy or alter epinephrine are often even more effective than sympathetico-mimetic amines. Some, like marsilid and a new group of semi-

carbazides derived from these amines, block amine oxidase. Cocaine, for instance, blocks not only amine oxidase but also sulfoesterase, an enzyme which some people believe conjugates sulfate to epinephrine.

PSYCHOLOGICAL

Landis and Hunt (1935) found that after they had injected epinephrine into subjects and patients, many reported that they had experienced anxiety. Many psychiatric patients including those labelled manic-depressive and schizophrenic had the physiological accompaniments of anxiety after such epinephrine injections. It was found that when the subject had been given epinephrine, he could only accept his feelings of anxiety as genuine if he could equate these feelings with some previous situation in which he had been anxious. Landis (1924) and Cantril and Hunt (1932) found that most of their subjects had to find some reason for their emotion which seemed adequate to them before they could look upon it as being real. It seems that up to this time there had been an assumption that epinephrine could only produce the autonomic and physiological aspects of anxiety. Emotion is usually felt or developed in a psychosocial context. Biochemical change is an essential component of emotion. As rational beings, people demand an explanation for their anxiety. They want to know why they feel so uncomfortable. Thus an increase in the secretion of epinephrine in itself does not produce real anxiety unless the subject can associate this with a real situation. Many people find that anxiety without a "why," especially if prolonged, is extremely distressing. It may be that this is why some patients who are experiencing anxiety to which they cannot ascribe a special cause become so very disturbed. When this happens any reasonable formulation which accounts for the anxiety will help to allay it. This may be why therapists whose ideas diverge widely or are even diametrically opposed have very similar results for their efforts.

PHYSIOLOGICAL

Cannon's famous "fight or flight" model gave epinephrine an important role in the emergency responses of mammals. It was

based upon the observed similarity between the autonomic and other changes which follow the administration of epinephrine, and those changes found in people who are anxious. These changes seem to prepare the threatened creature for violent motor activity. They include (1) redistribution of blood from visceral organs to muscle, heart and brain, (2) redistribution of glucose from storage depots to blood, (3) dilatation of bronchioles. These must have often been life saving to primitive man although they play a lesser part in the life of civilized man. Thus the sympathetic nervous system plays an important part in the production of anxiety. Epinephrine appears to effect and to sustain the necessary feeling.

BIOCHEMISTRY

As yet we do not know how epinephrine produces sensations of anxiety. In his recent review of the pharmacology of anxiety Altschule (1954) showed that epinephrine does not produce anxiety by altering the cerebral blood flow. Anxiety is not related to the hypertensive nor the hypotensive effects of such substances. Thus hexamethonium which prevents the reflex liberation of epinephrine from the adrenal medulla also reduces anxiety.

Since epinephrine does not readily pass the blood brain barrier, it is difficult to see how it induces anxiety, possibly enough can sometimes enter the brain. Marrazzi (1957) found that epinephrine inhibits synaptic conduction markedly. Thus free epinephrine in the brain would prevent it functioning properly. Leimdorfer and Metzner (1949) put epinephrine directly in the brain ventricles of animals and man. It produced sleep and surgical anesthesia and did not interfere with glucose metabolism peripherally.

As well as having a direct action on synaptic conduction, epinephrine may be converted into other substances which could produce anxiety. On the other hand, it may be that some people cannot produce substances which protect the brain against epinephrine, Hoffer (1957).

In reviewing the evidence, Altschule observed that many sympathomimetic amines such as methoxy phenylethylamine, etc. produce anxiety. Many methoxy and ethoxy phenylethylamines produce manifestations of fear in animals. Mescaline, trimethoxy

phenylethylamine, induces anxiety not only during the hallucinogenic experience but often before perceptual changes are reported and when physical discomfort is experienced. These compounds resemble degradation products of epinephrine. Osmond and Smythies (1952) discussed the possibility that methoxy derivatives of epinephrine might be involved in the etiology of schizophrenia. This question has not been thoroughly explored even though 3-methoxy derivatives of epinephrine are now thought to be important metabolites of epinephrine, Shaw, McMillan and Armstrong (1956) and Axelrod (1957).

The relationship between the levels of epinephrine in plasma and the intensity of anxiety is fairly well established. Woods, Richardson, Richardson and Bozeman (1956) used various drugs to stimulate the sympathetic nervous system of deeply anesthesized dogs. Many of these caused marked increases in plasma amines. The largest increase occurred in epinephrine rather than in norepinephrine. The final value depended directly upon the initial value. Nicotine (20 μg/kg I.V.) brought about the following changes μg epinephrine/liter):

1. From 0.4 increased to 16.2.
2. From 1.2 increased to 29.2.
3. From 2.0 increased to 57.8.

Ether (0.1 ml. I.V.) raised total amines from 5.2 to 137.1 μg/liter. Histamine did not alter the values. These final values correlated well with indices of sympathetic activity such as blood pressure, heart rate.

Liddell and Weil-Malherbe (1953) observed that when 40-60 mg. of methamphetamine was given by vein, the level of epinephrine in plasma changes in this way: (1) an initial rise, (2) a decrease well below the baseline, and (3) a second rise to or above the baseline values. They reported "the phase of falling epinephrine concentration seemed to be associated with relaxation and euphoria, that of rising epinephrine concentration with tension and anxiety, often accompanied by a sensation of shivering and the appearance of gooseflesh."

In phaechromocytoma, this relationship between anxiety, tension and epinephrine secretion is well known. Manger, Wakim

and Bollman (1955) report that with increased intracranial pressure one finds that the level of epinephrine and norepinephrine in plasma is often as great as that found in pheochromocytoma. Bilateral adrenalectomy reduced but did not completely prevent either the increase in blood pressure or the elevation of pressor amines.

It seems fairly certain that the high levels of epinephrine in plasma are associated with anxiety. While these plasma levels are probably indicative of the secretion of epinephrine, it is curious that after Bain, Gaunt and Suffolk (1937) and also Cohen (1959) demonstrated that epinephrine is absorbed by erythrocytes, biochemists still continue to measure the quantity of epinephrine in plasma only. Platelets also held appreciable quantities of epinephrine. Born, Hornykiewicz and Stafford (1958). There must be an adsorption equilibrium between the concentration of epinephrine in solution in plasma and the amount held by the adsorbent (erythrocytes and platelets). This equilibrium relationship between substances in the free (plasma) and adsorbed state can often be given by simple adsorption isotherms as shown in Figure 1.

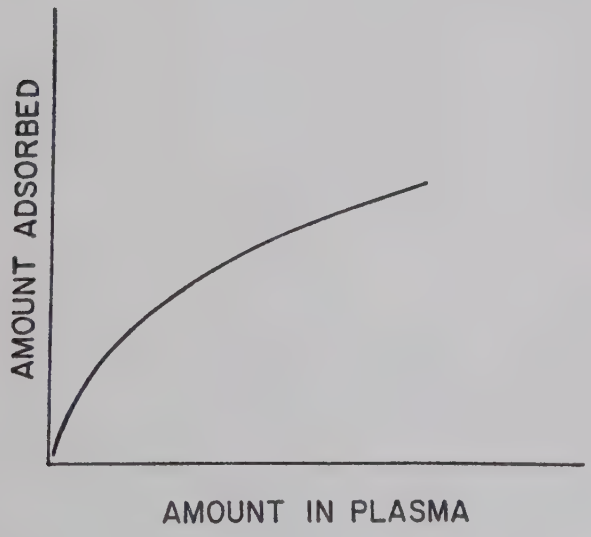


Fig. 1.

In a system of this type there may be large quantities of adsorbed epinephrine associated with minor changes in plasma levels. This is a buffered system, for only when the quantity of bound epinephrine increases sufficiently to saturate the adsorbing substances will there be any great fluctuation in the plasma levels of epinephrine. Unless the adsorption isotherms are known one cannot estimate the total quantity of epinephrine in the blood.

Consequently most of a heavy secretion of epinephrine may enter the platelets and erythrocytes and escape measurement. Raab and Gigee (1955) have shown that myocardial and vascular tissue also adsorbed large quantities. It appears that epinephrine is held preferentially within cells (intracellular) rather than in extracellular fluids.

Fleetwood's (1955) work supports this point of view. He used a biological assay for measuring the equivalents of norepinephrine and epinephrine in the red cells, in plasma and in whole blood. A rat colon preparation, which is relatively insensitive to epinephrine was used for measuring norepinephrine. A rat uterus preparation which is relatively insensitive to norepinephrine was used to measure epinephrine. Fleetwood found that erythrocytes contain most of these amines. The quantity of amines in plasma varied between 12 to 33 percent of the whole blood amines. The ratio of amines in plasma to red cells was reversed in a small proportion of Fleetwood's cases. In them anxiety was easily mobilized and was increasing at the moment the blood was drawn. This could be due to an incomplete adsorption of epinephrine as the rate of production was greater than the rate of removal.

TABLE 1

CONCENTRATION OF NOREPINEPHRINE AND EPINEPHRINE IN RED CELLS AND PLASMA ACCORDING TO FLEETWOOD (1955)

Quantity of Amines, μg/liter

	Erythrocytes	*Plasma*
Norepinephrine	0 to 4000	0 to 500
Epinephrine	7 to 300	7 to 50

One would expect greater fluctuation of these amines in cells than in plasma and indeed this is what Fleetwood found as his data shows. This is summarized in Table 1.

The range in variation is six to eight times greater in cells than in plasma. Fleetwood also found a high and significant correlation between the concentration of these amines in whole blood and the intensity of anxiety as shown in Table 2.

TABLE 2

NOREPINEPHRINE AND EPINEPHRINE CONCENTRATIONS IN BLOOD OF NORMAL AND ANXIOUS SUBJECTS AND PSYCHIATRIC PATIENTS

Quantity of Amines in Blood, μg/liter

Subjects	*Norepinephrine*	*Epinephrine*
Normal Subjects	0	8 to 20
Anxious Normals	250-750	8 to 50
Psychiatric Patients	750-4000	12 to 500

ROLE OF ISOPROPYLNOREPINEPHRINE

Diethelm and his colleagues found that red cells from tense alcoholic patients contained more sympathomimetic amines than those of normals or alcoholics who were not tense. Taking alcohol reduced this concentration. More than one substance was apparently involved. One of the substances resembled norepinephrine in biological properties. However, Garb, Tiwari and Chapman (1957) do not believe norepinephrine alone can be the tension mediator. By itself, it does not produce anxiety in humans. It appears to be simply a vasodepressor. Thus Swan (1952) found that it produced mild symptoms usually unfamiliar to subjects. Fear was found occasionally. This could readily be due to the unfamiliar reaction. Moyer (1956) found minimal side effects to subcutaneous and intravenous norepinephrine. This is consistent with Burns' (1952) view that norepinephrine acts primarily at its site of liberation where much of it is destroyed by amine oxidase.

Isopropylnorepinephrine is another sympathomimetic amine

present in minute quantities in the body. It contains an isopropyl radical rather than a methyl group on the nitrogen atom. Garb *et al.* suggest this substance may play an important role in mediating anxiety. Their evidence is (1) that isopropylnorepinephrine is more potent than the other two amines in producing auricular tachycardia—a common feature of anxiety, (2) within ten minutes of giving volunteers small quantities (10) μg subcutaneously, they felt anxious. One subject wandered about aimlessly and restlessly. His face became pale, his hands were cold and tremulous. Another subject refused to take it sublingually because of side effects which he described as jitteriness, tachycardia and anxiety. Epinephrine produced much less anxiety in proportion to the amount of bronchiolar dilatation. Jaques, Bein and Meier (1956) reported it is a very strong antagonist to 5-OH tryptamine. They also suggested it might have some function in the body.

Garb has made the interesting suggestion that this compound in combination with other amines may be related in some way which is still unclear to the development of tension and anxiety.

Isopropylnorepinephrine in contrast to both norepinephrine and epinephrine augmented the action potential of the superior cervical ganglion of the cat. This led Matthews (1956) to suggest it sensitized additional ganglionic cells to stimulation. The effect was characterized by slow onset and long duration of activity. The other two amines act quickly and for a short time. Perhaps the isopropyl derivative must first be converted into a long acting substance whereas norepinephrine and epinephrine can act directly until they are metabolized.

RELATIONSHIP OF MOOD TO INDOLES

The hypothesis that people feel anxious when they are secreting too much epinephrine or isopropylnorepinephrine raises other problems. If these substances were the major biochemical variables in the production of anxiety, then anxiety should be present as long as the secretion is high and should decrease when the levels are reduced.

During a period of emergency or stress, the secretion of epinephrine probably is high. But usually anxiety is felt at the begin-

ning of such an emergency. And it tends to decrease as the situation continues. While it is true that in extreme emergencies people have become completely immobilized by anxiety, this is not usual. Far more often they become somewhat acclimatized, but when it is all over are relaxed, fatigued and sleep heavily.

Epinephrine itself may be converted into some other substance whose action opposes that of epinephrine and also produces fatigue. Kaufmann and Koch (1959) found large quantities of adrenochrome and adrenolutin like substances in the urine of one subject grossly fatigued by bicycle racing. In such a model the degree of anxiety experienced would be a function of the ratio of epinephrine to this hypothetical buffer of anti-epinephrine substance. Another possibility is for the extra epinephrine to be very quickly bound by cells and thereafter is released slowly as the rate of secretion returns to normal.

Although there are many possible metabolites of epinephrine very few have so far been isolated and studied. One group of these metabolites, the methoxy derivatives, have become available for study recently. They seem to produce few detectable changes in animals and their part in the mediation of anxiety is unknown. Another group goes to adrenochrome and from this into a series of dihydroxy and trihydroxy indoles. These compounds have been measured in urine by Sulkowitch, Perrin and Altschule (1957). The method of Shaw (1938) for measuring amines also measures dihydroxy indoles. There is an extensive chemical literature about adrenochrome and adrenolutin and Heacock (1959) in Chemical Reviews refers to over two hundred chemical studies alone.

ADRENOCHROME

In our early studies with adrenochrome when we gave 25 mg. of this compound by vein to chronic and deteriorated mental hospital epileptic patients, we did not expect to see much evidence of psychological change. Not only were these patients poor verbalizers but it may well be that epileptics are not the most suitable subjects in whom to measure such change. Denber and Merlis (1955) for instance reported that they did not show the expected psychological response to 500 mg. of mescaline although there was

a marked change in the EEG. They felt that epileptics have a different pattern of cerebral organization from schizophrenic patients. Szatmari, Hoffer and Schneider (1955) also found that although adrenochrome markedly modified the EEG from surface electrodes, there was little psychological change. To our surprise two of the more verbal patients remarked spontaneously that they felt more alert, more relaxed and mentally brighter. One of these patients had narcolepsy. Several years after this test, this man clearly remembered the sense of well being he had noted immediately after the injection of adrenochrome.

When one of us (H.O.) received adrenochrome by subcutaneous injection, he experienced psychological changes similar in many ways to those he had previously had with LSD, Hoffer, Osmond and Smythies (1954). Although this was very exciting to the observers, H.O. showed very little elation at this discovery. Not until several days later did he seem to appreciate the implications of these previously unknown properties of adrenochrome fully, and developed an adequate degree of interest. Although he was preoccupied with the experience, he did not seem to be emotionally involved.

Recently we have given 10 mg. of crystalline adrenochrome, dissolved in saline, intravenously to a series of psychiatric patients. They were informed that this was a routine test and had no expectations of feeling either better or worse for it was not considered a treatment. They were in fact told that they would feel no change whatever.

Their alteration in tension and other psychological changes were recorded following the injection. A summary of this is shown in Table 3.

Half of the schizophrenic group were eased of their tension for at least one hour. All the patients with anxiety (3 out of 3) were free of tension one hour. One depressive subject was eased, the other became more tense. Three (out of five) alcoholics had some relief from tension but for less than one hour.

Six (out of ten) schizophrenics and three (out of five) alcoholics had visual changes. None of the patients with anxiety (three) or depression (two) noted visual changes.

TABLE 3

CHANGES INDUCED IN VARIOUS GROUPS OF PATIENTS BY 10 MG. OF ADRENOCHROME GIVEN INTRAVENOUSLY

Group	N	Tension			Other Changes	Visual Changes
		Increase	No Change	Decrease		
Schizophrenic	13	2	4	6	10	8
Anxiety	5	0	0	5	1	2
Depression	3	1	0	2	2	0
Alcoholic	5	1	2	2	3	3
Total	26	5	6	15	16	13

If, as our evidence suggests, adrenochrome allays anxiety, it is possible that marked anxiety (tension) present in chronic anxiety states and in many depressions might be due to an inadequate supply of adrenochrome. As a result, the ratio epinephrine/adrenochrome becomes too high. If the production of adrenochrome in the body is reduced, its level in the cerebrospinal fluid would be lower and blood should be able to destroy injected adrenochrome more quickly. Hoffer (1958) found that patients with tension and depression have half as much adrenochrome in cerebrospinal fluid as schizophrenics and less than do normals. Table 4 shows eight patients with anxiety in whom an adrenochrome tolerance test was done. There was little increase in adrenochrome levels after fifteen minutes; while after thirty and sixty minutes, the level remained lower than the initial value. Contrast with this five normal subjects in whom the fifteen minute value was doubled but the thirty and sixty minute values were normal.

TABLE 4

PLASMA ADRENOCHROME VALUES DURING ADRENOCHROME TOLERANCE TEST

Group	N	Adrenochrome μg/liter			
		Initial	15	30	60 min.
Anxiety	8	62	86	42	54
Normals	5	54	106	53	53

None of the five anxious or depressed subjects reported any visual changes and four of them noted a marked decrease in tension. We suggest that the adrenochrome injection temporarily restores the balance between epinephrine and adrenochrome. The adrenochrome is removed from plasma so rapidly that there are no psychotomimetic changes. These occurred only in schizophrenics and alcoholics who did not remove adrenochrome as quickly. Normal subjects free of anxiety when given adrenochrome by injection have more pronounced visual responses than do subjects who are tense and anxious. This loss of tension and relief of anxiety which follows the injection makes them feel more comfortable and relaxed without visual changes.

ADRENOLUTIN

In our early studies when 25 to 50 mg. of adrenolutin was given orally to volunteers nearly half of them felt much less anxious. Those who received a placebo continued to be more tense and anxious than those who had the adrenolutin. Eccles (1957) reports an interesting clinical finding noted by physicians many years ago, that ten drops of epinephrine taken as a drink proved very effective in controlling vomiting of pregnancy. This has been used recently with success. Epinephrine may have been converted into adrenolutin in the alkaline medium of the duodenum and this may well be the active factor.

Here are excerpts from the accounts of normal volunteers who took adrenolutin.

> *Subject L* (psychiatrist): "I don't feel very talkative. I felt sort've contented and a little detached. As a matter of fact at that time you were talking to me and yet I didn't want to be left alone. It feels like I've had a mild sedative."
>
> *Subject H* (psychiatric nurse): She became drowsy one half hour after taking 50 mg. of adrenolutin by mouth. She tried to dispel this by walking up and down a long corridor but the drowsiness remained and lasted twenty minutes. Later, her arms felt more relaxed than the rest of her body and then she became completely relaxed. That evening at home, she felt unusually lazy and allowed her guests to straighten up her apartment after a party without helping them.

Subject C (psychologist): He had a general feeling of lassitude and apathy.

Subject C (psychiatrist): "I took 50 mg. of the drug yesterday at 5:50 P.M. I can remember quite clearly all that happened. Before taking the drug, I was aware of mild anxiety as I had no idea what was going to happen and I suspected that the experience might prove quite a terrifying one. My anxiety increased a little after taking the drug. At 6:05 P.M. I recall being aware of my heart pounding a little. I looked at my watch and decided that this was unlikely to be the effect of the drug so soon after taking it. Then, over the next twenty minutes or so the anxiety steadily decreased until by about 6:30 P.M. it was replaced by a feeling of complete indifference. This feeling is difficult to describe. It was unlike anything I have experienced before. I felt peculiarly detached but quite well aware of what was going on. Also from this point on I think I became a very passive participant in the experiment. Previously I had felt a keen sense of interest, curiosity and even slight apprehension about the experience; now I felt no urge to cooperate in volunteering information about my feelings. They put me through a few tests of perception of time and distance. These gave me no trouble and I felt mildly pleased at being able to do them. The tests required only short answers which was just as well as I did not feel any desire to talk for more than a few seconds. Although I was well aware of what was going on, I felt very little interest in it. At 7:30 P.M. I went to the EEG department. I remember contrasting this visit with the one in the afternoon before I took the drug. During the afternoon I chatted away with the technician and was interested in all that was going on; now as a person he hardly existed for me. I felt no interest in him whatsoever. As he moved my head around to apply the band I remember thinking that I was like one of the monkeys treated with serpasil in a recent Ciba film—passive, compliant, emotionally flat but awake and well aware of what was going on. I know that if I communicated this thought with . . . he would ask for more details and I felt I could not be bothered pursuing the matter so I remained silent. Generally I think there was marked poverty of thought by this time. For long periods I would just be content to remain in the one position. I remember thinking while sitting in a chair in the EEG department that I would remain there for hours. Occasional thoughts passed through my mind while the EEG was

being taken, e.g. that this was probably what a leucotomized patient, or perhaps a simple schizophrenic, felt like but I was quite incapable of pursuing or elaborating on this thought. I also remember feeling that I had lost the capacity to feel joy, sorrow or indeed any powerful emotion. I thought of John Stuart Mill's remark 'better an unhappy man than a contented pig' which he made in discussing the qualities of pleasure but to continue any philosophical train of thought was beyond me. I did feel though that I had been reduced to a vegetative level. For long periods, my mind was quite blank; I felt contented to lie and not think about anything. I realize this now—but about 8:20 P.M. when . . . said he was having to almost force answers out of me, I was mildly surprised and I did not seem to be as clearly aware of this change as I am now. I did not care about . . . remark as I had now no interest in the experiment, his feelings or anything else. During the time the EEG was taken, I lay perfectly relaxed. I was mildly anxious to know what would happen when photic stimulation was applied. As it turned out the sensation was not particularly striking. I saw many colored dots in asymmetrical patterns. I think all the colors of the spectrum were there. Earlier in the afternoon I had merely seen concentric circles of light against a background which was first black then dark blue. While the EEG was in progress . . . came back into the room. For a moment his face looked much more dark and sombre than usual, almost threatening. So did . . . but the impression was momentary. Otherwise, I was unaware of any perceptual disturbance. When I left the EEG department at 8:00 P.M. or thereabout, I was beginning to feel more 'alive.' On my way over to the Munroe Wing, I saw some patients playing croquet. I felt a transient rush of pleasure at the sight of the grass, trees and the activities of the patients and recall realizing with a jerk just how automaton-like I had been feeling. I still felt dull and detached nevertheless, and not at all interested in talking to anyone. More tests of perception were now administered; these I did without difficulty and then . . . gave me some of Sargent's Insight and Empathy Tests to do. For some reason, I felt most unwilling to do these. In the first place I did not read the instructions properly and thought I was to tell a story around the theme mentioned. Then I noticed I was supposed to put myself in the position of the people mentioned. I found this hard to do. I felt no interest in the test. I did one

question, then hoped . . . would forget about the other. When he did not I proceeded slowly with the second. It seemed to me that I merely applied previously acquired psychological knowledge to the situations. I did not really feel myself in them. I felt little interest and tried to make my answers as succinct as possible. I found this test involved a definite unpleasant sense of effort, whereas I rather enjoyed the perceptual ones. At 9:00 P.M. I left for home. I now felt much better. When I reached home my wife remarked that my pupils seemed somewhat dilated. She also noticed that I was slightly withdrawn. I now felt much better, however, but fatigued (which I had not noticed before). I was glad to turn into bed around 10:30 P.M. Prior to that I was able to enjoy 'Pictures from an Exhibition' by Mussorgsky and Ravel though less intensely than usual. This morning after leaving home I felt rather dull and flat but the phenomenon was quite mild. Now (12 noon) I feel almost normal. This morning I carried out my usual duties without difficulty (including an L.P.); less interested in the patients than usual."

In summary, the outstanding features of the experience as I remember were:

(1) Marked reduction in drive and interest with resulting poor concentration.

(2) Inability to feel deeply. Diminished empathy towards others.

(3) Complete absence of anxiety.

(4) No gross perceptual anomally. (The feeling about . . . face was slight, fleeting.)

(5) Subjectively the intellectual functions seemed undisturbed but I seemed to lack the drive necessary to continue a thought out to its conclusion.

(6) Lack of interest in myself and indifference to what others thought of me. Although clearly aware that a change had occurred in me, I found it hard to make a critical appraisal of this because I seemed to have lost the urge to do so.

The subject's account was in agreement with observations made of him by Dr. D. Blewett[1] and myself. Fifteen minutes after taking the drug, he had a "far-away feeling." At 20 minutes, he

[1]Supervising Psychologist, Psychiatric Services Branch, Department of Public Health, Regina, Saskatchewan.

had a strong feeling of being far away or indifferent similar to the feeling he once had on very prolonged guard duty (36 hours). He had to fight physical exhaustion and fatigue. Toward the end of the duty, things appeared mechanical and far away. He had the same feeling now but without weariness or fatigue. At 35 minutes, when he was describing his feelings, I asked him "Have you ever felt this way when you were extremely anxious?" He replied, "Well, no, no." "I don't feel anxious at all now. I don't feel at all like that." At 45 minutes, he reported he was very relaxed and could stay where he was for long periods of time without becoming anxious.

ADRENOCHROME METABOLISM AND TENSION

Payza and Mahon (1959) have developed a method for measuring adrenochrome accurately when it is injected by vein or is added to plasma in vitro. Using this method when blood is taken from a human subject who has not been injected with adrenochrome, a fluorescence is found in the plasma which is equivalent to about 60 μg/liter of added adrenochrome. At present no other substance is known to effect this test, so that it is proper to infer that the fluorescence comes from adrenochrome which is normally in human blood.

The rate at which injected adrenochrome is removed from plasma varies with different groups of patients. It is measured by injecting 10 mg. into a vein and determining the quantity remaining in plasma 15, 30 and 60 minutes later. This we call the adrenochrome tolerance test and is similar in principle to the intravenous glucose tolerance test.

The adrenochrome tolerance for different groups of patients is shown in Table 5.

Patients who are tense lose adrenochrome from their plasma more quickly than do normal volunteers or schizophrenic patients. The adrenochrome may be converted into adrenolutin and other indoles and/or stabilized in blood. The latter can occur by adsorption into red cells much as does epinephrine or by binding to plasma proteins. Osinskaya (1958) found that epinephrine deriva-

TABLE 5

ADRENOCHROME TOLERANCE OF SOME DIAGNOSTIC GROUPS AFTER INJECTION OF 10 MG. ADRENOCHROME I.V.

		Initial Adrenochrome	*15 min.*	*30 min.*	*60 min.*
Diagnosis	*N*	*μg/liter*			
Tension and alcoholic	8	62	86	42	54
Normal	5	54	106	53	53
Normal—LSD (35 μg)	6	43	165	86	72
Normal—LSD (100 μg)	2	46	—	—	124
Schizophrenic	6	43	163	75	89

tives are bound to protein. Melander (1957) found adrenolutin was bound by ceruloplasmin.

Not only do tense patients lose adrenochrome from plasma more rapidly but they also react in an unusual way to LSD which probably acts by increasing adrenochrome plasma levels.

Smith (1958) noted that alcoholic patients when sober require much more LSD than do normal subjects if they are to develop the usual psychological changes occurring after LSD. Schizophrenic patients also require more LSD although this observation is less reliable since it is often very difficult for schizophrenics to verbalize their experiences. Our observations show that subjects with severe tension do not have the usual experience. They tend to become more tense, depressed and suffer anguish which may be very severe. Giving them more LSD may merely increase their discomfort.

The evidence so far indicates that the ability to respond to LSD does not only depend on personality factors, but also in a capacity to mobilize adrenochrome in the body. The evidence for this is (1) Normal subjects given 100 μg LSD show a greater increase in plasma adrenochrome compared to alcoholic subjects given to 200 to 300 μg (Table 6) and (2) Alcoholic subjects who have responded to LSD with a decrease in plasma adrenochrome, an increase in tension and little physiological response, show a marked decrease in tension and increase in the intensity of the experience of the usual type after 10 mg. of adrenochrome has been given by intravenous injection.

TABLE 6

RELATIONSHIP OF INCREASE IN ADRENOCHROME LEVELS TO INTENSITY OF THE LSD-25 EXPERIENCE

Group	*Number*	*Maximum Adrenochrome Increase, %*	*Anxiety*	*Experience*
Alcoholics	2	328	Moderate	Moderate
Alcoholic	1	140	Moderate	Marked
Alcoholic	1	80	Marked	Mild
Alcoholic	1	−50	Very marked	Mild
Normal	3	240	Moderate	Marked
Normal	1	90	Moderate	Mild

Elmadjian and Hope (1956) also reported that chronic schizophrenics showed no reaction to LSD nor was there any change in the excretion of amines. Involutional depressions showed a marked increase in emotional reaction and in excretion of epinephrine, as did manic depressives who excreted more norepinephrine and epinephrine.

5,6-DIHYDROXY-*N*-METHYLINDOLE

In 1957 one of us (A.H.) had the good fortune to meet Dr. Deltour, Medical Director of LABAZ and Drs. Melander and Hellstrom of KABI at the psychopharmacology meeting in Milan. Dr. Deltour and A. H. had a detailed private discussion of the properties of adrenochrome and its semicarbazide (adrenoxyl). Adrenoxyl is recommended for use as a hemostatic substance. There is no general agreement that its hemostatic activity is remarkable. However, many physicians use it regularly for their patients who have undergone surgery. Apparently this use is expanding. If its hemostatic properties are so uncertain why is it used? There are two possibilities: (1) that these physicians have blindly accepted the advertising claims and that their patients would do as well on placebo, or (2) that the physicians have observed that the patients either feel better or do better when given adrenoxyl. We prefer for the moment to accept the second possibility as more probable.

If there is some improvement in the way these patients feel (most surgeons lean heavily on the subjective response of their patients and do not use objective tests) even though the increase in hemostatic ability is not remarkable, then there must be another reason. Perhaps adrenoxyl makes people feel better because, like marsilid, it is a euphoriant. Their physicians would ascribe the improvement to the only known property of adrenoxyl which is its hemostatic action.

Pursuing this line of thought, Dr. Deltour remembered that some surgical patients did remark on their feeling of well being after receiving adrenoxyl.

We have made a few preliminary trials with adrenoxyl on normal volunteers. It seems to have some euphoriant activity. It would not be very surprising if it inhibited amine oxidase for it is a semicarbazide and has some similarity in chemical structure to marsilid and some newer analogues.

But adrenoxyl is normally not present in the body nor is it readily hydrolyzed. Our interest has been in naturally occurring anti-tension substances so we studied derivatives of adrenochrome which might be present in the body.

Discussions with Melander reinforced these possibilities. According to Melander, adrenochrome and adrenolutin in small quantities produced changes in behavior in their animals. But if several times the amount of adrenochrome which will produce these changes in animals is treated with ascorbic acid and then all of this decolorized preparation is injected, no psychotomimetic changes are seen. This colorless substance was thought to be leucoadrenochrome which suggested that it, not being a psychotomimetic, might have some desirable properties—possibly as an anti-tension agent.

We could not explore this possibility until Heacock (1958) showed that "leucoadrenochrome" consists of several substances of which one is 5,6-dihydroxy-*N*-methylindole (DNMI).

This was synthesized and crystallized and became available for study late in 1958. Since then, we have run a substantial series of trials of this compound. Briefly, it has anti-tension or anti-anxiety properties when given in small dosages either sublingually or orally. These results with a few case histories will be given now.

Reactions of Normal Individuals (Not Patients)

In general, when normal subjects were tense and anxious they noted a slight or more often good response in that they felt more relaxed, more optimistic and functioned more efficiently. The environment appeared visually more clear. If they took the compound when feeling normal they noticed no effect.

Good Response

Subject P.L. became very tense or anxious for a variety of reasons. This kept building up until early in the afternoon. She was taut, her hands had a marked tremor and she had a severe headache, being also on the verge of tears. At 2:35, she received 3 mg. sublingual DNMI. In seventeen minutes all the tautness was gone and some of the headache was gone. In an hour she was cheerful, vivacious and relaxed. She reported her throat which was sore all day felt normal. In two hours she was well relaxed and her headache was no longer present. She reported her face felt as if it was mildly burning at one hour, but no flushing was seen.

Subject S.G. Mrs. S.G. reported five days after Mr. S.G. took 3 mg. as follows: "I persuaded S.G. to try one and the change in him was dramatic. He was lifeless before he took it. In a matter of minutes he fell into a relaxed sleep. From then on it was fascinating to watch the difference. He got up in the morning, became interested in his work, was cheerful and relaxed and normally hungry. During the night he slept without twitching and still feels fine."

Subject L.K. This subject developed a very painful bursitis over the right shoulder. There was marked limitation of movement and she was not able to lift her arm above the shoulder level. Several times 3 mg. DNMI was given and was followed in a few minutes by a marked relief from pain lasting about four hours. After two months the shoulder was normal. She had now however peptic ulcer pain (no x-ray evidence for ulcer) and could tolerate very few foods. She regularly consumed atropine like compounds. For the third and fourth month, she took 6 mg. DNMI per day. By then she was able to eat nearly all the foods she normally ate and required very moderate quantities of atropine drug. If she reduced the DNMI to 3 mg. per day the symptoms recurred and she became very tense, irritable, suffering from

pain, anorexia and insomnia. After another few months, she was well on DNMI alone.

Subject C.N. This subject, a graduate biologist, had neglected his studies. He came in the day before an exam feeling very tense and nervous with a headache. He was given 3 mg. DNMI at 4:10 P.M. One hour later he felt relaxed and his headache was gone. However, he was not convinced much change had occurred. Between 6:30 P.M. and 1:00 A.M. he felt very relaxed and good. He studied the entire period without once feeling bored or sleepy. This was very surprising to him as he usually had difficulty studying subjects repugnant to him as this one was and he had expected a very difficult evening. At 1:00 A.M. he took 10 mg. (DIN) (described later in this chapter) and falling asleep immediately awakened refreshed at 7:30 A.M. He wrote his exam, was well relaxed and did well. To his surprise he passed the course.

No Response

Subject M.K. Suffered severe sunburn over the weekend and felt very uncomfortable with great pain. After receiving 3 mg. she reported no change in pain associated with the burn and no change in mood. Her muscles ached a little less.

Two weeks later she had gardened too enthusiastically and was again complaining of aching muscles. She felt sad but not tense or restless. She was given placebo and after 30 minutes reported no change. She was then given 3 mg. DNMI and a few minutes later had a slight flush. Three hours later became somewhat apathetic and therefore less concerned about her pain.

Subject S.W. Was very tense and anxious several months. He took 3 mg. twice a day for three days and noted no effect whatever.

Subject C.N. Took 3 mg. when feeling normal. He noted no effect whatever.

A brief summary of these results for normal subjects is shown in Table 7.

Reactions of Depressed Subjects

Subjects who are depressed and anxious respond very well to DNMI. Only a small series has been treated but the results are good. Usually there is a marked response within one hour after

the medication is taken. Some of these subjects have responded after noting no response to identical placebo tablets. Most subjects have done well on occasional use of DNMI. They were instructed to take one whenever they were very tense with a maximum of two per day. The results are shown in Table 7. A few patients who had failed other treatment responded.

TABLE 7

RESPONSE OF NORMALS AND PSYCHIATRIC PATIENTS TO DNMI

Group	*N*	*Total Number Times Given*	*Response*		
			None	*Slight*	*Marked*
Normals (tense)					
a) Occasionally	5	5	5	–	–
	4	4	–	4	–
	35	35	–	–	35
	1	8	–	1	7
b) Regularly	1	1 year	–	–	yes
	1	9 months[1]	–	–	yes
	1	11 mos. (6 mg/day)	–	–	yes
	1	6 months[1]	–	–	yes
	1	12 days (6 mg/day)	–	–	yes
Depressions					
a) Occasionally	4	16	16	–	–
	3	5	–	4	1[2]
	8	18	–	–	18
	1	2	–	–	1[3]
b) Regularly	1	1 year[1]	–	–	yes
	1	2 weeks[1]	–	–	yes
	1	1 year (6 mg/day)	–	–	yes
	1	2 weeks (6 mg/day)	yes	–	–
	1	6 months (6 mg/day)	–	–	yes
	1	8 months[1]	–	–	yes

[1]Uses when tense.
[2]Panic reaction.
[3]Nausea.

Subject G.D. Became ill two years ago when she noted loss of interest in community and in housework. She became irritable, depressed and unable to carry on at home. Tranquilizers were of no help to her. She felt very discouraged, blaming her condition on her husband and her in-laws. Her thinking was slow and she was slightly suspicious.

About one year before this admission, she was in a psychiatric ward of a general hospital where she was given brief but intense psychotherapy. She did not feel better. An attempt was made to remove her and her husband from home for a few months to "make things easier." This did not make her feel any better. Indeed her husband became resentful and she felt more guilty. Eventually she was referred to one of us (A.H.). Having assessed her, she was given 3 mg. DNMI at 3:50 in the presence of a research resident (J.G.). At that time she was rigid with tension, spoke slowly and hesitantly. She was asked to take the pill with the brief statement "It might help you." In fourteen minutes she reported she felt a little relaxed and found it easier to talk. She now felt things were not pressing in on her so much. Twenty minutes later when I asked her how she felt she began to cry. After this, she spoke more readily and freely about her problems. About thirty minutes later she returned to the living room of the psychiatric ward. One hour later I found her curled up in an easy chair feeling much relaxed. She smiled at me and reported "I feel so good. I did not think I would ever feel this way again." She took 3 mg. of DNMI twice a day for four days. During this time she was completely free of tension. Four days later she reported she felt unreal but very good. The pills were discontinued. The feeling of unreality left her in one day. She remained relatively free of tension nearly four months. Being free of tension she began to work on her personal problems constructively and began to realize her attitude had something to do with her problems. During this interval, she was seen three times. In order to assist her, she was given an LSD treatment as described by Smith (1958), and Chwelos, Blewett, Smith and Hoffer (1958). Since then the family problems have begun to be resolved and she has taken DNMI occasionally. She has since become pregnant and at three months remains well.

Subject Miss G. (an account by H.O.). Miss G., who is in her mid-twenties, has suffered recurring depressions from the

age of eleven. She was first seen as a patient on 21:8:58. This depression which had become increasingly severe during the previous three weeks, had many of the features which had been present in her earlier illness. These were insomnia with early morning wakening, loss of appetite with dulling of food flavors, colors seemed less bright, a tight feeling in her skull, pressure behind the eyes, muscular tension with aching, stomach ache and an extreme lack of energy. Mentally she was low spiriited, felt life was futile, tended to be much more introspective than is usual for her, had difficulty in concentrating, could not make up her mind, was seclusive and was afflicted by despairing thoughts which were sometimes suicidal. She appeared tense and pale and her manner was distraught. Her thinking seemed slightly slowed and she sat rather woodenly in her chair. She gave clear indications of being fairly severely depressed. From her history I found that she had seen many doctors for her illness, several psychiatrists and psychologists as well. She had once been in a mental hospital about eighteen months previously. She had received chlorpromazine at that time and developed jaundice. Later when her depression had lifted she received a course of E.C.T. Her present depression followed ten days of enforced bed rest due to a back injury, for which she had been lying flat much of the time.

Miss G. was, for her, moderately ill and from her history it seemed likely that her illness would continue for about another three weeks, and then it would slowly remit. During this period of remission she would have brief periods of tense elation followed by a return of depression. The main question was whether she could remain at work under supervision. There was some danger of suicide but she could talk about these fears so that I felt it would be safe to see her as an out-patient. I gave her a few slow release capsules of dexedrine and amytal. On 22:8:58 she took one of these with some transient benefit but on 23:8:58 she was still severely depressed so that it was very difficult to sustain any conversation with her. On 24:8:58 when I saw her again she was in much the same state. It happened that I had a single 3 milligram tablet of DNMI, one of about twelve which had been made as samples. Without much hope that it would help her I decided to try it, knowing that it could do no harm and this was in fact what she was told. "It can't harm you and it may help." At about 2:30 P.M. she put the tablet under her tongue. I did

not question her at all closely because I did not want to suggest improvement—though I have never previously had any success from suggestion in depressions of this sort. In about an hour she seemed more relaxed and remarked spontaneously that "the muscles in the back of my neck feel easier." From this point she was clearly calmer, more cheerful and more spontaneous. She went on night duty and slept well later which she had not been doing before. Her appetite returned. Five days after she had received this single three milligram tablet she still looked very well and remarked that her depression had lifted far more quickly and dramatically than usual. This first episode was so unexpected that I did not observe the crucial hour after taking the tablet as closely as I did later on. A remarkable change had undoubtedly occurred but how far was leuco adrenochrome responsible for this? On the next two occasions when she needed leuco adrenochrome which were September 4th and September 22nd I was able to observe her far more closely. This is how she describes her condition on September 22nd: "Very difficult to arouse enough interest to establish contact with people. Suicidal thoughts present. A dull, tight feeling just above and behind the eyes and at base of the skull. Colors dull. Could not become interested in surroundings even with exertion of will. Air of unreality about surrounding objects. Felt they did not exist. But could not rouse from apathy enough to be interested in them or to be affected by them. Felt like crying but also felt unable to summon enough energy to do so. At supper almost started to cry when spoken to. Given DNMI by Dr. O. at approximately 9:15 P.M. At 9:40 began to feel completely neutral, neither happy nor unhappy as though there has been a cessation of everything but existence. No desires or wishes. Conscious only of breathing, physical existence. 9:45: Suddenly felt like laughing, felt a need to move about, to break spell. Feeling of unreality. Giggled several times for no apparent reason. 9:50: Felt very much alive, cheerful, wished to smile. Conscious of sudden complete mood change including physical symptoms, and somewhat bewildered by it. Felt confident I could maintain a conversation. Somewhat talkative. Colors brighter. Interested and aware of surroundings. 10:30: Relaxed feeling of sleepiness setting in. Returned home. Cheerful, alert, self-confident. Chatted with several people. Very conscious of complete mood shift and inwardly pleased and excited about it. Eight hours quiet sleep. Excellent appetite. Finished

book, light fiction, with enjoyment on September 23rd. Wished to study. No difficulty in concentration or comprehension. Realistic. Neither unduly optimistic or pessimistic attitude on problems."

My own notes taken at the time on the identical episode, written without reference to Miss G.'s notes, are: "She was clearly not well, looked tense, edgy, pallid—a tautness of the facial skin. Her words came slowly, her conversation was not spontaneous and I felt she might at any moment burst into tears. She had been well until September 20th. She said she did not feel tense, just depressed and described her condition as 'quite rough'."

21.55 hours: I gave her three milligrams of my second batch of DNMI sublingually. I gave no special suggestion except to say what she already knew, that it had helped before. She sat on the chesterfield opposite me rather stiffly, as if she was a doll stuck in one position. Her expression and voice were all slightly wooden and it was an effort to talk with her.

22:10: She made no comment and no questions asked. Shortly after this she began to *look* easier. The tautness seemed to have gone out of her face.

22:12: I asked if DNMI had dissolved and she said yes.

22:15: She laughed a little and picked up a book and began to read which she had not attempted to do before.

22:20: She spoke much more spontaneously and said about herself: "This was an unpleasant happening, out of the frying pan into the sieve." She walked around the living room into our kitchen and began to laugh. I thought she might be crying at first but she was not. She returned to the living room at 22:25 saying, "It seems very stupid to laugh at nothing." She was clearly feeling much better.

22:30: She was very talkative and cheery.

22:40: She was much more talkative and easy. Much more relaxed. Her face beams and is more mobile. Her voice has a different timbre. Discusses the unfortunate happening as, 'this very, very unpleasant business.' She did not volunteer what this was and was not pressed to do so.

22:43: Talkative, laughing, cheery, moving her hands freely.

22:45: She is asked directly, "How are you feeling?" She then said that at about 22:15 there was this "indescribable lull. You don't feel happy or depressed. Nothing good or bad. Noth-

ing right or wrong." However, this is a great improvement on her previous feeling. She now feels that she could concentrate which she could not do last night or earlier this evening. Colors look brighter.

H.O.: "When you are low they don't feel so bright?"

G.: "No, I no longer feel like crying."

H.O.: "How does this compare with the previous time?"

G.: "More like the first time I took it."

H.O.: "How?"

G.: "There was not the very sudden change I noticed the second time."

H.O.: "You were different?"

G.: "The second time I felt extremely tense but not depressed."

H.O.: "How does this compare with Dexamyl?"

G.: "The Dexamyl feels as if I were under sedation. You feel there was an artificial lid."

H.O.: "How does this feel?"

G.: "At the moment I feel there has been a rapid change." She then added that she felt relieved and happy about this because she is not used to a change in mood upward at this speed. Mood change upward usually takes a day or more.

H.O.: "Different from Dexamyl?"

G.: "Yes, definitely."

H.O.: "How about your feelings about this misfortune?"

G.: (confidently and smiling) "It will clear up."

H.O.: "How did you feel before?"

G.: "I could realize it would straighten out but I didn't really believe this. (Spontaneously) Another thing, suicide thoughts were very strong today, twice, and seemed to remain in the background. At the moment the whole thing seems pointless and there seems no good reason for wanting to do so."

23:00: She was playing with the dog at this time and smiling easily.

H.O.: "What happens when you study?"

G.: "Very little, it is very difficult to concentrate." Reading assignments which should take half an hour would take a whole evening. Last night she read two and a half pages in three quarters of an hour which she would expect to do in fifteen minutes.

23:45: When she left she was cheerful and relaxed, friendly

and talking freely. She said that she felt tired and needed a good night's sleep. She was clearly not depressed. Just before she left, she said, "I wondered whether it would work. The first time I was depressed and tense. The second time tense but not depressed. This time depressed and not tense." Clearly she had never gone from depression to normality so smoothly and quickly.

I think it proper to add that I was far from confident on this occasion but the result was clearcut and gratifying. There was no borderline improvement. In less than an hour a very depressed girl stopped being depressed. It was a dramatic and extremely convincing demonstration. At 22:00 she was obviously depressed. At 22:30 she was obviously not depressed. The breakup of her depression came between 22:10 and 22:25. It was like one of those speeded up films in which a flower suddenly unfolds in front of your eyes. It is the sort of thing one has never in fact seen before because it is not usually seen naturally and so is very disconcerting.

For the next ten months Miss G. continued to take DNMI. Apart from unusual happenings, such as being confined to bed, she appears to need about one 3 milligram tablet every fourteen to twenty-one days. At the time of writing these notes, June 10, 1959, she has taken thirty tablets in two hundred and eighty days. (Breakdown on tablets taken: Time: August 24, 1958-May 31, 1959: 280 days. Number of tablets:* 30.) In recent months she has not waited for her depression to develop fully but has taken the tablets when the first symptoms appear. She believes her life has altered substantially and she writes about her present condition in a recent note:

"When I first started taking DNMI in August, 1958, it was used only when I was noticeably depressed or extremely tense, as a treatment for a condition already present. Now (June, 1959) I am using it at the onset of a depression to prevent a depression from developing.

"Understandably, the use of DNMI has produced a marked change in my pattern of living. Over half my life (age 11-23) has been a pattern of recurrent depressions and longer or shorter intervening periods of normalcy. Thus this past ten months has been a period unlike any other that I can clearly remember.

*Including: 2 for car sickness, 6 in nineteen days bedrest, and 4 in 2 double doses in three days.

Inevitably, it has been a period of unalloyed joy at having a 'magic cure' for an unpleasant illness. Though a physician may have an almost unbounded faith in the efficacy of his treatment, his patient may not. Where the condition recurs, as depressions do, there is uncertainty whether the treatment will always effect a cure, and there is always a period of testing the limits of a new treatment too. During the last ten months I have learned that DNMI is quite effective in controlling the mood drop that usually occurs when I spend any long period in bed, but that its efficacy may be affected by certain other drugs, the exact types of which are not clear.

"Then there is the adjustment to a continuous normalcy—the reassessment of plans for one's vocation, another look at one's friendships and relations with other people, a settling down to a normal tempo of existence, that does not include preparation for periodic relative incapacity.

"As I stated earlier I now use DNMI at the first indication of a depression's onset. I feel that I can distinguish the symptoms of depression from normal mood swings and thus am not using it unnecessarily. Thus, I may feel unhappy, or not sleep well one night after an exciting evening, or notice a sharp drop in my appetite due to fatigue or hot weather, or develop soreness in the muscles of my back, arms and legs after an upsetting evening and restless night's sleep; I may feel apathetic and lacking in energy one day at work. None of these are, to me, indications of a need for DNMI. These are normal occurrences or personal idiosyncracies. Only if several of these are present concurrently and are accompanied by some disturbance of thought patterns do they indicate to me the onset of a depression.

"DNMI has not brought about any levelling of what I consider to be normal mood swings. I may be particularly enthusiastic or happy one day, lose my temper on occasion, have days in which I may accomplish a good deal, others in which I may putter aimlessly. But through using leuco, essentially as a prophylactic, I am producing a protracted 'normal period' that I now expect to continue over a period of years."

Response of Schizophrenic Patients

The response of schizophrenics is not good. Often they respond with a decrease in anxiety and tension but there may be

a marked accentuation of their schizophrenic symptomatology. This probably is due to the high concentration of these and other indoles already present in them. We do not recommend this compound for schizophrenia.

5,6-DIACETOXY-*N*-ISOPROPYLINDOLE (DIN)

5,6-Diacetoxy-*N*-isopropylindole is readily hydrolyzed to 5,6-dihydroxy-*N*-isopropylindole in vitro. The same reaction probably occurs in vivo. It is derived from isopropyl norepinephrine in an analogous way to the formation of 5,6-dihydroxy-*N*-methylindole from epinephrine.

Isopropylnorepinephrine is present in the body in small quantities in the adrenal medulla, lung and perhaps in autonomic ganglia. Its function is unknown but may be related to the production of anxiety as has been suggested by Garb *et al.* Since DNMI can quickly moderate or reverse anxiety and depression, we felt the equivalent indole derived from it might act in the same way.

In a series of subjects, we observed three general reactions of normal subjects. The dosage was 5 to 10 mg. taken orally in the evening.

Reaction A (One-third of Subjects)

Sleep was light. Often a typical twilight sleep was experienced. This we define as a state of sleep in which the sleeping subject is not quite sure that he is or is not asleep. The general tendency is to claim that he did not sleep. This condition is not infrequent in psychiatric patients and may account for the discrepancy between the patients report that he did not sleep and the nurses objective report that he had slept. This twilight sleep is accompanied by a remarkable sense of indifference to this situation. Normally when people cannot sleep they are concerned and will try various things such as reading, eating, taking sedation or tossing about. After taking DIN the subject lies perfectly relaxed and disinterested. Nevertheless, in the morning he "awakens" quickly and the remainder of the day has a sense of well being. One of us (A.H.) has described it as a feeling similar to that when one has made a scien-

tific discovery. The feeling is not one of euphoria in the manic sense. With this feeling of well being one can work more effectively and is quite relaxed. It is difficult (but possible) to become angry but one makes allowances for other people and seems to be more sensitive or empathic for other people. This is more remarkable in that it follows a night of very light sleep. The number of hours of sleep apparently matters little as this feeling of well being and alertness has followed as little as one and one half hours of deep sleep. Many subjects report they have had many dreams. This has usually been reported spontaneously. Most subjects remarked on the fact that they had not dreamt for months previously.

The following night sleep comes very readily at the appropriate time without any medication. In this case the sleep is of normal depth and no reports of either dreams or twilight sleep have been received. The feeling of well being may continue up to three days when it is followed as one subject put it "On the fourth day I just felt ordinary, worst luck." There is no rebound into apathy or depression.

The subjects who react in this way do so every time they take the compound. The only disadvantage of this type of reaction is the twilight sleep. This may be overcome by taking along with DIN a quick acting barbiturate such as seconal sodium.

Subjects who have steadily had Reaction B to be described below may occasionally have Reaction A. One subject took 5 mg. DIN five days after an LSD experience which turned out badly. She did not sleep the entire night. However the next day she felt as if she had slept normally.

A.H. October 14, 1958: 10 mg. DIN at 10:00 P.M. He slept fitfully and was up several times during the night as R. had a severe cold. He was not irritated by being up. He awakened at 8:00 A.M. and felt refreshed and relaxed.

October 21, 1958: He awakened at 5:00 A.M. for an emergency and worked until noon when he became very sleepy. He took 5 mg. DIN sublingually (for rapid effect) at 12:45 and slept in ten minutes until 1:15 P.M. He awakened alert and refreshed. Usually such a short sleep leaves him groggy and irritable. He remained refreshed and alert all day and continued working until 12:00 midnight. He slept well.

November 5, 1958: 5 mg. orally at 7:00 P.M. He worked until 2:00 A.M. and then went to bed. He did not sleep well (twilight sleep). He awakened easily and refreshed. He was much more cheerful and alert than was warranted by the lack of sleep.

Reaction B (One-third of Subjects)

In this type of reaction, the subject falls asleep normally about one half to one hour after taking DIN. The compound induces a sense of relaxation and normal fatigue that is common after a useful and hard working day. The sleep which follows is of normal depth and dreams are not common. The next day there is the same sense of well being as described for reaction A. This may continue several days.

S.W. This resident had developed marked tension of several months duration due to his having given up a busy practise which had kept him very busy, due to his uncertainty and insecurity in his new profession but above all due to great personal involvement in an illness in a member of his family. He complained that he was tense, could not read or study and could not sleep well.

On November 4, 1958, he was persuaded to take some DNMI with encouragement that it would relieve his tension as it had done in others. He received 6 mg. per day for three days. He reported that he had noticed no effect from it whatsoever. He was then given DIN with the statement "since you have failed to get relief from leuco, try this. It helps some people." He agreed to try it but privately did not think it would work. At 10:00 P.M. he took 10 mg. DIN. Since he did not think it would work he began reading a book. To his surprise the next thing he noticed was his awakening in the morning feeling much better. The chronic anxiety of the past few months was now gone. At work he was very alert, cheerful and relaxed. Since that time his tension and anxiety have not recurred and he has been sleeping well.

M.J. This subject has been taking 5 mg. DIN about every ten days since October 5, 1958. She has responded the same way each time by falling asleep within the hour and awakening refreshed and alert. During this time she has taken practically no barbiturates and only one highball each evening. Before this

medication was started, she took between 200 to 400 mg. of barbiturate nearly each evening accompanied by two to three highballs before falling asleep. During this interval this subject has had the feeling of well being described above which she had not had for ten years.

Reaction C

In this type of reaction, sleep is of normal intensity but prolonged into the morning. Two subjects felt sleepy all morning. They had no sense of well being the remainder of the day.

Synthesis

The evidence presented indicates a close relationship between the sympathetic nervous system, its amine hormones, anxiety and mood. It may be summarized as follows:

1. The amines are essential for active life. They act as stimulants and anti-depressants. Until recently the best chemical stimulants were substances like benzedrine. These substances have some similarity to epinephrine in chemical structure.

Recently new classes of compounds have been developed. They inhibit amine oxidase and in effect increase the efficiency of these amines. Reserpine depletes sympathin stores as well as serotonin. However, reserpinized animals are reactivated only by these amines or their immediate precursor, but not by serotonin, or 5-OH tryptophane, its antecedent. Increasing the complexity of the side group on the indole nitrogen from norepinephrine to isopropylnorepinephrine increases the anxiety or tension producing property.

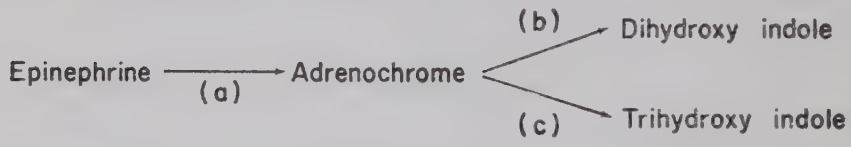
2. Adrenochrome, one of the immediate derivatives of epinephrine, decreases anxiety in normal subjects and in patients and is clearly related to the mechanism of action of LSD. In a few cases subjects given LSD do not show any increase in plasma adrenochrome. These subjects remain very tense and anxious. Injection of adrenochrome solutions intravenously markedly reduces the anxiety.

3. Adrenolutin, a derivative from adrenochrome, also reduces anxiety. It is however often associated with undesirable psychological changes.

4. 5,6-Dihydroxy-*N*-methylindole, the dihydroxy indole derivative of adrenochrome, reduces tension and anxiety. This it does by removing the person's awareness of tension. Therefore it has no effect on a person already free of anxiety.

5. 5,6-Dihydroxy-*N*-isopropylindole, derived from N-isopropyl norepinephrine, results in a mild disturbance in sleep followed for some days afterwards by a feeling of well being. The feeling of well being is present even if the sleep is superficial.

These observations can be accounted in this way:



Pathways (a) (b) and (c) are catalyzed by enzymes.

The preferred pathway of epinephrine oxidation as related to anxiety is through reactions (a) and (b). Epinephrine has the role of maintaining drive, interest and emotion. Dihydroxy indole has the role of protecting against the anxiety caused by epinephrine. Adrenochrome is an unstable intermediate and adrenolutin seems at present to be an unnecessary chemical with undesirable properties.

The level of anxiety depends upon the ratio of epinephrine to the dihydroxy indole, i.e. $\text{Anxiety} = \frac{\text{epinephrine}}{\text{dihydroxy indole}}$

The normal mediation of anxiety therefore depends upon an adequate conversion of epinephrine through adrenochrome into dihydroxy-*N*-methylindole so that their ratio remains within certain limits. When there is too little DNMI or too much epinephrine, the subject will be anxious.

Theoretically, it follows that three biochemical types of anxiety are possible. These will be defined chemically in terms of an anxiety ratio which is the ratio of epinephrine to DNMI. A high ratio indicates there is more epinephrine than can be neutralized by DNMI.

A. Excess Production of Epinephrine

1. Inadequate conversion to DNMI. The anxiety ratio is high

and the anxiety level will be out of proportion to the exciting event. The abnormal anxiety breeds more anxiety by interfering with the persons social relationships. This in turn aggravates the existing anxiety. Such a reverberating cycle can become autonomous and will then continue until it gradually dampens down or is blocked by direct interference from treatment.

If the block occurs at enzyme "a," the net result will be anxiety with no thought disorder. If the block occurs at reaction "b", the excess adrenochrome may be diverted into adrenolutin resulting in some relief of the anxiety combined with some changes in thought. If prolonged this might lead to schizophrenia. This will be considered in detail in the next section.

This equation provides a rational explanation of the different diurnal rhythm of depression and schizophrenia. Many people suffering from depression[1] and anxiety suffer most shortly after awakening. During the day their anxiety decreases and their mood becomes more normal. By evening they may feel relatively well. The next day the cycle is repeated. Arising in the morning is associated with increased secretion of epinephrine. The simple act of changing one's position from prone to erect increases epinephrine secretion in the urine five-fold, Sundin (1958). Thus at this time the anxiety ratio is high. During the day the production of DNMI will slowly continue and by evening the anxiety ratio will be low. During sleep these beneficial indoles will be excreted and result in a fresh cycle the following day. Early morning awakening, a very important symptom, may be due to an early secretion of epinephrine.

Cameron (1958) reported that when the depression had lifted during the day sleeping at that time for even one hour may bring back the depression. In sharp contrast schizophrenic patients tend to have their most lucid moments after arising, Naumova (1939) and become more schizophrenic as the day continues. In them the increased secretion of epinephrine is followed by additional accumulation of adrenochrome and adrenolutin.

2. Oversecretion of epinephrine and adequate conversion to DNMI. In this system the increased secretion of epinephrine is

[1]Some depressions have the opposite diurnal rhythm. This will be discussed further on.

followed by a rapid conversion to DNMI. Since the anxiety ratio is normal these people will feel normal anxiety. It is difficult to know what would be the resultant clinical condition but we would guess this would result in mania. It has been shown that mania is associated with very high excretion of epinephrine. Clinically, people during the manic phase feel alert, euphoric and active and show little of the lethargy so typical during the depressed stage. They are also tense, irritable and impatient.

B. Normal Production of Epinephrine

1. Inadequate conversion to DNMI. This is similar to A. 1. above.

2. Adequate conversion to DNMI. This is the normal condition.

3. Excess conversion to DNMI. Excess dihydroxy-*N*-methylindole might be formed with normal production of adrenaline if the process should become unusually efficient. This condition could be duplicated by giving excess DNMI. This has inadvertently occurred in three of our subjects.

Miss D.G. received 6 mg. per day (in two doses) for three days. The anxiety and tension had vanished after her first medication. Four days later she developed a strong sense of unreality in the absence of tension. This feeling disappeared twenty four hours after the tablets were discontinued.

Miss G. being curious whether it was possible to take too much took 3 mg. when feeling well. That same evening she had about two and a half ounces of vodka. Vodka normally when taken with her meals does not have much effect upon her. Four hours after taking DNMI, she was restless and irritable and paced restlessly. Within one hour she became quite cheerful and talkative. Her pulse was 115 and respiration rate 40 (normally they are about 60 and 15). She felt so alert and active that she stayed up and worked all through the night. The next day she was cheerful and felt as if she had had a very restful night's sleep.

Between 10 A.M. and 5 P.M. she became aware of a change in her vision. The visual field was covered by a plaid pattern consisting of reds, yellows and greens. This pattern was in constant movement and obscured real objects. In addition, everything seemed two dimensional. She was restless and easily irritated.

About 7 P.M. she became aware of great fatigue. Several times she fell asleep during the evening. She slept from midnight to 7 A.M. and was again normal.

Mr. W.B. had taken 6 mg. DNMI per day for two and one-half months and felt extremely well for the first time in twenty five years. He then attended a three day convention where he played a leading role as speaker, etc. He reported later "It was just about the most strenuous three-day activity in my whole experience." He enjoyed the meeting, and felt he had escaped unscathed. During this time he took 9 mg. per day.

He then started on his vacation. After a day he felt detached and mentally sluggish. After one week pain from chronic bursitis returned which had disappeared soon after he had started on DNMI. He became lame and suffered chronic generalized pain as if he had grippe. Finally he developed a catarrhal drip, hoarseness and cough. These were barely present in the morning but came with increasing severity in afternoon and evening. After three weeks (he had continued to use 6 mg. DNMI per day) he discontinued the tablets. Within one day he felt better and noted more interest. Within one week his catarrhal drip was gone but some cough remained. He returned to work but felt pleasantly lazy having "a cow-like complacency." This is most unusual for him. In three weeks he was normal and as well as he had ever been while on DNMI.

C. Insufficient Epinephrine

1. Under production. Although we have not yet seen this described in psychiatry, we suspect that it is not rare. So far as we know no one has looked for it. Perhaps this is the condition associated with those listless and apathetic states commonly found in a group of patients labelled neurotics. These patients do not suffer from tension and anxiety, but might feel sad and be depressed. Their chief difficulty would be a lack of energy and drive. Thus the morning would be difficult as the normal outburst of epinephrine would be lacking. During the day some epinephrine would build up and their inertia would tend to vanish. It would be easy to confuse these patients with those depressions associated with anxiety and tension. However, there should be no physiological manifestations of anxiety, i.e. an absence of perspiration, no rapid pulse, etc.

This condition could be reproduced by administering chemicals which remove epinephrine. Reserpine is such a compound. Reserpine rapidly lowers the amine content of the brain and of other amine depots. In animals depletion can be so marked there is not enough present to allow transmission across sympathetic synapses. Serotonin is also depleted but this does not seem fundamental. Reserpinized animals quickly regain their activity if given marsilid plus epinephrine, benzedrine, epinephrine alone or dihydroxyphenylalanine, a precursor of epinephrine. Neither serotonin nor its precursor 5-hydroxy tryptophane counter the reserpine inactivity.

A proportion of patients who receive reserpine for many months become depressed. This has usually been considered to be a type of psychotic depression. Ayd (1958) who has objected vigorously to this term, believes these patients are apathetic and disinterested rather than depressed in the usual psychiatric sense.

In addition, extreme fatigue may deplete epinephrine stores. Part of the syndrome of severe fatigue may be due to a lack of epinephrine.

Nicotinic acid may decrease epinephrine levels. It has been used for the treatment of schizophrenia and for lowering cholesterol levels. Thompson and Proctor (1953) used a combination of nicotinic acid with phenobarbital to treat depressive and anxiety reactions. One third of the patients were improved. However a few people become extremely apathetic and say that they feel depressed after taking nicotinic acid.

This condition is best treated by using sympathomimetic amines such as amphetamine or methedrine. Amine oxidase inhibitors would decrease the destruction of epinephrine and should be very useful in the treatment.

2. Over utilization. In this condition there is a too rapid rate of destruction of epinephrine. The supply of epinephrine which is formed rather slowly (large stores are available for immediate emergency use) cannot keep up with its requirements.

Hoffer and Callbeck (1960) recently observed an unusual reaction of a volunteer to LSD following two days treatment with penicillamine. Penicillamine is $\beta\beta$-dimethyl cysteine and is a well known chelating agent. It is used to bind excess heavy metals in

cases of poisoning or to bind copper in Wilson's disease. Penicillamine destroys adrenochrome in vitro by converting most of it into 5,6-dihydroxy-*N*-methylindole, Heacock (1959). It was thought that pretreatment with penicillamine for several days would protect the subject against LSD because adrenochrome would not build up in the plasma (as when given ascorbic acid) but in addition the quantity of adrenolutin would be kept down.

However, the reaction was most unexpected. This subject had had LSD twice before, the last one about a year before this experience. Her affect was in both cases maintained and she was able to feel keenly fear, horror, euphoria or great interest. This time she had the usual visual reaction but there was no affect whatsoever. She reported that she was not able to feel anything, neither fear, nor sorrow, nor terror, nor interest.

Five days later she developed marked autonomic disturbances. She became very cold, her pupils remained pin point for the whole five days. She suffered from a lack of perspiration, extreme dryness of mucous membrane, and her pulse was slow. At this time she was placed upon methedrine. For the next five days she required about 30 mg. per day. Each time she took 10 mg. there was the following reaction. Within one to two hours she began to feel warm, her skin lost its vasoconstrictive pallor, her pupils dilated to about 1/3 of the corneal size, and she began to experience some feeling. There would be a short period of energy and interest. In about two hours her chill would return, her skin would develop its former pallor, her hands become cyanosed and her pupils became pin point and once again all feeling disappeared.

This sequence was observed about twenty times for about two weeks after the initial experience when she became normal but easily fatigued.

It seems very likely that she suffered from an insufficiency of epinephrine. When epinephrine levels are depleted by reserpine in animals, it requires about two weeks before they become normal. It took approximately two weeks for this subject to recover.

It is thus possible that some schizophrenics may convert too much epinephrine to adrenochrome and suffer from its lack. This may explain their complaint of "no feeling," their apathy, indifference and disinterest.

This condition would best be treated by decreasing the over utilization of epinephrine, e.g. amine oxidase inhibitors and by administration of sympathomimetic amines.

This brief outline is simply a working hypothesis derived from our findings. We cannot tell whether it is right or wrong. However, certain predictions are possible. This is shown in Table 8.

As the biochemical knowledge of the human indoles expands it will become possible to test these predictions.

Sulkowitch, Perrin and Altschule (1957) have developed a method for measuring "epinephrine" which includes epinephrine, norepinephrine, trihydroxyindoles and 3,5-dihydroxy-6-oxy indoles

TABLE 8

AMOUNT OF EPINEPHRINE AND ITS INDOLES IN URINE OF VARIOUS PSYCHIATRIC CONDITIONS

Condition			
Epinephrine	*Adrenochrome*	*DNMI*	*Urine Will Contain*
A. High	1. Low	(i) low anxiety state depression	1. much epinephrine 2. little di or tri hydroxy indoles
	2. High	(ii) low anxiety and schizophrenia	1. much epinephrine 2. much trihydroxy indole
		(iii) high schizophrenia (little anxiety)	1. much epinephrine 2. much di and tri hydroxy indoles
B. Low	1. Low	(i) low (normal)	1. little epinephrine 2. little di or tri hydroxy indoles
	2. High	(ii) low (schizophrenia)	1. little epinephrine 2. much trihydroxy indole
		(iii) high (schizophrenia)	1. little epinephrine 2. much di and tri hydroxy indoles

as well as other catechol amines. Using their method, we would expect high values for all the conditions listed in Table 8 except B. 1. (i) the normal condition.

For a series of forty five controls, they found a mean excretion of 20±2.9 (range 0 to 59.5) μg per hour. The psychiatric patients who included schizophrenic, depressed and anxious people showed values greatly in excess of this, even approaching those seen in phaeochromocytomas. For eight patients depressed or anxious, the mean excretion was 578 μg/hour (range 119 to 1184) and for fourteen schizophrenics was 466 (range 0 to 800). These values are calculated from Table 1 of the article by Sulkowitch *et al.*

Schizophrenics excrete about the same quantities of these substances as other very anxious patients. The authors remark "neurotic patients with high values seemed in general to be more anxious and more subject to excess perspiration and palpitations. Such a relation was not so evident in the psychotic group" and "the finding of increased 'epinephrines' in neurotic and psychotic patients raises, of course, the question why physiological and biochemical abnormalities are observed less frequently in this group than in patients with phaeochromocytomas. This question cannot be answered fully; however, one fact might be the increased rate of oxidation commonly found in schizophrenia."

The scheme we have described here predicts that this would be the case. Table 8 shows that in anxiety states and depressions most of the "epinephrines" will be epinephrine and norepinephrine. There should therefore be a good relationship between high epinephrine and its physiological expression. In contrast, schizophrenics have either little or much epinephrine so that their "epinephrines" will contain varying quantities of epinephrine, i.e. some schizophrenics with high "epinephrines" may come from group A. 2 (ii) with much epinephrine or from Group B. 2 (ii) with little epinephrine. ("Epinephrines" is the sum of epinephrine and di and trihydroxy indoles.)

Similarly in most schizophrenics since high "epinephrines" are not synonymous with high epinephrine, one can find the curious situation queried by these authors, i.e. a situation marked by high "epinephrines" but no physiological signs of anxiety. The

tentative explanation put forward by Sulkowitch *et al.* seems reasonably good.

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Chapter 5

CHEMICAL TREATMENT OF DEPRESSION AND ANXIETY

The many and diverse chemicals used to allay anxiety and to treat depression appear to have little in common with each other. That so many different substances are effective to a greater or lesser extent suggests that they act by some final common pathway. Antidepression drugs may be divided into several classes: (1) substances which resemble epinephrine in structure, (2) substances which inhibit enzymes known to metabolize epinephrine, (3) substances which decrease the concentration of epinephrine in the blood, (4) substances which reduce the reactivity of receptors to epinephrine, (5) indoles, (6) acetyl choline like compounds, (7) acetyl choline esterase inhibitors.

In brief, chemicals which increase the production or concentration of epinephrine-like substances (factors 1, 2, 6 and 7) and those which remove epinephrine (factor 3) or buffer the body against it (factors 4 and 5) are all used in the treatment of depression and anxiety. It appears to make little sense. However, if we recall the discussion in the previous chapter on the two types of depression, things become more logical. Depression which is a mood may be associated with too much epinephrine and is a response to anxiety or with too little epinephrine accompanied by apathy, disinterest, etc. These different forms of low spirits will be termed anxiety depressions and anergic depressions. The anxiety depressions will respond to treatments 3, 4 and 5 while the anergic depressions will respond to treatments, 1, 2, 6 and 7. Some compounds may be effective for both types, for example, Marsilid which increases the activity of epinephrine thus assisting the anergic depressions and increases the production of 5,6-dihydroxy indoles which would be useful for the anxiety depressions.

ANERGIC DEPRESSIONS

A. Epinephrine-like Compounds

Many compounds which are now being used for treating depression and anxiety have chemical configurations very similar to epinephrine. The epinephrine molecule can be seen in them. Apparently enzyme receptors are avid for these compounds which can act as substitutes for epinephrine. Since they are not natural mammalian metabolites, they are eliminated with greater difficulty than epinephrine and thus will have quite different properties. They will share the ability to be stimulants.

There are five main classes of epinephrine-like substances: (a) the benzedrine or methedrine group, (b) the piperidines, e.g. pipridol and ritalin, (c) tofranil, (d) the benzoquinolizines and (e) the indoles.

The first three groups of substances activate anergic patients and energize fatigued normal subjects. If given in excess, they cause tension, anxiety and psychosis usually characterized by overactivity. They are not indicated for the anxiety-depressions. The benzoquinolizines and indoles will be discussed later.

1. The Sympathomimetic Amines

These are the best known. In general, amphetamine, methedrine, dexedrine, etc. are most useful for the anergic depressions. If taken to excess they produce agitated states and even schizophrenic-like psychosis. They are less useful for treating agitated depressions. This is why they have been combined with barbiturates, e.g. dexamyl. The amytal is given to counter the excitant action of benzedrine.

2. The Piperidines

These compounds like Meratran or ritalin are more modern anti-depressants. They act very much like the sympathomimetic amines.

3. Tofranil

This is the first member of a new class of anti-depressants. It acts very much as does Marsilid but is somewhat less toxic. Apparently it is most satisfactory for the anergic depressions.

4. Benzoquinolizines

This is a psychosedative which has some promise. In animals and man, it produces tranquilization similar to reserpine. It decreases serotonin in brain. Also it depresses appetite in man. The structural similarity of this compound to epinephrine suggests it may act by replacing epinephrine. Similar compounds are found in Peyote where they may modify the action of mescaline.

B. Substances Which Inhibit Enzymes Which Act on Epinephrine

The compounds related to ephedrine were originally considered to be inhibitors of amine oxidase, one of the enzymes known to destroy epinephrine and norepinephrine. It is now believed this inhibition is not their major mode of activity. Certainly they do not compare in potency as an inhibitor with iproniazide and some of the more recent semicarbazide compounds.

1. Marsilid

Iproniazide (Marsilid) is the best known inhibitor. It was until recently the most active inhibitor of amine oxidase, Zeller and Barsky (1952). It was natural to assume its activating or euphorient action was due to the accumulation of amine oxidase substrates including norepinephrine, epinephrine and serotonin. Since these amines are more clearly involved in the production of anxiety, it would be expected they would be implicated as the most likely substrates. Strangely serotonin was first suggested as a mediating factor for Iproniazide activity. The relationship of the amines and serotonin to mood is shown in Table 9.

TABLE 9

RELATIONSHIP OF SEROTONIN, NOREPINEPHRINE AND EPINEPHRINE TO MOOD

Response	*Serotonin*	*Norepinephrine*	*Epinephrine*
1. Anxiety	No	No	Yes
2. Euphoria	No	No	Yes
3. Positive reward	No	No	Yes
4. Positive reward after Iproniazid	No	No	Yes
5. Antagonism of Reserpine Depression	No	Yes	Yes

Neither serotonin nor norepinephrine are related to anxiety and tension, nor do they produce euphoria. Epinephrine infusions following treatment with Iproniazide produced euphoria in eight of ten volunteers, Friend (1958). Apparently Iproniazide converts the tension of the epinephrine into euphoria since epinephrine alone aggravates anxiety.

The positive reward self-stimulation experiments may be a useful analogy in animal behavior for human euphoria. It seems reasonable, although one cannot be dogmatic, that substances which increase the rate of self-stimulation may be considered as euphorizing drugs for the animals, at least they come back for more. Olds and Olds (1958) and Eiduson (1958, 1959) found that Iproniazide was positively rewarding as was epinephrine. But neither serotonin, its precursor 5 hydroxy tryptophan, nor norepinephrine produced any reward. Olds and Olds concluded that Iproniazide "is an excitant of reward functions in this motivational system of the hypothalamus with and that quite probably it has this excitatory function in common with epinephrine." This is supported by Carlsson, Lindquist and Magnusson (1958) and Everett and Toman (1959) who found that depletion of norepinephrine and epinephrine was correlated with decrease in motor activity produced by reserpine. Reserpinized mice and monkeys in a state of inactivity and catatonia were immediately restored to normal activity by injections of small doses of desoxyephedrine or dihydroxyphenylalanine (norepinephrine precursor) but not by serotonin or its precursor 5-hydroxy tryptophan. Marsilid potentiated the sympathomimetic effect.

Apparently norepinephrine and epinephrine are more closely linked to central activity than is serotonin. Holzbauer and Vogt (1956) reported that reserpine markedly decreased norepinephrine levels in the hypothalamus of the cat and in the adrenal medulla but not in the denervated medulla. Amphetamine also released serotonin as did reserpine. Amphetamine antagonized the quieting effect of reserpine, Plummar, Maxwell, Ross and Furness (1958).

Serotonin levels are increased in the brain by the following pharmacological substances (1) tranquilizers, e.g. reserpine, (2) anti-convulsants, Bonnycastle, Giarman and Paasonen (1957), (3) central nervous system depressants, e.g. pentobarbital; Anderson,

Hutcheon and Bonnycastle (1958) found that 50 mg/kg of pentobarbital doubled brain serotonin levels five minutes later at a time when the animal was so anesthesized the righting reflex was gone, (4) central nervous system stimulants, e.g. amphetamine, (5) 5-hydroxy tryptophan.

Pletscher, Besendorf and Gey (1959) reported that two closely related benzoquinolizines had a similar action on brain serotonin levels but were not equally active on norepinephrine levels. The compound which reduced norepinephrine levels more profoundly had marked sedative properties and prolonged ethanol sleeping time 110 minutes. The other substance which was less active in decreasing norepinephrine had some slight sedative action and prolonged ethanol sleeping time only 7 minutes. They conclude "the pharmacological effects of compounds I and II in the central nervous system may possibly be related to the depression of norepinephrine but probably not to that of 5-hydroxy tryptophan (serotonin)."

It seems that there is no relationship between these five psychological and activity parameters and serotonin. Norepinephrine is related to one and epinephrine to all five. It is difficult to see how one could account for all these changes by means of an excess or lack of serotonin.

5-Hydroxy tryptophan produces excitement in some animals, Udenfriend, Bogdanski and Weisbach (1956), but an overactive animal is not strictly comparable with a happy person. Pharmacologists often write as if an inactive animal is necessarily the equivalent of a calm or tranquil human being and an overactive animal a cheerful and contented one. Yet we know very well from common experience and clinical observation that cheerfulness need not coincide with bodily movement while immobility does not imply any calmness. Indeed depression and utter despair may occur in people who are so inert as to be almost stuporose or greatly agitated and moving constantly. While euphoria and ecstasy may be associated with much movement as in most manic illnesses or with complete inactivity in some catatonic states, in mystical experiences and in the rare manic stupors. While serotonin must play some part in the workings of the brain there is little evidence to suggest that it is related to mood change in particular.

It does not seem likely that the accumulation of epinephrine in itself is responsible for euphoria, for excess epinephrine in the brain ventricles induces anesthesia, Leimdorfer and Metzner (1949). Perhaps Iproniazide by blocking amine oxidase forces epinephrine into another pathway. Axelrod, Inscoe and Witkop (1958) reported that Iproniazide increased the conversion of epinephrine into methoxy epinephrine in rats from 25 to 50 percent. Other possible pathways might lead to the production of epinephrine sulfate or to adrenochrome, Kaufmann and Koch (1959), and to an indole family of compounds. The euphoriant activity of Iproniazide may therefore be due to a diversion of epinephrine or methoxy epinephrine to adrenochrome or its derivatives.

In 1957, Hoffer suggested that anxiety and tension were functions of the ratio epinephrine to adrenochrome and its family of compounds. It should follow from this that adrenochrome and its family of compounds are antitension or euphoriant compounds and that Iproniazide may act by increasing the amount of adrenochrome formed or preventing destruction much as does LSD, Hoffer (1959), Hoffer, Smith, Chwelos, Callbeck and Mahon (1959).

Axelrod (1958), Labrosse, Axelrod, and Kety (1958) and Resnick, Wolfe, Freeman and Elmadjian (1958) have indeed shown that when huge quantities of Iproniazide are given (100 mg/kg or 7 grams per human) that the output of methoxy epinephrine goes up greatly. But since such a dose is much larger than those used therapeutically, it is difficult to decide what this implies.

Hoffer (1958) found that Iproniazide altered adrenochrome tolerance markedly. The effect of two days treatment (150 mg/day) is shown in Table 10.

When adrenochrome is injected into the blood of animals, Fischer and Landtsheer (1950), Fischer and Lecomte (1951) and Kaufman and Koch (1959), it is quickly converted into adrenolutin and other substances. Adrenochrome is changed by human plasma to adrenolutin, Hoffer and Kenyon (1957). Apparently similar changes take place when it is injected into humans. Table 10 shows how much adrenolutin is formed before and after treatment with Iproniazide. It can be seen that neither the conversion of adrenochrome into adrenolutin nor the rate of destruction of adrenolutin

TABLE 10

EFFECT OF IPRONIAZID ON ADRENOCHROME LEVELS IN PLASMA AFTER INJECTION OF 10 MG. AND ON FORMATION OF ADRENOLUTIN

	Before Iproniazid				*After 2 days Iproniazid*			
	Time, minutes							
N	*0*	*15*	*30*	*60*	*0*	*15*	*30*	*60*
	Adrenochrome μg/liter							
6	90	234	77	112	91	134	100	67
	Adrenolutin μg/liter							
6	—	264	122	29	—	250	91	73

was changed by Iproniazide. Over the latter half of the test adrenolutin decreased from 264 to 29 μg/liter, while after Iproniazide it decreased from 250 to 73 μg/liter. Although Iproniazide increased the rate of destruction of adrenochrome in blood during the first half hour of the test, yet the same amount of adrenolutin was formed. This we suggest shows that the adrenochrome goes somewhere else.

Adrenochrome is converted in aqueous solution into dihydroxy and trihydroxy indoles by some reducing materials such as ascorbic acid, glutathione, cysteine and others, Heacock and Laidlaw (1958). Ascorbic acid decolorized adrenochrome very quickly in alkaline medium. This product has been called leuco adrenochrome. It may undergo further chemical change to form other dihydroxy indoles. Since Iproniazide markedly increases the destruction of adrenochrome without increasing the quantity of adrenolutin, it is possible there is an increase in the production of the dihydroxy indoles or leuco (colorless) substances.

Hoffer (1957) suggested that anxiety or tension depends upon the ratio of epinephrine to adrenochrome. We now suggest that tension is related perhaps more closely to the ratio of epinephrine to some of these still little known dihydroxy indoles. Iproniazide may then reduce tension and depression associated with it by increasing the amount of these substances in the body. The slow action of Iproniazide may be accounted for by supposing that with

the known concentration of adrenochrome in the brain this transformation may take some time.

There was a curious difference in clinical response to the combination of adrenochrome and Iproniazide. All the schizophrenics became clinically much worse over the two days they received Iproniazide. Before Iproniazide, adrenochrome produced relaxation but an increase in visual changes. After Iproniazide visual changes were rare and there was little relaxation. In contrast, the neurotic patients either felt better or showed no change. As with the schizophrenics, visual changes were less frequent. After Iproniazide the same degree of relaxation occurred.

In one subject who had reactive depression, the adrenochrome tolerance curve was changed from one which is within our range of normality to one which resembles that seen in schizophrenia. It may be that this is what happens to those patients who develop schizophrenic-like symptoms after receiving Iproniazide for some time.

We suggest that the antidepressive activity of Iproniazide may be due to increasing the amount of dihydroxy indoles in the brain. If this does not occur, then adrenochrome metabolism shifts towards the formation of trihydroxy indoles producing a "toxic psychosis" which closely resembles schizophrenia.

2. Cocaine

"All this related to that wonderful plant erythroxylon coca which Francesco Pizarro in 1533 found in general use as a euphoric when setting out from San Miguels Bay he penetrated with his troops into the interior of Peru. According to the Indian legend narrated by Garcilasxo de la Vega the children of the sun had presented man with the coca leaf, after the formation of the empire of the Incas, to "satisfy the hungry, provide the weary and fainting with new vigour and cause the unhappy to forget their miseries." It is probable however that the Indians already cultivated the plant before they formed a federation, and the Incas invented the story of its divine origin in order to reserve it for themselves. They made of it a royal emblem. The queen called herself Mama Cucà, and the priests assisted in upholding the divine honours of the plant by using it in various religious ceremonies. The idols of the

time as a sign of divinity were represented with one cheek stuffed with coca leaves. Its use gradually extended to the people and it was not only applied for supernatural purposes but for the very worldly object of allowing the plant to act on the organism. Time has changed nothing in this state of affairs except that the desire for pleasurable sensations now forms the principal motive for the use of the leaves in South America and of cocaine, their derivative in the rest of the world."

"Coca is for the coca-eater the source of his greatest delight. Under its influence the troubles of life are forgotten and he experiences in imagination many of the substantial pleasures which reality refuses to give. After breakfast and before going to work he takes some coca from his leather bag and some lime or ashes from his gourd and moulds a fragment and sometimes lays up a stock of these small lumps. Between 25 and 50 grains is a moderate daily consumption. While chewing he strives to remain idle. An apathetic feeling of internal peace from which he can not be awakened overcomes him for about an hour."

These quotations from Lewin tell of that remarkable plant coca. Lewin warned against the use of cocaine. His warnings were fulfilled as the habit of cocainism spread. Cocaine is an addicting drug and is no longer recommended for use as an euphoriant. It is historically interesting that Freud, the founder of psychoanalysis was much excited about the remarkable properties of cocaine. He often urged his betrothed to use this unusual substance. Of course, its vicious properties were not recognized. A compound modelled upon cocaine would be very welcome to psychiatry if its fangs were removed.

Seevers (1958) distinguishes two sorts of cocaine addicts, those who use moderate or even excessive quantities every day and those who occasionally take enough to produce intoxication to the point where psychosis develops.

The coca-chewing Indian of South America is an example of the first kind. The user experiences a pleasurable state, freedom from anxiety, pain, hunger and fatigue so that life for them loses some of its suffering. Long continued use often leads to intellectual and general physical deterioration. Cocaine snuffing also falls

into this group. The second sort of addict often found in the United States uses cocaine by intravenous injection intermittently. The addict experiences an intense feeling of pleasure and delight associated with increased physical ability and the abolition of fatigue.

Mode of Action

Cocaine is an euphoriant drug of very wide use. It would be used much more if it were not for its addictive properties which lead to mental deterioration. If we understood how it worked, we might be able to synthesize substances which while retaining its good properties avoided the dangerous ones.

Cocaine stimulates both the autonomic and the central nervous system. The central nervous system does not develop tolerance to cocaine. Cocaine appears to sensitize the brain to epinephrine so that it responds to smaller quantities. The addict develops marked states of excitement and therefore uses depressants to counter this. It has been suggested that cocaine sensitizes the sympathetic nervous system to epinephrine perhaps by inhibiting amine oxidase. This would put it in the Marsilid class. However, the evidence is by no means clear. According to Weatherby and Haag (1958) there is no certain explanation for cocaine's action. Torda (1943) found that it inhibits the enzyme which forms a sulfate ester from epinephrine. Perhaps cocaine acts by partially inhibiting two of the enzymes which destroy epinephrine. Rothballer (1957) reports that cocaine and metamphetamine lower the threshold of the reticular activating system to epinephrine. In large quantities they both produce a sustained activation which is abolished by destruction of the mesencephalic tegmentum. He suggests cocaine acts by sensitizing the adrenergic component of the reticular activating system.

C. Acetylcholine-like Substances

1. Arecoline

Acetylcholine stimulates the sympathetic ganglia to secrete norepinephrine and epinephrine. Repeated administration can deplete the adrenal medulla, Butterworth and Mann (1957). It should therefore be useful in the treatment of anergic depressions

and in other inactive states where there is a deficiency of epinephrine. Pfeiffer and Jenney (1957) found that pilocarpine and arecoline, both cholinergic drugs, and eserine, an indole acetylcholine esterase inhibitor, inhibit conditioned response in rats. This was prevented by atropine. When schizophrenic patients were given subcutaneous doses of arecoline and methyl atropine, they developed lucid intervals of short duration (15 mg. arecoline plus 3 mg. methyl atropine). Methyl atropine is used because it protects the peripheral body against the toxic mucarinic action of arecoline but allows the muscarinic activity to continue in the brain. However, pilocarpine and arecoline also stimulate the sympathetic autonomic nuclei, thus involving epinephrine as a possible mediator. In a further report Fulcher, Gallagher and Pfeiffer (1957) confirmed these findings but pointed out that arecoline was not more effective than amobarbital or carbon dioxide inhalations in producing such lucid moments. Andel (1958) reported that eserine (5 mg.) following probanthine (20-25 mg.) temporarily removed catatonia from schizophrenics without affecting the disorder of mood and thought. There was no effect on hysterical or encephalitic catatonia. Atropine, alone, made the catatonia worse.

Arecoline is the active ingredient of Betel, a euphoriant consumed by many millions regularly. Lewin states "to cease to chew betel is for a betel-chewer the same thing as dying. The greatest privations and suffering of human life, insufficient or bad nourishment, hard work, rough weather and illness lose their disagreeable character before the comforting action of betel."

Lewin considered betel was a mild excitant with narcotic and stimulating properties. It is less objectionable from a toxicological point of view than alcohol and tobacco. The ill consequences are trifling.

2. Deaner

Deaner is an organic salt of 2-dimethylaminoethanol. It is methylated in the body to choline, one of the precursors of acetylcholine, and may increase the synthesis of acetylcholine. In common with acetylcholine it lowers the convulsive threshold for audiogenic seizures in rats.

Deaner is a mild stimulant used to counteract lassitude, fatigue

and depression. It increases muscle tone, improves power of concentration. Subjects report they require less sleep and are more alert in the morning. It appears to be best for moderate depression and states of lassitude. According to preliminary reports about seventy percent of patients are improved. Side effects are rare and include muscle tenseness, over alertness and insomnia.

D. Inhibitors of Acetylcholine Esterase

The Xanthines including caffeine from coffee and the kola plant, theobromine from cocoa and theophylline from tea, are mild inhibitors of esterase. These are central stimulants used by the millions of pounds in these beverages. They are gentle and are not followed by a let down period. According to Brooks, Ransmeier and Gerard (1949) their action cannot be accounted for by this property alone. Each compound has some other metabolic effect.

Why cannot these potent substances, such as eserine, be used in treatment if inhibition of acetylcholine esterase is always associated with lack of depression? Unfortunately, these agents interfere too much with parasymphathetic function. Mild inhibitors are required which elevate acetylcholine slightly in order to increase epinephrine output. However, epinephrine output must not be excessive or the anxiety ratio will be disturbed and this balance is not easy to achieve.

ANXIETY DEPRESSIONS

A. Indoles

We have already described the indoles derived from adrenochrome and isopropylnoradrenochrome. Ascorbic acid plays a vital role in the intermediary metabolism of epinephrine and adrenochrome. We should therefore expect a close relationship of ascorbic acid to mood and to schizophrenia.

Ascorbic acid protects epinephrine against oxidation both in vitro and in vivo. We do not know whether the same protection occurs in cells where pH and other chemical conditions are different, than they are in body fluids. Any adrenochrome that is

formed would be converted into dihydroxy and trihydroxy indoles. Ascorbic acid is a catalyst for this reaction.

It is not surprising that ascorbic acid levels are highest in tissues most closely related to epinephrine metabolism. The richest source of ascorbic acid in the body is the adrenal cortex which surrounds the richest source of epinephrine, the medulla. The next richest organ is brain which has about twenty times as much ascorbic acid per gram as has plasma. It also is high in epinephrine.

In plasma there is an inverse relationship between epinephrine and ascorbic acid. Stresses which increase secretion of epinephrine, Kayahan (1952), deplete the adrenal gland of ascorbic acid. Injections of epinephrine lower ascorbic acid levels. The depressed and tense who probably have increased levels of epinephrine have low serum ascorbic acid.

Chakrabarti and Banerjee (1955) found that there was a marked shift in the ratio of dehydroascorbic acid to ascorbic acid in serum during infections. Normally about ninety percent of the total substances are ascorbic acid. In subjects with meningococcal meningitis about eighty percent was dehydroascorbic acid. Other infections had ratios somewhere in between. According to Heacock (1959) ascorbic acid is partially oxidized to dehydroascorbic acid by adrenochrome. It is possible the ratio of dehydroascorbic acid to ascorbic acid will be altered whenever the production of epinephrine is increased.

LSD increases adrenochrome levels in plasma and in urine and decreases the rate of destruction of injected adrenochrome. It should therefore increase the use of ascorbic acid. Costa and Zetler (1958) reported that pretreatment of rats with 10 μg/kg of LSD potentiated the depletion of ascorbic acid induced by 25 μg/kg epinephrine. Brom LSD was not effective.

LSD alone should produce depletion of ascorbic acid. Glutathione and cysteine also reduce adrenochrome. Perhaps they too vary in concentration with anxiety as does ascorbic acid.

1. Reserpine

Reserpine is extracted from the root of Rauwolfia serpentina. For many centuries, this plant alone or combined with other ayurvedic drugs, Dews (1958) was used in India as a treatment for

insanity. The isolation of crystalline reserpine was quickly followed by large scale investigations of its use in medicine and psychiatry. It has two main uses: (1) for the treatment of certain hypertensive states, (2) for the treatment of psychiatric disorders characterized by marked anxiety, tension and over activity. It does not help depressed patients who are retarded and apathetic. Indeed it may itself produce apathy and depression in anxious patients and in hypertensives who are not anxious. These patients become increasingly lethargic, chronically fatigued and their muscles feel weak. This may develop into severe depression characterized by feelings of self deprecation and guilt. A neurological sign of overdosage is Parkinsonian tremor. Reserpine is now considered to be more useful in depressions associated with anxiety rather than for the anergic type.

Apparently there are two types of overdosage effect. Both have been classed as depressions. Ayd (1958) in a pertinent report questions the validity of this grouping. He studied seventy patients who were treated with either thorazine or reserpine or its derivatives for many months. Twenty-three of these patients failed to have the usual symptoms and signs of endogenous depression. He labelled them pseudo depressions resulting from excessive medication. "They complained of being languid and discouraged because their lassitude and enervation interfered with the maintenance of their self-imposed standards. Not one mentioned even transient suicidal ideas. Few cried but all recovered from their so-called depressed state when the dosage of the drug was reduced and a stimulant (dexedrine or ritalin) or an anti-Parkinsonian drug (cogentin) was added to their medication."

In contrast forty-seven patients had many of the findings common to endogenous depression. Apparently most of these were depressed before medication was started. Of these, eighty-three percent had received psychiatric treatment before starting on these drugs compared to eight percent of the pseudo depressed group.

The immediate response of the pseudo depressed group to dextro amphetamine resembles the response which reserpinized animals make to benzedrine or dihydroxyphenylalanine. We suggest that this group suffered from a similar depletion of epinephrine.

Ayds true depression would fit into our category of anxiety depressions. Reserpine apparently does not deplete epinephrine here—perhaps because the rate of production is greater.

Mode of Action

Reserpine acts primarily upon the central nervous system. Thus, it increases body temperature, miosis (this is the first sign to appear and the last to disappear), relaxes the nictitating membrane and lowers blood pressure. It is not an adrenergic blocking agent nor is it adrenolytic. After reserpine the response to norepinephrine and epinephrine is augmented. It decreases the brain level of serotonin, norepinephrine, epinephrine and hydroxytyramine. There is also a decreased uptake of methionine. Reserpine itself leaves the brain quickly but its effect continues for many hours.

Brodie, Pletscher and Shore (1955) (1956), and Shore, Pletscher, Tomich, Carlsson, Kuntzman and Brodie (1957) have postulated that the sedative or relaxing action of reserpine is due to the release of serotonin from brain stores as a result of a decrease in the ability of tissue stores to bind serotonin.

There is no doubt serotonin is liberated for its metabolite 5-hydroxyindole acetic acid appears in the urine in increased quantities. Supporting this contention were the observations that massive doses of 5-hydroxy tryptophane which is converted into serotonin in the brain prolongs the action of anesthetics in mice, that both this compound and serotonin are antagonized by LSD and that 5-hydroxy tryptophane placed in the ventricles of animals has a reserpine-like action. Against this hypothesis are the observations that many other compounds prolong the action of anesthetics, that the LSD antagonism is not specific, that intra-ventricular epinephrine also produces anesthesia, that reserpine decreases norepinephrine, epinephrine and hydroxy tyramine as well as serotonin and that the inactivity induced in animals by reserpine is antagonized by epinephrine and dopa but not by serotonin nor 5-hydroxy tryptophane. Finally as we showed earlier there is no relationship between mood and serotonin while there is a very clear relationship with epinephrine and perhaps to isopropylnorepinephrine.

The relationship of serotonin, norepinephrine, epinephrine

and hydroxy tyramine to mood and to reserpine is shown in Table 11.

TABLE 11

RELATIONSHIP OF ANXIETY TO VARIOUS COMPOUNDS

Property	*Serotonin*	*Norepi-nephrine*	*Epi-nephrine*	*Hydroxy Tyramine*
1. Relation to Anxiety	No	No	Yes	No
2. Response to Reserpine	Decrease	Decrease	Decrease	Decrease
3. Antagonism to Reserpine	No	Yes	Yes	?
4. Antagonism of avoidance response of reserpine	No	No	Yes	?
5. Response to amphetamine	Decrease	No	No	?
6. Changes after intraventricular administration	Mild sedation	Anesthesia	Anesthesia	?

It does not seem reasonable to us to suggest the reserpine acts by releasing serotonin alone. It also releases several other substances and there may be more that have not yet been measured. Of those which we know about, epinephrine seems to be more closely implicated.

Reserpine therefore appears to act by decreasing levels of bound epinephrine. Being an indole it may directly antagonize the anxiety producing effect of epinephrine as do the two indoles discussed in the previous chapter. This could be readily tested by giving epinephrine to subjects pretreated with reserpine. There may be an augmented pressor response but the ability of the epinephrine to produce anxiety should be decreased.

Reserpine should act best on anxiety states where there is too much epinephrine but it would make anergic states worse. Its proven capacity to produce apathy may be due to depleting the stores of epinephrine.

Ascorbic acid might be used to protect the epinephrine and so prevent its depletion. Indeed, Delay, Deniker, Fourment, Eurie-

ult and Mordret (1958) report ascorbic acid counteracts the asthenia induced by reserpine. Of course ascorbic acid may also increase the rate of destruction of reserpine as it does for amphetamine, Beyer (1941), and would increase the rate of conversion of adrenochrome into 5,6-dihydroxy-*N*-methylindole and other indoles.

2. Indolylethylpyridines

These are a new series of indole derivatives described by Mirsky, White and O'Dell (1959). They prolonged anesthesia in mice induced by barbiturates and antagonized motor activity stimulated by amphetamines. There was little effect on voluntary motor activity. One of them exerted a calming effect on monkeys without evidence of sedation. They were more potent than meprobamate but different from chlorpromazine. These authors referred to clinical trials by Ferguson which indicate these substances may be valuable for treating mentally agitated patients. If these observations are confirmed, they will enlarge the variety of indoles which will be used for treating anxiety. They will probably not be used for anergic depressions.

B. Substances Which Reduce Reactivity of Receptors to Epinephrine

These are the adrenolytic or adrenergic blocking agents. They include yohimbine, dibenzyline, dibenamine, regitine, priscoline, etc. and the ergot alkaloids. The ergot alkaloids are used to treat migraine headache, essential hypertension and anxiety. The other substances are recommended for some vascular diseases to control the hypertension of phaeochromocytoma.

These compounds do not destroy epinephrine. Therefore, epinephrine metabolites could increase in quantity so long as the body was able to tolerate larger quantities of epinephrine in circulation. Conditions likely to be aggravated by these compounds, e.g. schizophrenia, would either show no response or be made worse.

A new compound Tofranil has been introduced. This substance is anti-histaminic, anti-epinephrine and has atropine-like properties. It appears to be useful for the treatment of depression. Side effects are rare but schizophrenia may be made worse. There may in a few cases be increased anxiety or agitation.

C. Substances Which Decrease Epinephrine Production

Few such substances are known but according to Diethelm (1955) alcohol is such a substance. This may account for the use of alcohol by many people to control their anxiety and tension.

Nicotinic acid and its amide may decrease epinephrine levels by competing with norepinephrine for methyl groups. Hoffer, Osmond, Callbeck and Kahan (1957) reported these compounds which they used for the treatment of schizophrenia had some sedative properties and recommended that patients receiving three grams per day or more should receive less barbiturates for sedation than would ordinarily be given. They suggested nicotinic acid by decreasing the methylation of norepinephrine would reduce the formation of adrenochrome which would be therapeutic for schizophrenia. Udenfriend, Creveling, Ozaki, Daly and Witkop (1959) recently showed nicotinamide inhibited methylation of norepinephrine 15 to 16 percent and increased its half life from 22 to 29 minutes. Woolley (1958) found that 25 mg. nicotinamide per mouse produced marked lethargy and tranquilization. Salvador and Burton (1959) report that nicotinamide potentiated the action of reserpine and chlorpromazine.

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Chapter 6

THE MODEL

Men make models to illustrate, demonstrate or illuminate natural phenomena. They have been used to encourage changes in social and moral standards. Utopias are examples of social models created by men to guide other men. When first constructed they often have little or no relevance to the existing social structure. Yet their effects have sometimes been very far reaching and have generated and directed great social forces.

Although models have been used for a long time their function is seldom understood. This lack of understanding makes it possible for some critics to complain that model psychoses do not reproduce faithfully every aspect of natural psychoses. Such an exact reproduction would not be a model.

Many chemicals change behavior in animals and produce unusual experiences in man. They have been chiefly studied as agents for producing models of the natural psychoses, usually schizophrenia. This type of reaction has been termed psychotomimetic. However when used in other ways in different settings, they produce psychological changes which resemble the mystical states much more than they do psychoses. This reaction is more aptly termed psychedelic. Both models will be described in this chapter.

Although there has been a recent recrudescence of interest in model psychoses there is much criticism aimed at the use of this sort of model. Critics say that the model psychoses have little or no relevance to schizophrenia because they resemble the exogenous type of organic psychosis. These objections have been made on the following evidence; (1) The experiences induced by mescaline and LSD are primarily visual. Visual changes are said to be rare in schizophrenia. Kraepelin and Bleuler denied that perceptual changes were present in this great illness. (2) Auditory hallucinations are rare in model psychoses and more frequent in schizo-

phrenia. (3) Model psychoses are known to be caused by the ingestion of chemicals while the cause of schizophrenia is unknown. It is called a functional psychosis. (4) The differences between model psychoses and the clinical illness are more important than the similarities. Since these objections are of crucial importance to the argument we shall answer them in some detail.

Objection One

Early descriptions of those experiences which follow the taking of hashish, peyote, mescaline and d-lysergic acid diethylamide (hereafter LSD) emphasized the visual component. Many of those who have taken these substances find the visual changes very striking and are therefore likely to report them. Many, though not all people, can describe visual changes spontaneously, more subtle visual changes, other perceptual changes and anomalies of thinking and mood require considerable descriptive and introspective abilities, which must sometimes be combined with special examinations and tests. The early studies set a fashion in research; this has led to an over emphasis on visual changes and a neglect of others which may prove to be of at least equal importance. It is not difficult to devote whole sessions solely to the study of visual phenomena.

There is also some evidence that these phenomena are at their most striking on the first occasion that these substances are taken. Many of the early studies were done with subjects who had had little experience with psychotomimetics. It is not yet certain why visual changes should predominate in first experiments—it may be that they are in some way related to the anxiety of a "first performance," but it should not be forgotten that most people are more able to describe what is seen than what is experienced in other ways.

There is now evidence that some subjects never have marked visual changes. Rothlin (1958), during the symposium on chemical concepts of psychosis held during the Second International Congress of Psychiatry, stated that although he had taken LSD five times he had never had hallucinations and had few visual changes. He nevertheless considered that his experience had been valuable and illuminating. We have some evidence that when LSD is taken

many times the visual changes become less prominent. But with both LSD and mescaline true hallucinations, false perceptions are much less frequent than a casual acquaintance with the literature might make one suppose.

In schizophrenia, visual hallucinations if present, and this is not very frequent, are found in acute and very anxious patients. If the illness persists, the visual hallucinations tend to be replaced by auditory ones. Tactile, olfactory and taste hallucinations also occur, but seem to be reported more rarely than the others, though this may simply mean that they are listened to less keenly because psychiatrists are not so interested in them. It is, therefore, illogical to compare the visual changes found in model psychoses with those found in schizophrenia as has been frequently done. The model experience is a single episode of short duration occurring in a healthy volunteer, who usually knows that he may have an experience of this sort and how long it is likely to last. Most experiments of this sort are conducted in a friendly atmosphere and the volunteer is encouraged to report his experiences to others who are often keenly interested in what is happening to him. Contrasted with this the schizophrenic patient may have been ill for months or even years, has no rational explanation for his experiences; the friends who remain to him are not interested in his experience, and may even refuse to believe what he tells them. In addition he cannot tell whether he will endure this for the rest of his life or even for eternity.

It is still quite uncertain whether there really is any great difference in the frequency with which visual changes occur in the model psychosis and schizophrenia. Mescaline and LSD produce changes in the perception of size, distance, space, time as well as distortions of visual imagery and auditory stimuli. These changes are also found frequently in schizophrenic patients. They occurred in nearly half our early schizophrenics while Weckowicz (1957, 1958) has demonstrated their presence in chronic patients. Psychiatrists who are insensitive to perceptual changes usually miss them on mental examination even though the patients are troubled by them. Patients don't know how to describe such changes and fall back on catch phrases such as "feeling unreal." One of us recently talked to a schizophrenic girl who was at that time ill in a mental

hospital and had been under psychiatric care for at least seven years. She told her doctor that she did not want to do recreational therapy because it made her feel unreal. When she was asked what she meant by "feeling unreal" she described how the room became brighter, how the faces of those around her changed while she watched them and how her sense of time was distorted. She talked of experiences so frequently found shortly after taking LSD or mescaline or when their effects are wearing off. When asked why she had not described these happenings before she said that no one had ever enquired about them. Perhaps the current preoccupation with dynamic explanations of various sorts has blunted our interest in what our patients actually experience. We have found that generally speaking subtle visual changes occur not gross hallucinations. These subtle changes have received so little attention until recently that they are commonly thought to be very infrequent. However, if one reads the autobiographies of schizophrenic people—(there are at least two dozen, Sommer and Osmond (1959), very satisfactory ones—from that of High Judge Shreber (1955) on)—it seems likely these are a rarity because lack of interest by clinicians has made it generally supposed that they are infrequent. Renees extraordinary account of her perceptual experiences illustrates the types of changes that may occur, Sechehaye (1951).

Objection Two

Auditory hallucinations are usually held to be more common than visual ones in schizophrenia. While there may be some truth in this, it is doubtful whether this helps those who wish to emphasize the differences between schizophrenia and model psychoses. They occur less often in early schizophrenia. The supposed differences between schizophrenia and model psychoses may be due to an obvious selection bias. If one compares acute schizophrenia of sudden onset with a model psychosis the similarity is often very striking. It has not been possible to give psychotomimetics to humans for long periods of time. One naturally hopes that it will never become possible to do this. So that we will have to depend on observation and natural experiments like that reported by Osmond and Hoffer (1958).

What is usually compared is a chronic illness of insidious onset. Acute illnesses clear up quickly and so may never reach the stage of auditory hallucinations. They are often classified as something other than schizophrenia. There are even those who hold that auditory hallucinations are pathognomonic of schizophrenia and so will not diagnose the illness until these are elicited. The matter is further confused by the fact that there is some doubt as to whether auditory hallucinations are very frequent. The investigator can easily push the patient into agreeing that autochtonous ideas are "voices."

Ostfeld, Abood and Marcus (1959), Ostfeld, Visotsky, Abood and Libovitz (1959) have developed atropine like psychotomimetics which tend to produce auditory changes which may culminate in hallucinations, rather than visual ones. Such auditory disturbances are apparently common after the administration of taraxein.

Objection Three

In our opinion this objection is a crucial one which has led to much unnecessary confusion. Few psychiatrists will deny that we are still ignorant of the cause or causes of schizophrenia. However, in spite of this, once a known cause can be assigned to a schizophrenic like condition most psychiatrists agree then that it is not schizophrenia. For instance a psychiatrist who examined a volunteer who had taken LSD might conclude that he was seeing a patient with schizophrenia, but once he was told about the administration of LSD he would feel obliged to alter the diagnosis. This is not an academic matter but has been vividly illustrated in the discussions about schizophrenic like illnesses following massive and continuous taking of amphetamine derivatives.

What has happened is that diagnoses and cause are being confused. The current description of schizophrenia as a "functional psychosis" is a misleading one because it implies a known cause—that schizophrenia is a function of something. An example of our present illogical approach will be found in those few patients whose schizophrenic symptoms are found to be "caused" by a brain tumor. The diagnosis of schizophrenia is then eliminated. In effect we imply that we do know the causes of the schizophrenic

syndrome and brain tumor is not one of them. We are also more or less sure that schizophrenia is not "caused" by syphilis, encephalitis, bromide, amphetamine, mescaline or LSD. Yet how if we do not yet know the cause of schizophrenia can we confidently exclude these as factors in some schizophrenias. "Cause" and diagnosis have been confused.

We make diagnoses to guide ourselves in treating and prognosing. Where diagnosis has little or no bearing on treatment, it is of academic interest rather than clinical use. Unfortunately for many psychiatric patients diagnosis plays a small part only in determining treatment which still tends to be on a hit or miss basis. However, it is unnecessarily pessimistic to assume that diagnosis will never be linked to specific treatment. The whole history of medicine strongly suggests that someday diagnoses in psychiatry will be as precise as they are in other specialties.

Today it may appear to be of minor interest whether a patient is labelled obsessive compulsive neurosis, paraphrenia, hysterical psychosis or schizophrenia. There may come a time when it will be as unpardonable to miss an early schizophrenia as it is now to fumble a diagnosis of cancer, pernicious anemia, syphilis, or tuberculosis.

There are three logical steps in diagnosis: (1) Data is collected, i.e. symptoms and signs are obtained both from the history of the illness and from physical, mental and examination by special means (x-ray, chemistry, etc.). (2) A syndrome is abstracted. Those symptoms and signs considered most important are grouped together as a syndrome. According to the Oxford International Dictionary, a syndrome is "a concurrence of several symptoms in a disease, a set of such concurrent symptoms." The Dorland's Illustrated Medical Dictionary defines a syndrome "a set of symptoms which occur together; the sum of signs of any morbid state; a symptom complex." There is no reference to cause in the definition of syndrome. It is an abstraction from the data. (3) The final stage of diagnosis is to determine the cause of an already established syndrome. Thus a patient presenting with the syndrome of general paresis of the insane is diagnosed as having syphilis of the nervous system if the Wasserman and other tests are positive.

Cause can only be determined when cause is known and can be shown to be operating by specific laboratory tests. Psychiatry can seldom make this third step. The exceptions to this are syphilis, pellagra and psychosis arising from the ingestion of drugs such as bromide, amphetamine, etc. These exceptions are noteworthy because the diagnosis is established by chemical tests.

Much of our current confusion arises, we believe, from our habit of using diagnostic labels as if they described etiology when they don't necessarily do so. Table 12 which follows shows how a system of classification can be applied to psychiatric diagnosis.

All patients having the syndrome characteristic of schizophrenia would be so labelled. The etiological diagnosis would depend upon the cause (or explanation) found during subsequent investigation. If as would very often be true now, no cause was found the label would be "schizophrenia of unknown origin." This scheme is logical and defensible. As progress is made in research the schizophrenic syndrome will be related increasingly to definite causes whether psychological or physiological. The schizophrenics whose cause is known, i.e. amphetamine schizophrenia, will receive specific treatment related to causation.

TABLE 12

THE LOGICAL SEQUENCE OF DIAGNOSIS

First Order	*Second Order*	*Third Order*
Symptoms and Signs	Syndrome	Etiology
	1. Schizophrenia	1. Unknown
		2. Hormonal
		3. Chemical
		4. Tumor
		5. Infective, etc.
	2. Depression	1. Unknown
		2. Hormonal
		3. Chemical
		4. Tumor
		5. Infective, etc.

Neurologists diagnose epilepsy this way. The syndrome, epilepsy, consists of a peculiar sort of convulsions and changes in consciousness. The cause may be a brain tumor, an infection or unknown. In the latter case it is called idiopathic epilepsy (or epilepsy of unknown origin).

PSYCHOTOMIMESIS

There are few substances which, when taken in large enough quantities, will not produce great alterations in the working of mind and brain, as shown by changes in the experience and behavior of the person who takes them. If these changes are accompanied by gross disturbances in bodily functioning, with great discomfort, loss of consciousness or even death, they are unlikely to interest the psychiatric researcher. By a process of trial and error, primitive man was very successful in tracking down many plants containing pharmacologically active substances—not a few of which affected the psyche. Until recently, apart from a few great specialists like Louis Lewin, there was little interest in most of these plants and few had been investigated with much rigor from the psychopharmacological viewpoint. Twenty-five years ago even an expert would have been excused for only knowing much about hashish, peyote, and the vine, ayahuesca; apart, of course, from the opium poppy and the coca leaf which come in a different category. He might well have omitted to mention the ancient soma, cohoba, ololiuqui, the Syrian rue, the fungus teonanacatal, the two amanitas pantherina and muscaria, the iboga bean, betel nut, kava-kava and the fierce virola snuff. At that time the only pure chemicals available for experiment would have been mescaline (from the cactus peyote), harmine (from ayahuesca, the vine banisteria caapi) and possibly bulbocapnine (from corydalis cava) though at that time this had not, we believe, been used in humans. The active principle of hashish was not then available and it is not available now. In so limited a field in which so few were interested, niceties of classification and terminology were not very important.

Things are different now when the researcher may have access to many new pure compounds including d-lysergic acid diethylamide, 3,4,5-trimethoxyphenyl-β-aminopropane, dimethyl and di-

ethyl tryptamine, psilocybin, Abood's family of atropine derivatives, ibogaine from vegetable sources, adrenochrome, adrenolutin, possibly bufotenine from animal sources, and in a slightly different category since it seems to be a protein derived from schizophrenic blood, taraxein.

All these substances have been reported as producing psychological changes which resemble to a greater or lesser extent those found in the great psychotic illnesses. To them it would seem that Gerard's useful term 'psychotomimetic,' Kety (1957),—psychosis mimicking—agent could properly be applied, for in many subjects they can reproduce various aspects of the great so-called functional psychoses.

However, there are still a number of scientists, particularly in Britain and Europe, who prefer to consider that these psychotomimetics more closely resemble exogenous, toxic or delirious conditions. In all textbooks of psychiatry the hallmark of a delirium is confusion—clouding of consciousness with inability to recognize one's whereabouts in time and space, combined with memory disturbances. Long ago Louis Lewin emphasized that this was not a feature of the mescaline experience—and so far it seems to apply only to Abood's atropine derivatives and also perhaps to Nalline. This disagreement is apparently a semantic one which we shall discuss in greater detail later on.

There seems no reason why psychotomimetic agents should not be developed to mimic deliria, mood swing illness or even dementias rather than schizophrenia. If this happens a particular psychotomimetic agent will doubtless be given certain specifications which it would be expected to meet. Abood's atropine derivatives suggest that he has already some deliriants which may be very useful in enlarging our knowledge of these conditions. We noted earlier that if one gives almost anything in large enough amounts poisoning accompanied by mental confusion will result. To be classed as a psychotomimetic agent a drug must not only reproduce the symptom complex of a particular psychiatric illness, but its action must be both readily reversible and of limited duration. Furthermore, the drug must not result in gross bodily disturbances and, when it is taken in the dosage necessary for psychotomimetic effects, it should not be dangerous.

A schizogenic psychotomimetic might then be defined in this way: "A substance which will produce insidious changes in mood, perception, thinking and sometimes bodily posture, occurring either alone or in concert without major disturbances in the autonomic nervous system or confusion, etc. in the usual dosage." A mood swing psychotomimetic might have a very different specification; for this would depend upon whether the change in affect was in the direction of mania or depression, and whether the accompanying tempo was one of agitation or anergia. Our ignorance of differences in human metabolism which is still very considerable makes it difficult to predict with any accuracy the effect of a particular psychotomimetic in a particular person. Once a human typology, such as that of William Sheldon (1954), has been extended to include the intimate chemistry of the autonomic nervous system, some of our current deficiencies may be remedied.

PSYCHEDELICS

The substances, which we have been discussing, would be of great interest if their only use was to increase our knowledge of psychotic illnesses. But we have already indicated that the experience which they induce resembles those which come to a variety of creative people. Such accounts as those of Ward (1957), Zaehner (1957), and Michaux (1957) show that psychotic-like states certainly do occur and can persist for many hours. Those of Havelock Ellis (1898), Lewin himself (1931), Aldous Huxley (1954) and Christopher Mayhew (1956), with many more of the records which we have and reports that have been made to us, indicate that some people have very different kinds of experiences. These have been classified in the handbook for the therapeutic use of LSD, Blewett and Chwelos (1959). Our reporters include authors, artists, scientists of many types, a number of medical men including a famous pharmacologist, philosophers, psychologists, businessmen, a junior cabinet minister, several journalists and a hero. They agree that although the experience may be so unfamiliar as to be frightening, it is also astonishing, beautiful and valuable. There is a concensus that the experience enlarges one's ideas of reality and is not simply remembered but is unforgetable. All from the most highly edu-

cated to Slotkin's (1956) unlearned Indians emphasize that much of what happens cannot be contained in the language which we commonly use.

This is not new. It is our particular medical interest in these happenings, a product of the last 100 years which is unusual. Men have pursued these happenings since the dawn of history and probably long before that. They have used an extraordinary variety of techniques to achieve this state, from dervish dancing to prayerful contemplation on tops of pillars; from solitary confinement in dark, noiseless caverns to inhaling carbonated air emitted from the earth; from chewing peyote buttons to prolonged starvation in the wilds; from rotating with thongs in their pectoral muscles until they tear out to diving far under thick ice after ingesting the dangerous amanita muscaria. Such persistent exertion found in widely different cultures and continuing for millenia suggests that the goal or goals must be valued greatly. Enormous efforts have been made to induce these states readily and it is believed that great systems such as Yoga are attempts, sometimes almost successful, to do just this.

In what does their peculiar excellence consist? We cannot answer such a question here. We can, however, discuss a smaller one which may whet the appetite for further enquiry. William James (1950) said that "Genius in truth means little more than the faculty of perceiving in an unhabitual way." That "little more" includes the selection, organization, communication and useful application of what has been perceived in an unhabitual way, none of which can be underestimated. Nevertheless, without unhabitual perception could there be any genius—any creation of the new—of what had never been thought or conceived before?

All of us most of the time are and must be creatures of habit. We perceive, feel, think and act in an habitual way. No other seems possible for us. So uncomfortable do we find the unusual and unfamiliar that we make haste to label it as daydreaming, fantasy, nonsense, and so deny its reality. Some of the substances to which we have referred in the section on psychotomimetics, but not all of them, used under the correct conditions allow and may favor this unhabitual perception. Even the possibility of this could not be dismissed lightly. Anyone who reads reports from, or talks

with those who have had such experiences cannot doubt that the impact on their mind has been remarkable.

The problem is how to make the most of brief accesses to unhabitual perception. How to select, organize, communicate and use for the best the ideas to which it gives access. Smith (1958) has already given LSD-25 with some success in chronic alcoholics. Hubbard (1954-59) in his very extensive work, suggests that it is not only the ill who benefit, but those whose lives have become bogged in stagnant notions and trite emotional gambits repeated so mechanically that they cease to have any meaning. There seem to be few ways more likely to encourage a strongly motivated attempt to realign one's personality than unhabitual perception of oneself and one's relationship with other people.

As we indicated in an earlier report, Osmond (1957), we sought a word which would exemplify this potential for enlarging and enriching the mind. In this context "psychotomimetic" is not only inappropriate but misleading. The aim is not to mimic madness but by exploring and fathoming our own nature to increase our understanding and awareness. After examining many possibilities including Mr. Aldous Huxley's elegant 'phanerothyme' = soul manifesting — (phaneroein = to make visible or manifest thumos = soul), we chose, because it was clear, euphonious and little contaminated by other associations, "mind manifesting" — psychedelic.

Our beliefs, what we take for granted, as the Ames (Cantril, 1950) demonstrations show, influence the way in which we perceive the world. Our mould for world making, once formed, resists change stubbornly. Psychedelics, properly used, let us divest ourselves of some of those protective yet also dulling layers of acquired assumptions and rationalizations with which we are encumbered. For a little while we can see the Universe again with an innocent, unshielded eye. This gives us a chance to follow T. H. Huxley's advice when he wrote to Charles Kingsley, "Sit down before fact, like a little child, be prepared to give up every preconceived notion, follow humbly to wherever and whatever abysses nature leads or you shall learn nothing." Or as a 17th century English mystic, Thomas Traherne put it, "to unlearn the dirty devices of the world and become as it were, a little child again." Psychologist, biologist

and mystic have much the same recipe for the truth seeker. But has this any importance for us now?

Our inventive cunning and technical virtuosity thrusts change upon us willy nilly. In our headlong rush there is an increasingly grave danger that out of date habits of perceiving, feeling and thinking persisting for no better reason than that we are used to them and find them comfortable will culminate in actions that could destroy our species. "Let the dead bury their dead" may sound harsh, but if we are to survive in the present we must not clutter it with emotional and intellectual leavings of the past. This entails discarding our worn out assumptions and developing new ones appropriate to the new conditions and less contaminated with habits that no longer have any meaning. Psychedelics skillfully used can, we think, help us to do this.

Our present psychedelics are probably as crude as our ways of using them. Some are gleanings from stone age peoples. None has been specifically designed for its task, but even so they can enlarge our experience and widen our vision. We have to learn to develop substances and techniques for reaching specific goals. Much hard work and skillfully applied unhabitual perception will be needed if we are to succeed.

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Chapter 7

PSYCHOTOMIMETICS SIMILAR IN STRUCTURE TO EPINEPHRINE

A. MESCALINE

The cactus, Anhalonium Williamsia or lophophora williamsii, called when dried Peyote, contains at least eleven alkaloids. It has long been used by American Indians as a psychedelic. Mescaline was identified as the active substance by Heffter as long ago as the 1890's. Although for many years it was the only pure chemical psychotomimetic, it has been studied only sporadically since then. We know of no comparison between mescaline and the peyote induced experience. It seems likely that the other alkaloids modify the action of mescaline. One of us (H. O.) has found the experience to be different but the psychosocial settings differed greatly. Experimentation and inquiry is needed here.

The experience induced by both mescaline and LSD resemble each other very closely. The variations due to these compounds are well within the range of variation of either one. The suggestion that mescaline produces a catatonic-like response and LSD a hebephrenic-like one, does not accord with our clinical experience or with the observations of many psychologically sophisticated authors. There are however many differences which are shown in Table 13.

The dose relationships hold for both intravenous or oral administration but not when the compounds are placed in the brain ventricles. Schwarz, Wakim, Bickford and Lichtenheld (1956) reported that 1 mg. of mescaline (0.3% of the human dose) produced much greater changes in the behavior and EEG of cats than 15 μg. of LSD (15% of the human dose). By this route mescaline is more active than by any other route.

TABLE 13

COMPARISON OF LSD AND MESCALINE

Property	*LSD*	*Mescaline*
Quantity required/human	100-200 μg.	300-500 mg.
Rate of onset	30-60 min.	60-120 min.
Maximum intensity	2-4 hrs.	3-5 hrs.
Average duration	6-8 hrs.	8-12 hrs.
Modified by niacin	Yes	No*
Modified by succinic acid	?	Yes

*Hoffer. Many observations over past five years.

Mode of Action

1. Direct

Mescaline probably acts directly on the brain. It is very active when placed in the brain ventricles. Perhaps large quantities are required when given by other routes because it does not pass into the brain readily. It is not yet clear why this should be so. However, epinephrine also does not cross readily into the brain.

Mescaline interferes with the metabolism of brain tissue. Quastel and Wheatley (1933) found that mescaline inhibited the oxidation of glucose, lactate, pyruvate and glutamate by guinea pig brain tissue slices. It did not inhibit the oxidation of succinate. This was confirmed by Schueler (1948) who found inhibition when mescaline was incubated with brain tissue for 2½ to 3 hours in the absence of substrate. The ability of brain tissue to metabolize succinate in the presence of mescaline led Schueler to use succinate for modifying the mescaline experience. Within 5 to 10 minutes of an intravenous injection of 3.5 to 6.0 grams of sodium succinate subjects who had previously taken mescaline reported that perceptual changes including visual disturbances and distortions of time and space were markedly decreased, while mood changes such as low spirits and respiratory depression became normal. This lasted for ½ to 1 hour and then these symptoms returned. Pupillary contraction was not restored. Although Hoch (1956) could not confirm these findings, other workers were able to do so. Steven-

son and Sanchez (1957) gave twelve volunteers 400 mg. mescaline. After the mescaline experience was well developed, they were given 12 to 18 grams sodium succinate by intravenous transfusion over a period of 30 to 90 minutes. They found some antidotal action in every subject. This ranged from slight to almost complete removal of the mescaline experience. However, the effect was transient, probably due to the excretion of succinate which is very rapid.

Compared with the doses usually given the amount of mescaline required to produce in vitro inhibition seems large. This may be due to the relative insensitivity of resting tissue cells to inhibition compared with cells which are more active. Lewis and McIlwain (1954) found that 10^{-2} M. mescaline had no effect on guinea pig brain. However, if the tissue was stimulated electrically 10^{-3} M. mescaline produced 50% inhibition. But 10^{-4} M. of mescaline produced no inhibition. This means that in an in vitro system one must be given ten times as much mescaline as is thought to be present in the in vivo experience. In our opinion, it is encouraging to get within a factor of 10, for it must be remembered that the in vivo system, i.e. the brain, could not function at all with 50% inhibition. Very slight in vivo inhibition will play havoc with brain function. Ashby (1954) has shown that in a chain of synapses such as exists in the brain, a small amount of inhibition occurring at each link in the chain will result in a severe dysfunction of the system as a whole.

The biochemical defect produced by mescaline is unknown. Bain (1957) reported it has no effect on oxidative phosphorylation of rat brain mitochondria.

Electroencephalogram

Marrazzi (1957) found that mescaline inhibited the post synaptic component of the trans callosal response. In this it resembles adrenochrome and adrenolutin. These three substances are relatively weak compared to LSD and serotonin. Yet when injected into brain ventricles these three compounds are much more effective in producing changes in the EEG and in behaviour. The correlation between inhibition of synaptic transmission and psychotomimetic activity is therefore not high. It seems that active

inhibitors such as serotonin which would completely stop function are rapidly bound or destroyed.

Mescaline produces some alternation of spontaneous electrical activity. An alert EEG is produced by 5 to 10 mg./kg. of mescaline given intravenously. As was stated earlier Schwarz *et al.* (1956) found that 1 mg. of mescaline placed in the ventricle produced intermittent spike and slow waves as well as marked changes in behavior. In humans the results are variable. Some authors have reported a decrease in amplitude of alpha rhythm lasting for several days while others have found an increase. Munroe, Heath, Mickle and Llewellyn (1957) reported that mescaline altered the depth encephalogram. When anxiety was present, there was an increase in beta activity and a decrease in alpha activity in the cortical and subcortical areas. Paroxysmal activity in the hippocampal, amygdaloid and septal regions was associated with overt expression of psychotic behavior. This paroxysmal activity spread until it was general throughout the cortex and apparently at this time interfered with a full expression of psychotic behavior.

2. Indirect Action

Mescaline may have an indirect action in addition to its direct action on tissue. It may be converted in the body into small quantities of more active psychotomimetics. Thus Block (1958) suggests that mescaline must first be incorporated into body proteins before the psychological activity appears. During this phase the reaction to mescaline is a neurovegetative one consisting of pupillary dilatation, nausea, tremor, etc. This coincides with the maximum concentration of mescaline in the body. Later there is the typical psychotomimetic experience which in mice coincides with a minimal concentration of free mescaline in plasma and a maximal concentration of bound mescaline in the liver. Block believes that the body protects itself against the usual toxic amines by means of amine oxidase which converts them into less toxic acids. But since there is no specific amine oxidase for mescaline, it circulates for a long time. Consequently, there is ample time for it to be incorporated into the body proteins. This binding occurs chiefly in mitochondria and microsomes. Block's scheme is interesting. It is supported by the observation that rabbits which have mescaline amine

oxidases can tolerate large quantities of mescaline whereas they are very sensitive to LSD. However, Block's scheme does not tell us whether it is the bound mescaline itself or some metabolite coming from the bound complex which is the toxic factor nor does he explain how the toxic protein complex enters the brain tissue.

Harley-Mason, Laird and Smythies (1958) reported that they recovered about one third of ingested mescaline free in urine. In addition, a new glutamine conjugate was found comprising 1 to 2 percent of the total. These authors suggest that mescaline might be converted into a dihydroxyindole which would be the active hallucinogen as are some other well known indoles.

In humans LSD elevates adrenochrome levels in plasma and urine but mescaline has no effect on the levels of adrenochrome in plasma, Hoffer (1958).

In conclusion very little is known about the way in which mescaline works except that we know that its action differs from LSD and that it is incorporated in the brain in some essential enzyme (protein) and thus directly interferes with function. There is no evidence to suggest it produces more active metabolites (degradation products). Mescaline competes with epinephrine for receptors, Speck (1957). Perhaps there is a clue here.

B. MESCALINE ANALOGUES

Peretz, Smythies and Gibson (1955) described the psychotomimetic effect of 3,4,5-trimethoxyphenyl-β-aminopropane (TMA) which is structurally similar to mescaline, epinephrine and the sympathomimetic amines. The subjects reported that they felt drunk and seemed more restless after about 1 to 2 hours. Their inhibitions seemed to be less and they talked more. These symptoms depend so much upon the enthusiasm of the investigator and the particular technique used that they aren't easy to evaluate. The experience continued for three to four hours and subjects are described as being normal after seven hours. When exposed to a stroboscope some of the subjects reported vivid visual hallucinations. The subjects were enthusiastic about the visions. According to Elkes, Elkes and Bradley (1954), the stroboscope can intensify LSD experiences in human subjects. Hoffer (1957) also found that

the stroboscope can induce visual hallucinations in a few of the subjects given adrenolutin. This small trial of TMA has not yet been repeated by others but it suggests that analogues of mescaline may be psychologically active. These authors did not suggest how TMA might work.

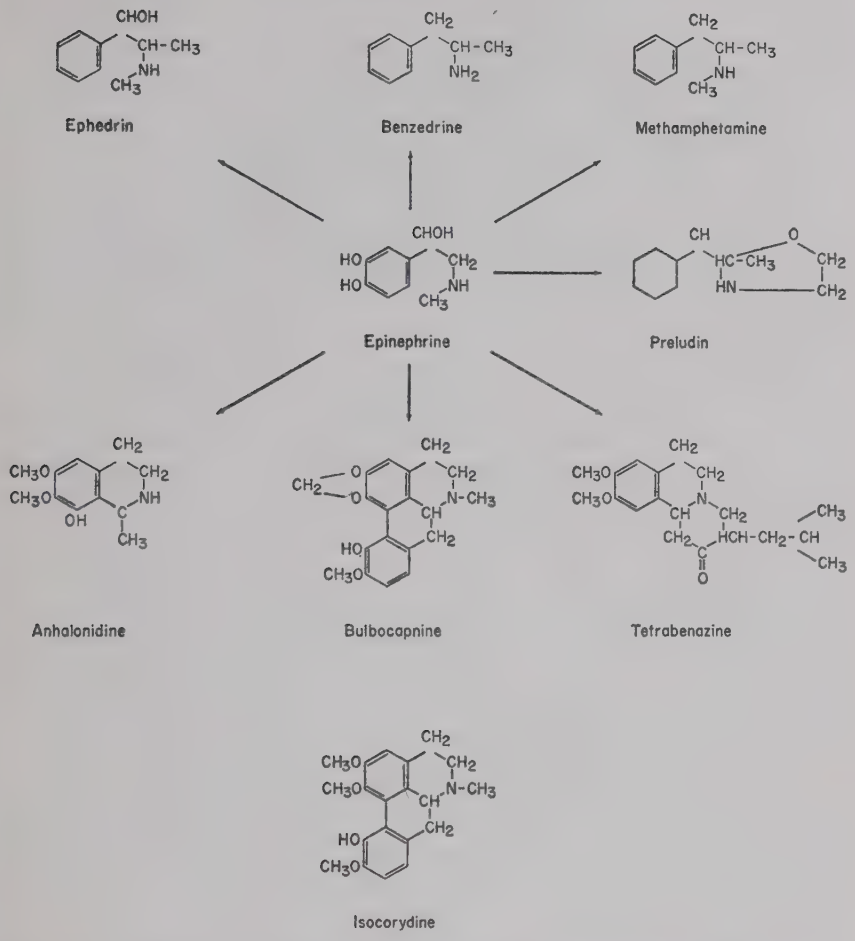
C. ADRENERGIC COMPOUNDS

Most adrenergic drugs are chemically related to phenylethylamine. Some occur in nature. Compounds having an unsubstituted phenyl ring and a methyl group on carbon are corticomedullary stimulants. In man they usually produce anxiety, tremor, insomnia and mental alertness. In animals, they produce convulsions when given in large quantities.

A few of the common amines are shown in Table 14. These compounds are addicting drugs. Occasionally they produce psychosis indistinguishable from schizophrenia. This occurs when very large single doses have been taken, or when more moderate doses have been taken for a long time. Some people seem to be unusually sensitive to amphetamine and similar compounds. In Japan, psychoses resulting from these compounds are now a major problem. The psychosis may have some of the characteristics of a toxic confusional state but may frequently simulate schizophrenia. Connell (1958) in a recent report emphasized the impossibility of diagnosing amphetamine psychosis on clinical criteria. The original diagnosis by psychiatrists who were unaware a drug had been taken was nearly always schizophrenia. Many were diagnosed paranoid schizophrenia. This diagnosis was sometimes maintained even after it was known they had ingested amphetamine. Four patients were given deep insulin therapy during previous admissions as a treatment for their schizophrenia even while some were taking amphetamine. Obviously their response to insulin would be good. In many patients in Connell's series disorientation, usually thought to be the hall mark of a toxic state, was absent.

TABLE 14

SOME COMPOUNDS RELATED TO PHENYLETHYLAMINES



D. SUBSTANCES WHICH MAY BE DERIVED FROM DIHYDROXY PHENYLALANINE

In addition to mescaline, peyote contains a second class of chemicals, the tetrahydroisoquinolines according to a scheme presented by Reti (1950). These bases are probably synthesized in plants from tyrosine through dihydroxy phenylalanine. This series

of compounds may influence the effect of mescaline in producing psychological changes. In themselves, they have been studied very little as possible psychotomimetics. Reti refers to Lewin's finding that anhalonidine (shown in Table 14) can produce hallucinations. There is little doubt they can be central excitants. Thus anhalonidine produces hyperexcitability in rabbits and frogs. Pellotine produces convulsions in dogs and cats (and may also be a narcotic). Carnegine also causes excitability and convulsions.

Of great interest is the observation of Buzard and Nytch (1959) that norepinephrine can combine with pyridoxal phosphate to form a substituted tetrahydroisoquinoline. By doing so, it inhibits 5-hydroxy tryptophane decarboxylase. If this occurred in vivo to excess it might result in marked psychological changes. These could be either central excitement leading to convulsions or to sedation or depression. According to Pletscher (1957), Pletscher, Besendorf and Bachtold (1958) and Voelkel (1958) benzoquinolizines are non hypnotic sedatives. They decrease brain serotonin and norepinephrine levels as does reserpine. One of these compounds, tetrabenazine, is shown in Table 14.

Bulbocapnine seems also to belong to this series of compounds. De Jong (1945) showed that it produced animal catatonia in many animals and also in humans (1956). In 1955 de Jong showed a moving picture of a man who had been injected with bulbocapnine. This man was mute and showed typical catalepsy. The catatonia lasted one hour after intravenous injection of 150 to 200 mg.

De Jong states that animal catatonia consists of (a) hypokinetic phenomena with diminished motor initiative, catalepsy and physiological negativism, or (b) hyperkinetic phenomena encountered with large doses of bulbocapnine and (c) autonomic nervous system changes.

Bulbocapnine is a member of the aporphine alkaloids, Manske (1954). Another compound, isocorydine, also produces catatonia in animals. Waud (1959) injected isocorydine intramuscularly (25 mg/kg) into cats. It produced catalepsy, salivation, tremors, plaintive mewing, terror, fright, hostility, and apparently hallucinations. Larger doses produced hyperkinesis and convulsions. These changes were modified by pentobarbital.

There are a large group of alkaloids derived from phenyl ethyl amines including the isoquinolines, the benzylisoquinolines, the protoberberines, the aporphines (bulbocapnine, isocorydine), the protopines, the phthalideisoquinolines (narcotine—a mild narcotic), the aconitum and delphinium alkaloids (highly toxic for man. The lethal dose is 2 to 5 mg.). All these compounds effect the function of the central nervous system—perhaps by replacing epinephrine or norepinephrine on certain receptor cells. Since they would be destroyed or removed slowly compared to epinephrine they would react for long periods of time. It may be possible to find which areas of the brain are selectively attacked by these alkaloids and thus relate known pharmacological activity to specific brain sites.

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Chapter 8

PSYCHOTOMIMETICS WHICH INTERFERE WITH THE FUNCTION OF ACETYLCHOLINE

The brain depends for its normal functioning upon a proper turnover of acetylcholine. Acetylcholine appears to be a neurohormone which somehow influences transmission of stimuli across parasympathetic synapses. Elkes (1958) suggests a substance should meet four conditions before it is considered a neurohormone. Acetylcholine approximates these better than any other substance. These desiderata are (1) the substance should be identifiable in the brain and distributed differentially, being in greater concentration in parts of the brain where activity is greatest, (2) enzymes which both synthesize and destroy acetylcholine should have the same distribution, (3) inhibition of these enzymes will alter the chemical and functional properties of brain, (4) if the substance is applied to or reaches specific areas of the brain the characteristic changes in function should occur.

Brain function can be disturbed by either too little or too much acetylcholine. Within narrow limits there is a relation between normal activity and acetylcholine levels. Elkes refers in his review to the findings that the concentration of acetylcholine in brain is higher in sleep and during anesthesia then in wakefulness. In general, when there are abnormalities in behaviour and in the electroencephalogram, there is also an increase in concentration. Substances which increase the concentration lower the threshold for convulsions. Rapid intravenous injection of acetylcholine itself can produce convulsions. Pope, Morris, Jasper, Elliott and Penfield (1947) suggest that when there is too much acetylcholine in certain parts of the brain, due perhaps to lack of binding substances, this may be responsible for electrical changes.

Too little acetylcholine should also result in abnormal brain functioning, but so far no clinical conditions have been ascribed

to this. Deaner, recommended for treating certain forms of depression, probably increases the synthesis of acetylcholine. Perhaps it is possible some depressions result from an underproduction of acetylcholine.

The concentration of acetylcholine depends upon two opposing factors: (1) The rate of synthesis, i.e. the activity of acetylase, and (2) The rate of hydrolysis or destruction, i.e. the activity of acetylcholine esterase. We still know very little about the synthesis of acetylcholine, how this can be influenced by inhibitors or activators and what changes occur in living persons. We still, therefore, discuss only factors which change the activity of the esterases.

Acetylcholine is hydrolyzed primarily by an enzyme known as true acetylcholine esterase. It is present in high concentration in brain, other nervous tissue and red blood cells. Another enzyme which acts on other esters is known as pseudo acetylcholine esterase. It is present chiefly in plasma and liver but is also present in brain. True acetylcholine esterase is more concerned with acetylcholine and brain function. Pseudo acetylcholine esterase has not been shown to be concerned in brain function here. But this may have to be re-examined, for intracarotid injection of very small quantities of a specific pseudoesterase inhibitor desynchronized the corticogram much more than a higher dose of a specific inhibitor of true esterase, Desmedt and La Grutta (1955). In addition, Thompson, Tickner and Webster (1954) found 10^{-6} M LSD causes 50 percent inhibition of human plasma cholinesterase (pseudo). True cholinesterase is not affected by ten times as much. Pseudo cholinesterase activity in the brain was also inhibited. This might account for the increase in brain acetylcholine found by these authors and also by Poloni and Maffezzoni (1952). LSD affects human esterase more than that of other species including the monkey.

There are two ways of interfering with brain acetylcholine activity: (1) by decreasing the destruction of acetylcholine. This is done by inhibiting acetylcholine esterase and as a result the levels of acetylcholine increase. (2) By preventing the union of acetylcholine with some of its receptors. Psychotomimetics may thus be divided into (1) esterase inhibitors and (2) acetylcholine antagonists.

A. ACETYLCHOLINE ESTERASE INHIBITORS

There are three types of inhibitors which produce changes in behaviour in man: (1) alkaloids such as eserine synthesized by plants, (2) modern synthetic fluorophosphates developed for war purposes and now used as insecticides, and (3) LSD.

The first two classes of compounds appear to act in the same way. Eserine and di-isopropyl flurophosphonate (DFP) caused cats to scratch and wash themselves when placed in the brain ventricles. Later they stiffened their limbs in flexion. This was followed by catatonia.

Eserine cannot be used as a psychotomimetic. It has not been studied in the same way as DFP. The nicotinic effects (stimulation of smooth muscle and glands) are so great that very little can be given to animals and man. According to Sherwood (1958) prostigmin, used as a treatment for patients suffering from myasthenia gravis, occasionally produced psychotic episodes. DFP too was once used for the treatment of myasthenia gravis. After a time patients refused to take it because of nightmares, mental confusion and hallucinations. Rowntree, Nevin and Wilson (1950) found that DFP made schizophrenic patients more psychotic. With the common use of anticholinesterase insecticides the incidence of poisoning and psychosis will undoubtedly rise. Some cases of severe poisoning followed by psychosis have already been reported.

B. ACETYLCHOLINE ANTAGONISTS

Substances which prevent the combination of acetylcholine and some of its receptors are known as blocking agents or antagonists. Acetylcholine has two main receptors and, therefore, two main activities. These are: (1) the nicotinic receptors which control operation of sympathetic synapses, and (2) muscarinic receptors which activate smooth muscle and secreting glands. Acetylcholine antagonists may block one set of receptors preferentially. They do not interfere with the synthesis of acetylcholine. It is therefore possible for the total quantity of acetylcholine to increase because the blocked receptors cannot signal that enough acetylcholine has been released.

The best known antagonists are substances related to atropine.

Atropine

Atropine blocks the muscarinic action of acetylcholine more than the nicotinic. It may therefore allow an increase in acetylcholine and of sympathomimetic amines. The secretion of the latter is partially controlled by the quantity of circulating acetylcholine. Atropine is found in Datura stramonium (Jimson Weed, Jamestown Weed or thorn apple). Jimson tea was known many years ago to produce a marked change in behaviour. Atropine psychosis occurs frequently and are described in psychiatric texts. Any psychosis associated with fever, dry skin, dilatation of pupils may be due to excess atropine. A history of asthma and ingestion of atropine establishes the diagnosis. However, sometimes these toxic phenomena are slight and discrimination between the atropine psychosis and schizophrenia can be very difficult. Usually the hallucinations are vivid and there is some clouding of consciousness. Recently Baker and Farley (1958) described an acute confusional psychoses which followed the routine use of 1% atropine sulfate instillations in the eye for post surgical treatment of retinal detachment. When this patient was first examined the differential diagnosis was either schizophrenia or a delirium, the latter being more likely. It seemed the psychoses followed the use of the atropine. This was confirmed later when a small test dose of atropine reproduced the psychoses in this patient. The intoxication was due to the atropine in the tears which were swallowed. The author suggested a re-examination of all psychoses appearing in patients after eye surgery. These biochemical factors have usually been ignored by those writers who ascribed all these changes to the psychological stress associated with a threat to vision, or more recently to visual isolation which could be a form of sensory deprivation.

Benactyzine

This compound has been recommended for the treatment of anxiety states. Gardes and Laulan (1957) found the effects spectacular in conditions where there was depression. It did not alter psychotic patients. Ayd (1957) was not quite so happy with it. He found the results inconsistent and variable. Not one patient was completely freed of symptoms. Out of 40 patients 8 benefited

considerably, 9 were improved, 11 were not changed and 12 had to discontinue due to side effects. It frequently caused some blocking of thought, depersonalization, anxiety, dizziness, lassitude and muscular weakness.

Piperidyl Benzilates

These substances, chemically related to atropine are according to Ostfeld, Abood and Marcus (1958) psychotomimetic. They gave doses between 10 and 15 mg. orally to volunteers. About 30 minutes after administration they developed a dry mouth, blurred vision and tachycardia (atropine-like changes). This was followed by distortions of visual images and visual and auditory hallucinations. During the experience thought disorder was present. Orientation remained normal.

Abood and Meduna (1958) reported that another member of this series also produced psychosis. In this study confusion and disorientation was prominant. Residual changes in mood persisted for some time after they had recovered. They suggested these types of compounds might be eventually used in the treatment of depressions.

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Chapter 9

PSYCHOTOMIMETICS RELATED TO ADRENOCHROME

Most psychotomimetic chemicals, whether they occur naturally in plants and animals or have been produced by chemical synthesis, are indoles. These include LSD, bufotenine, dimethyltryptamine, harmine, diethyl tryptamine, psilocybin, ibogaine, adrenochrome and adrenolutin. At present, the only exceptions to this rule are the substances similar in structure to epinephrine, e.g. mescaline which may be indolized in the body, the active principle of hashish whose exact nature still seems to be disputed, and the newer parasympathomimetic compounds discussed in chapter eight. In the search for a schizogen or schizogens—a naturally occuring substance or substances mediating schizophrenic illnesses—this fact must surely be borne in mind.

Hoffer, Osmond and Smythies (1954) suggested that since all these natural psychotomimetics were indoles, schizophrenia might be related to the occurrence of such an indole in the human body. To reconcile psychiatric and biochemical observation, this hypothetical substance ought to be related to epinephrine. This provided a far better target in any search for the toxine X of Jung (1906) and the M substance of Osmond and Smythies (1952).

This simple proposition has been so misunderstood that some people, Pennes and Hoch (1957), believe that we advanced the absurd notion that all indoles were psychotomimetics or conversely that all psychotomimetics must be indoles. Other critics have failed to understand the importance of a point which we have made repeatedly, this is that in searching for psychotomimetic substances which could cause schizophrenia, one is limited to those which are present in the body or might conceivably be there. This automatically excludes substances such as LSD, mescaline, ibogaine, and psilocybin leaving bufotenine, the two tryptamine derivatives, adreno-

chrome and adrenolutin as possibilities. Bufotenine has been reported once in human urine, Bumpus and Page (1955), but this has not been repeated. The tryptamines have not been found in the body nor has anyone suggested how they might be formed there. Adrenochrome has been measured in plasma and whole blood by Payza and Mahon (1959). While they have not proven absolutely that their test measures adrenochrome, they have found no other substance which it measures. Other authors have also reported adrenochrome to be present. If adrenochrome is present, adrenolutin must also be there for adrenochrome is changed into adrenolutin in blood or plasma. In addition, the body is known to contain the substrate and the oxidizing enzymes for the synthesis of adrenochrome. Until other substances are discovered, adrenochrome and adrenolutin remain the most likely candidates for toxin X.

This chapter will, therefore, be devoted to a description of LSD as a representative of the best known plant psychotomimetic. But adrenochrome and adrenolutin as the best known animal psychotomimetics will be discussed later. A few other indole psychotomimetics will be described.

A. ERGOT PSYCHOTOMIMETICS

The most active ergot psychotomimetic is d-lysergic acid diethylamide (hereafter LSD). The average normal volunteer responds to 100 μg whether given by vein or by month. Very few react to doses less than 35 μg. Alcoholic patients require about 200 μg and often do not respond to 400 μg. Schizophrenic patients also require more. Two more ergot substances very similar to LSD in structure are active but require larger doses (methyl LSD and lysergic acid monoethylamide). It is likely all three act by a common mechanism in the body. Since LSD alone has been studied intensively (over 400 papers since 1943), it will be discussed here. Other ergot derivatives which differ slightly in structure to LSD are not active psychologically in the same way.

Mode of Action

LSD produces its psychotomimetic effect by unknown mechanisms. Theoretically, it can act (1) by a direct effect on some brain function, (2) by causing the body to build another substance which then is active, (3) by some combination of these effects.

1. Direct Action

In an intricate system of checks and balances such as the body, it is hard to categorize the action of any chemical as direct or indirect because there is usually some overlap. We shall term an action direct when it interferes with the biochemical or physiological function of the brain without being transformed into another active substance or causing the body to produce one. Direct effects include interference with cerebral circulation, or with the utilization of glucose, or with the transmission of stimuli across synapses. We shall term an action indirect when it results in the production of or an increase in the concentration of another substance. In this case, the presence of LSD alone without these other changes will not result in psychotomimetic changes.

a. Effect of LSD on Cerebral Circulation

LSD does not alter the circulation of blood through the brain. It is, of course, possible there may be localized changes in the way in which blood is distributed to specific centres of the brain. But since there is no way of testing this idea presently we shall not discuss it here. It is possible too that if the high doses used in animals were used in man, changes in circulation might be found but this would have little bearing on LSD as a psychotomimetic.

b. Effect of LSD on Production of Energy in Brain

In human volunteers, normal doses of LSD do not effect the use of glucose or of oxygen, neither does the respiratory quotient change. This shows that there is no gross disturbance in energy production. On the other hand, in vitro studies have shown that LSD inhibits the use of oxygen by brain tissue and that electrically stimulated tissue is more sensitive to LSD. This shows how cautious one has to be when interpreting in vitro studies.

c. Effect of LSD on Transmission of Stimuli

LSD interferes with the transmission of stimuli across synapses in the brain. Marrazzi (1957) found that when a cat which he had pretreated with pentobarbital sodium is given 8 μg per kg. of LSD by intracarotid injection the intensity of the post synaptic component of the transcallosal response is reduced. Other substances including the sympathomimetic amines and some indoles were either more or less active.

Purpura (1956) found similar changes in cats not anesthesized and given LSD. Low doses such as 4 μg per kg. caused facilitation of the primary cortical responses to visual and auditory stimuli in cats immobilized with succinylcholine. The recovery cycle was altered by a shortening of the initial recovery phase and a prolongation of the phase of super normality. High doses, i.e. 40 to 60 μg per kg. depressed the auditory evoked potentials while facilitation of cortical potentials evoked by photic stimulation remained.

Evarts (1953, 1957a, 1957b) found 30 μg per kg. (intracarotid) decreased the amplitude of the geniculate post synaptic response to a single stimulus to optic nerve. This occurred within 5 to 10 seconds after administration with recovery in one hour. Intravenous administration requires 100 μg per kg. The synapses are most sensitive in descending order, the transcallosal, suprasylvian, striate, and lateral geniculate. In the retina and between the lateral geniculate radiation and the cells of the visual cortex, there was no inhibition.

Many of these studies have used doses which are so much larger than the amount needed to produce the characteristic responses in humans, that one must question their value in this regard. They prove that if enough LSD is given, it will affect various areas of the brain. They do not show that this is how it works in humans.

In normal human volunteers, slight EEG changes have been found consisting mainly of an increase in frequency of the rhythm. Bradley (1958) using cats found that 15 to 25 μg per kg given intraperitoneally produced an alert EEG pattern from deep electrodes. But if external stimuli—such as noise—was deliberately

excluded, there was little activation. After spinal section, there was no change in the EEG.

Bradley suggested LSD acts on receptors closely related to collaterals entering the reticular formation from afferent pathways. This was supported by his observation that LSD had little effect on the arousal threshold for direct stimulation of the reticular formation but caused a marked fall in the threshold for arousal to auditory stimuli. The latter required only 1 to 2 μg per kg. The threshold for click responses of the auditory cortex was not changed. This is one of the few studies showing a change with doses equivalent to those used in humans. His final suggestion was that LSD acts at the brain stem by in some way sensitizing the reticular formation to external influences.

To sum up—although there is electrical evidence that LSD can act directly on the brain, it has not been shown that this is the usual way in which it acts. In most human experiments much smaller doses are effective than those used in the animal work which we have discussed. So far the animal experimenters have not dealt with the rapid excretion of LSD in humans and the curious fact that some subjects do not respond to very large doses of it.

d. Antagonism of LSD to Serotonin

Woolley and Shaw (1954) noted that many indoles produce either psychological changes or convulsions. These substances were antagonistic to serotonin when tested in certain biological experiments in vitro. They therefore suggested that these substances might produce their characteristic effects in vivo by interfering with serotonin. Woolley and Shaw (1957) suggested even more specifically that these effects might be related to either a deficiency or an excess of serotonin. About the same time Gaddum (1953) reported that out of several hundred compounds which he had tested for antagonism to serotonin, LSD was the most active and he then suggested that its psychotomimetic activity might be connected with this antagonism for serotonin. In later work he came to doubt the value of this suggestion and frequently made his doubt public, Gaddum and Vogt (1956), Gaddum, Krivoy and Laverty (1958). Following Woolley and Gaddum, Brodie and his

associates became eloquent in claiming that serotonin played some part both in LSD activity and mental illness. This idea has received wide support although the evidence supporting it is contradictory and its relationship to clinical findings extremely tenuous. It has become clear recently that the activity of LSD can not be primarily due to an antagonism of serotonin, but the idea received so much attention that we shall summarize the evidence on which it was based and discuss its present status.

(a) Serotonin is present in the brain and its distribution is localized to certain regions. Acetylcholine, norepinephrine and epinephrine are also distributed in much the same way so that serotonin is not unique in this regard. LSD might act equally well by interfering with any or perhaps all of them.

(b) In many biological systems LSD is undoubtedly antagonistic to serotonin, but brom LSD and some other indoles which are not psychotomimetic are even better antagonists of serotonin in the same test system.

(c) LSD does not cause depletion of serotonin from brain, Cerletti (1958), as it might do if it were antagonistic here. Depletion of serotonin by reserpine is not altered by LSD.

(d) Barbiturate narcosis is potentiated by serotonin and this effect is inhibited by LSD but also by brom LSD.

(e) When given intraventricularly to cats, serotonin produces a state of lethargy from which they can be removed by large quantities of LSD but not by smaller ones. This is not specific for LSD. Many other drugs causing central sympathetic stimulation will do the same.

It seems from this evidence at least as likely that LSD and serotonin, both indoles, are not antagonistic but are complementary to each other. They are both psychotomimetic indoles; LSD a very strong one and serotonin very weak. This is supported by the finding that both cause relaxation and vacuolization followed by contraction of oligodendroglia and both are synaptic inhibitors.

(f) Marrazzi (1957) arranged the compounds which he had tested in three groups. The lowest group is 100 times less active in producing depression of response in his cat preparation than the highest. The groups are (1) *low activity* (mescaline, adreno-

chrome, adrenolutin and norepinephrine), (2) *medium activity* (LSD and gamma amino butyric acid), and (3) *high activity* (serotonin and bufotenine).

Marrazzi then suggests that the activity which he can measure in cats corresponds to their capacity to produce psychological changes in man. It is not easy to condone this bold extrapolation from a certain sort of cat preparation to changes in human experience—particularly when serotonin which is eight times as effective in inhibiting the synaptic transmission produces no psychological changes in man. Marrazzi believes that in spite of this, serotonin is most likely to be involved because of its very strong inhibiting activity. We think he is putting the cart before the horse. But even if we overlook these discrepancies, and they are large ones, is it likely that a substance such as this which, if allowed to accumulate, would almost totally inhibit brain function is involved? Highly active substances are almost always bound (acetylcholine, epinephrine, serotonin). Unbound substances are quickly destroyed by single very active enzymes (acetylcholine esterase) or by a combination of many enzymes working together (amine oxidase, sulfoesterase, phenolase, and methoxylase on epinephrine). It seems unlikely to us that substances such as epinephrine, acetylcholine and serotonin can accumulate to a marked degree without causing anesthesia or death. On the other hand, a weak inhibitor which would not endanger survival might build up enough to produce a mild degree of inhibition. In our view, quite a slight degree of inhibition which involved many synapses would be sufficient to disrupt a complicated organ like the brain. For instance, Schwarz et al (1956) found that when three of the compounds from the low activity group were given intraventricularly in doses of 0.25 to 1.0 mg. all were equally active in producing marked changes in both the behaviour and the depth EEG of cats. This is about 1 to 0.2 percent of the human dose of these substances required to produce a psychological change. In striking contrast 15 μg. of LSD (15 percent of the human dose) produced the same autonomic reaction as did ergotamine but very little behavioural change. While 75 to 500 μg of serotonin caused a cat to become quiet and relaxed with low muscle tone and unsteady gait.

2. Indirect Action

a. On Acetylcholine

Thompson, Tickner and Webster (1955) showed that LSD is a powerful inhibitor of acetylcholine esterase and so increased acetylcholine levels. This was more marked in humans than in animals. LSD might owe its psychotomimetic properties to this alone since acetylcholine levels are clearly related to psychological changes. It would then be classed with esterase poisons such as DFP, Abood's compounds, etc. Pseudocholine esterase is even more strongly inhibited by LSD than true choline esterase. This curious fact which has so far received very little attention makes one suspect that the part which these two esterases play in cerebral functioning should be re-examined. But once again brom LSD which is psychologically inactive is as strong an esterase inhibitor as LSD itself so that this inhibition can not be primary. The inhibition of esterase may be one component which contributes to LSD's astonishing potency.

b. On Epinephrine Metabolism

That LSD might owe its psychotomimetic properties to a disturbance of epinephrine metabolism was first suggested by Hoagland, Rinkel and Hyde (1951). Enough evidence has now accumulated for us to class this idea as an hypothesis.

(1) After LSD is given to human subjects, the level of epinephrine in plasma rises at first then the level falls below that obtaining at the start of the experience and slowly returns to normal.

(2) The adrenal medulla becomes more active after LSD. This is shown by its rapid uptake of radio active phosphorus. Adrenocortical activity is not altered which suggests that this is specific for LSD and not due only to "stress." The medulla secretes epinephrine into the blood stream. There are many other places from which it is released into tissues but it is thought unlikely that these contribute much to the level of epinephrine in body fluids.

(3) The following table shows that after LSD the level of plasma adrenochrome rises and that this rise is correlated with the intensity of the psychological experience. In those few instances where adrenochrome levels did not increase, the characteristic

LSD experience was absent, instead the subjects complained of and also showed marked tension and anxiety. If these people were then given adrenochrome by vein, within a short time their tension and anxiety decreased and a typical, sometimes prolonged LSD experience supervened. Brom LSD does not raise adrenochrome levels and is as we have already noted not psychotomimetic. From this it seems that the typical psychological response to LSD depends upon the adrenochrome level being raised. In urine too after LSD adrenochrome is increased. In a few cases the increase in urine adrenochrome following 100 μg. of LSD was as great as after the intravenous injection of the 10 mg. adrenochrome. Lysergic acid morpholide, which we have found does not give an LSD experience, did not elevate plasma adrenochrome.

Many subjects require much more than the 100 μg. dose in order to have the typical LSD experience. Alcoholics and psychopaths usually require at least 200 μg and sometimes as much as 400 μg. before they react, Smith (1958). Some have failed to react after taking 400 μg. In these subjects the increase in adrenochrome levels is not marked.

Ascorbic acid quickly decolorizes adrenochrome and produces a series of indole compounds. One of them is 5,6-dihydroxy-

TABLE 15

EFFECT OF LSD-25 WITH AND WITHOUT ASCORBIC ACID AND OF BOL-148 UPON PLASMA ADRENOCHROME LEVELS

Subjects	*Number*	*Treatment*	*Quantity LSD-25 or BOL-148 (μg)*	*Adrenochrome, μg/liter, hours after LSD-25*					
				0	*2*	*4*	*6*	*24*	*48*
Normals	4	LSD-25	100	63	198	197	142	62	75
Alcoholics	5	LSD-25	200-300	59	155	125	—	126	74
Normals	5	BOL-148	500	78	61	—	—	—	—
Normals	2	Ascorbic Acid before LSD-25	100	84	170	115	—	84	—
Normals	3	Ascorbic Acid during LSD-25	100	66	74	59	—	82	—

N-methylindole. It is not psychotomimetic. Large quantities of ascorbic acid in the blood should therefore quickly destroy adrenochrome. That this happens can be seen in Table 15. However, these subjects still reacted to LSD. The experience was altered in quality but not prevented. This suggests that either ascorbic acid did not keep brain adrenochrome levels as low as that in the plasma or that other indoles such as adrenolutin continued to act.

Penicillamine is another reducing substance which decolorizes adrenochrome. Heacock (1959) found it produced the best yield of 5,6-dihydroxy-*N*-methylindole from adrenochrome. Hoffer and Callbeck (1960) treated a normal subject with penicillamine and then LSD on the assumption the penicillamine would protect her completely against the LSD. Here although the experience was altered in quality the subject had no feeling of emotion for the two weeks that followed the experiment. Methedrine temporarily produced normal emotion and a normal autonomic balance. The penicillamine-LSD combination seems to have depleted brain epinephrine stores so greatly that it took two weeks for them to be replenished. It might also be that it continued to act for two weeks.

(4) LSD stabilizes adrenochrome in plasma. In normal volunteers adrenochrome is quickly removed from plasma. The capacity for holding adrenochrome in plasma is measured by injecting 10 mg. by vein and analyzing the plasma for adrenochrome before the injection and 15, 30 and 60 minutes afterwards. We call this the adrenochrome tolerance test. If these same volunteers are given 35 μg. or more of LSD two hours before the test they do not remove adrenochrome so quickly. The level of adrenochrome stays elevated for one to two hours after injection, depending upon the amount of LSD used. If only 35 μg of LSD is given for the pretreatment this alone will not raise the level of plasma adrenochrome.

In acute schizophrenia, the adrenochrome tolerance test is very similar but it is not, of course, necessary to give any LSD. When 100 μg of LSD is given, the subsequent adrenochrome tolerance is even more abnormal. Brom LSD has no effect on the adrenochrome tolerance.

(5) Small quantities of LSD which do not produce psychological changes in cats markedly potentiate their response to adrenolutin, Melander and Martens (1958) and in rats, Noval, Brande and Sohler (1959). This is also true for humans and we shall discuss it in the next chapter at some length.

(6) LSD increases the conversion of epinephrine to adrenolutin in plasma, Heath and Leach (1956).

(7) LSD increases the depletion of ascorbic acid from the adrenal gland by epinephrine. Costa and Zetler (1958) found that 2.1 mg. per kg. of bufotenine, the same quantity of serotonin, or one third this amount of LSD, increased the loss of ascorbic acid after treatment with epinephrine. The ascorbic acid levels did not change when these substances were given alone. Brom LSD did not potentiate the loss of ascorbic acid. The authors consider that LSD acts by potentiating epinephrine to increase ACTH secretion which is known to deplete the adrenal gland of ascorbic acid.

In the chapter on mood, we referred to the relationship of ascorbic acid to anxiety and stress. This suggests another explanation. Ascorbic acid partially converts adrenochrome into DNMI which is in turn oxidized. Thus, an increase in the production of adrenochrome would use up the stores of ascorbic acid. LSD increases adrenochrome in both plasma and urine and inhibits its loss when injected. It also increases activity in the adrenal medulla. Thus the potentiation of LSD may be explained by an increase in the formation of adrenochrome. If one method for destroying adrenochrome is blocked it seems likely that a greater load will be placed on reducing substances such as ascorbic acid, glutathione, etc. BOL does not elevate adrenochrome, nor inhibit its destruction in blood and is therefore inactive. Serotonin and bufotenine being simpler indoles may be directly destroyed by ascorbic acid much as are other sympathomimetic amines.

(8) Human subjects quickly acquire tolerance to LSD, Isbell, Fraser, Wikler and Belleville (1955), Cholden (1950), Abramson (1956). Pretreatment with methyl LSD (MLD 41), Abramson, Sklarofsky, Baron and Freemont-Smith (1957, 1958), itself hallucinogenic and with brom LSD (BOL-148), not hallucinogenic,

inhibits the psychosis induced by LSD. On the basis of these tolerance experiments, Abramson (1956) developed an hypothesis that "establishment of tolerance and rapid loss of tolerance are part of a unified mechanism which also involves the psychological actions of the drugs". This is an agreement with our view that LSD alters the metabolism of epinephrine, Hoagland, Rinkel and Hyde (1955), and more directly that of adrenochrome, its metabolite.

The quantity of adrenochrome available to the brain after LSD will depend upon the plasma levels. This will depend upon the quantity of adrenochrome which can be released from tissues, e.g. the red cells of blood and upon the amount of substrate available (epinephrine). The first administration of LSD may therefore yield higher adrenochrome plasma levels than subsequent dosages. The initial responsivity to LSD would then not be regained until the original stores of adrenochrome and epinephrine were restored.

LSD acts as its own best antagonist by depleting the brain of epinephrine. Anything which will deplete epinephrine stores slowly should decrease the response to LSD. Perhaps when Abramson (1956) gave initially small dosages of LSD and methyl LSD and gradually increased them, he accomplished this type of epinephrine depletion without the formation of excessive quantities of adrenochrome. Brom LSD may act the same way.

Reserpine also depletes the brain and other tissues of norepinephrine and epinephrine, Muscholl and Vogt (1958) and if given to subjects in adequate dosages for several days before LSD should partially block it by using up substrate. Reserpine given during the LSD experience should intensify the experience since it releases more epinephrine and is itself an indole. Giberti and Gregoretti (1955) found that reserpine given several days (5-12.5 mg. daily) before LSD blocked the experience. Isbell and Logan (1957) and Hoch (1956) found that reserpine given during the LSD experience increased the severity of the reaction or induced additional disagreeable changes of its own.

Theoretically, adrenochrome levels can be restored in two ways (1) by injecting adrenochrome, (2) by administering the norepinephrine precursor, i.e. dihydroxyphenylalanine (DOPA). Weil-Malherbe and Bone (1958) found that DOPA restored

norepinephrine and epinephrine levels in the brains of animals depleted by reserpine. It should be possible to restore the psychological experience induced by LSD in subjects who no longer react to it by giving them either adrenochrome or DOPA.

The powerful psychotomimetic activity of LSD is surprising because ergot alkaloids of which it is an essential constituent seldom produces such effects. According to Goodman and Gilman (1956), these compounds both excite and depress the central nervous system, i.e. vasomotor reflexes are depressed, the vasomotor center is depressed, the vagus is stimulated, vomiting is induced and respiration depressed. The dosage given by vein varies between 0.3 to 1.0 mgm. LSD ought to share these properties and perhaps it does if we assume that LSD shares the common capacity of ergot alkaloids to depress the central nervous system but that its psychotomimetic effect stems from a unique ability to cause adrenochrome to accumulate in the brain. If this is so, the depressant effect of LSD as a member of the ergot group would be countered by the exciting effects of adrenochrome. However, while there is no limit to the amount of LSD that can be given, the amount of adrenochrome which can be made in the body is limited by the available epinephrine. Consequently as the dose of LSD increases the psychotomimetic action will be modified by the interplay of these factors. For each subject provided he can make or release adrenochrome from tissues there will be an optimum level. Beyond this level, the ergot sedative activity may appear. Where adrenochrome is not formed, this sedative property would appear earlier. Jarvik (1957) reported that in several subjects very resistant to LSD, 225 μg produced drowsiness. Sebrell (1955) reports that a monkey was tranquilized by 1000 times the dose of LSD which produced a psychosis.

(9) The antidiuresis of LSD during the first part of the experience is replaced by diuresis. It is at this time that adrenochrome levels are increased. It will be shown in chapter ten that adrenochrome has diuretic properties.

B. OTHER PSYCHOTOMIMETICS

1. Psilocybin

Wasson (1959) added another indole to the known hallucinogens. In Mexico, Indian tribes cultivate sacred mushrooms belonging for the most part to the species Psilocybe. Wasson, the ethnomycologist, Heim the mycologist and Hofman the chemist, who first discovered the unique psychotomimetic properties of LSD, combined to discover that the active principal is psilocybin (o-phosphoryl-4-hydroxy-*N*-dimethyl tryptamine), Hofman, Heim, Brock and Kabel (1958). The psychological activity of this compound is very similar to LSD. Somewhat larger quantities are required. Few studies have as yet been reported. However, if psilocybin sustains its initial promise of having a shorter period of action than LSD and is no more toxic, then it may have some place in experimental psychiatry.

2. Dimethyl and Diethyl Tryptamine

These substances are found in seeds of Piptadenia perigrina along with bufotenine and a hydroxy indole of unknown structure, Horning and Fish (1956). Szara (1957), Boszormenyi and Szara (1958), and Boszormenyi and Brunecker (1957) established these substances as psychotomimetics. Both are active if given by intramuscular injection. After a dose of about 1 mg. per kg. the psychological changes appear in about 15 minutes and continue for about 2 to 3 hours. The experience is quite similar to that which follows LSD or mescaline. Dimethyl tryptamine differs from psilocybin in lacking the hydroxyl on the benzene ring.

3. Bufotenine

Bufotenine is said to effect monkeys much as LSD does. In humans, the results are not as definite. Fabing, Kropa, Hawkins and Leake (1956) showed that 0.06 to 0.25 mg. per kg. given intravenously produced transient hallucinations in humans. One of us (A.H.) has several times inhaled 2 mg. of bufotenine without any noticeable effect. Turner and Merlis (1959) had schizophrenic patients snuff up powdered seeds of Piptadenia peregrina, but they could discover no psychological changes. Their interesting human experiment does not seem conclusive to us. Indians who snuff up

cohaba do so with the expectation of a sensory reward as part of a ritual. They would do their utmost to get the dust into their lungs and have invented special equipment which allows them to do this. We wonder whether the schizophrenic volunteers were similarly motivated or equipped. These experiments ought to be repeated on normal volunteers who have been taught to snuff up the powder as the Indians do.

Bufotenine may not be the active hallucinogenic component of Piptadenia peregrina. But, it may modify the actions of dimethyl and diethyl tryptamine. In the same way, the many alkaloids present in Peyote probably alter the effect of the most active component mescaline.

4. Harmine

Harmine is the most active alkaloid found in Banesteria Caapi. According to Lewin (1931) banisteria is used by natives of South America. To attain the desired mental effects an extract is prepared which is then drunk at a special festival, or when an individual wishes to pass into a trance during which the future may be revealed to him or to his medicine man.

If enough is drunk, the subject becomes very excited and agitated. This may be followed by vertigo and narcosis. The Indians take it for the visionary dreams, and to develop a greater understanding of their personal problems. One white traveller saw beautiful landscapes, towns, towers and parks.

Pennes and Hoch (1957) found that crystalline harmine had psychological effects similar to those of mescaline and LSD. However, they observed slight drowsiness with harmine. Visual hallucinations occurred at medium to high doses. Occasionally harmine induced a shallow euphoria. This is in striking contrast to the changes induced in the Indians as described by Lewin. Either Banisteria contains other alkaloids which modify the action of harmine or else the experimental setting used by Pennes and Hoch encouraged psychotic like experiences. The Indians wish for and use conditions which result in a psychedelic experience. In the same way the LSD experience may be made either psychedelic or psychotomimetic by the actions and attitudes of observers.

5. Ibogaine

Schneider and Sigg (1957) reviewed the central stimulant properties of ibogaine. This is an unusual indole because it is a central stimulant which increases the threshold to ECT in mice. The alert response which follows ibogaine administration can be abolished by atropine.

Ibogaine is present in the roots of Tabernanthe iboga. The root is chewed by natives of the Belgian Congo as an excitant. Extracts of the root in high doses caused excitement, mental confusion and hallucinations. In lower doses it is used to combat fatigue. No psychological experiments have been reported in humans so far.

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Chapter 10

ADRENOCHROME AND ADRENOLUTIN

A. SYNTHESIS

Green and Richter (1937) first determined the structure of adrenochrome which they isolated from the products of enzymatic oxidation of epinephrine. For many years Kisch (1947) had studied the pink coloring agent in deteriorated epinephrine which he called omega. This substance was first crystallized by Weinstein and Manning (1935). Subsequently, many inorganic oxidizing agents especially silver oxide were used for oxidizing epinephrine and the adrenochrome was precipitated from methanol containing a little formic acid at —80° C.

Green and Richter's (1937) preparation was unstable both in the solid and liquid state. This has been the general experience of most chemists although Sobotka and Austin (1951) claimed their preparation was indefinitely stable if stored at 0° C.

The adrenochrome available until 1957 has always been unstable even if stored dry under nitrogen below O° C. Various preparations synthesized by Eade (1954) and others were bright red amorphous powders which on standing slowly turned black. The black powders readily dissolved in water to yield red solutions containing fine black particles. It was very difficult to synthesize batches of adrenochrome with similar properties as evidenced by the color of the preparation, its LD-50 for animals and its psychological activity for humans.

Heacock, Nerenberg and Payza (1958) found that the amorphous adrenochrome contained varying quantities of adrenolutin, water insoluble melanin-like pigments and metallic ions. They showed that the instability of these preparations was due to their impurities and when the contaminants were reduced by passing the oxidized epinephrine solutions through a resin (silver content

under 0.01%), a crystalline product separates easily at —20° C. which is quite stable at room temperature and in dilute solution in water for several days. Concentrated solutions of adrenochrome polymerize readily, Heacock (1959).

Adrenochrome has been synthesized from l- and d-epinephrine and dl- mixture. The crystalline adrenochrome may be used to synthesize adrenolutin. In contrast to adrenochrome, adrenolutin is not optically active. Apparently adrenochrome from l-epinephrine is dextro rotatory, Sobotka, Barsel and Chanley (1957).

Abood (1957) using an ingenious sandwich of phenolase between two resin columns has produced pure and stable adrenochrome. However, enzymatic preparations do not readily yield ample quantities of adrenochrome. The concentration of adrenochrome is low and it is very difficult to crystallize.

B. PROPERTIES OF ADRENOCHROME AND ADRENOLUTIN

Unstable and contaminated adrenochrome has generally been used in biochemical studies. As these preparations contained varying quantities of other substances, it is possible some of the properties attributed to adrenochrome may be due to other substances or to auto-oxidized or polymerized derivatives. The properties of adrenochrome will have to be restudied using crystalline adrenochrome. Nevertheless, it is likely the activity of adrenochrome which results when small concentrations of adrenochrome are used will not be substantially changed. Where large quantities of adrenochrome were required to demonstrate a biochemical property, it is possible impurities played a more important role.

Epinephrine solutions which have turned pink may not contain substantial quantities of adrenochrome, Bacq (1949). Furthermore, this deteriorated mixture will have different properties from pure adrenochrome. This pink epinephrine did not affect behaviour of Siamese fighting fish, Abramson (1955) nor of guppy fish whereas pure adrenochrome solutions did alter guppy behaviour, Abood (1957).

1. Chemical Properties

Pure adrenochrome, Heacock, Nerenberg and Payza (1958), consists of deep-violet crystals, melting point 112° C. with decomposition. Elemental analysis is within experimental error of the theoretical. The ultraviolet and visible absorption spectra in aqueous solution were λ max: 301, 487 mμ.; λ min: 262, 361 mμ.

Adrenochrome is decomposed in many solvents used for paper chromatography. Thus it is decomposed in propanol ammonia solvents and in n-butanol:acetic acid:water. Distilled water and 2% acetic acid in water are suitable solvents. In water, the R_f was 0.8 ± 0.02 on Whatman No. 1 paper washed with distilled water for 12 hours and dried prior to use.

Under alkaline conditions and in the presence of certain metallic ions, especially zinc, adrenochrome readily rearranges into adrenolutin N-methyl-3,5,6-indole triol).

Reducing agents discharge the red color of aqueous adrenochrome solutions, Heacock (1959). Apparently adrenochrome picks up one atom of hydrogen with the formation of an unstable intermediate. This changes into (1) an indole which readily loses water to form 5,6-dihydroxy-N-methylindole, (2) another indole which under the influence of alkali may isomerise into adrenolutin. Other reducing agents for adrenochrome are glutathione, dihydroxy-maleic acid, dihydroxy fumaric acid, cysteine and sodium borohydride, penicillamine, Heacock (1959).

2. Biochemical Properties

a. Carbohydrate Metabolism

In 1937, Green and Richter found that adrenochrome was a hydrogen carrier in the lactic and maleic dehydrogenase system at 6×10^{-7} molar concentration. Randall (1946) found adrenochrome inhibited glycolysis in brain tissue under anaerobic conditions and that glutathione by reacting with adrenochrome rendered it inactive. Meyerhof and Randall (1948) attributed this inhibition to inhibition of hexokinase and phosphohexokinase. Their work was also anaerobic and limited to the glycolytic sequence. Woodford (1959) found that adrenochrome also inhibited the uptake of oxygen by chopped rat brain tissue under aerobic conditions using

glucose, pyruvate, succinate and malate as substances. It is apparent that other enzymes also are inhibited. Reduced glutathione, adenosine triphosphate, nicotinic acid and ferrous sulfate did not reverse the inhibition.

Radmsa and Golterman (1954) studied adrenochrome in hydrogen transport system involving ascorbic acid. Oxidation of ascorbic acid was stimulated by 10^{-6} M. adrenochrome and oxidation of lactate inhibited by 10^{-4} M. In pure solution, ascorbic acid reduces adrenochrome to a leuco series of substances, Heacock (1959), which may account for the acceleration of ascorbic acid reduction.

Park, Meriwether and Park (1956) reported that 5×10^{-4} M. adrenochrome completely uncoupled oxidative phosphorylation in hamster liver mitochondria. This was not reversed by magnesium. Adrenochrome was more active in the presence of small quantities of thyroxin. Park, Meriwether, Park, Mudd and Lipmann (1956) added that glutathione and ethylene diamine tetraacetate counteracted this uncoupling effect. Glutathione (concentration 100 times adrenochrome) gave complete protection. The red color of the adrenochrome solution changed to yellow with added glutathione. Heacock (1959) found various reducing substances such as ascorbic acid, glutathione, cysteine, dithydroxy maleic acid decolorized red adrenochrome with the formation of yellow fluorescent solutions. Walaas and Walaas (1956) found that sarcosomes isolated from rat diaphragm oxidized epinephrine to adrenochrome. The adrenochrome inhibited hexokinase activity in extracts but did not decrease glucose uptake of intact diaphragm.

The interference with glucose utilization may be responsible for the antimitotic effect of adrenochrome for epidermis of mice, Bullough (1952). Epinephrine is inactive until it is changed into adrenochrome.

The inhibition of brain tissue glycolysis requires rather large quantities of adrenochrome. It is likely that interference of glycolysis is not the chief pathway by which adrenochrome interferes in brain tissue respiration.

b. Adrenochrome and Brain Inhibitor Factor

Florey (1954, 1956), Florey and Elliott (1956) and Bazemore,

Elliott and Florey (1956) found an inhibitor factor in mammalian central nervous tissue. Factor I is probably a transmitter substance of inhibitor neurons. It is present in an inactive form in brain from where it is released by heat and chemical treatment. Apparently, much of factor I activity is due to gamma amino butyric acid (GABA). It is possible a lack of GABA will result in increased state of nervous excitement. Thus, Woodbury and Vernadakis (1958) reported that brain excitability varied inversely with GABA concentration in the brain (r=0.66).

According to Holtz and Westermann (1956) adrenochrome (5 micrograms per gram) (3×10^{-8} moles) markedly inhibits decarboxylation of glutamic acid by brain tissue. This means that there might be a decrease in the formation of GABA which is produced by the decarboxylation of glutamic acid. The high degree of anticarboxylase activity of adrenochrome suggests this may be a major site of activity. Increased concentration of adrenochrome would therefore produce a state of excitement by decreasing the production of GABA.

c. Adrenochrome and Amino Acids

Greig and Gibbons (1957) found that adrenochrome stimulated the oxidation of glycine to carbon dioxide, ammonia and formic acid. In the presence of rat kidney tissue, glycine oxidation to glycolic acid was accelerated. Other amino acids such as glutamic acid, phenylalanine, tryptophane are also oxidized. This, they think, accounts for the apparent deficiency of glycine and the increased formation of phosphoglycolic acid in erythrocytes of schizophrenic patients.

d. Adrenochrome and Iron Metabolism

Green, Mazur and Shorr (1956) found Fenton's reagent (ferrous ion and hydrogen peroxide) oxidizes epinephrine to adrenochrome at pH 4.5. Ferritin in the presence of hydrogen peroxide also oxidizes epinephrine to adrenochrome. According to Green, Mazur and Shorr (1956), epinephrine oxidation at pH 7.4 to melanin is accelerated ten fold by iron chelating agents. Adrenochrome is a vasoconstrictor of smooth muscle of capillaries whereas melanin is not. This is why ferritin inhibits the constriction of muscle capillaries to epinephrine.

e. Adrenochrome and Melanin Pigmentation

Adrenochrome readily polymerizes in vitro to form dark substances and in vivo to form melanin-like pigments. In addition, it may react with amino acids to form red pigments in the presence of the phenolase complex, Mason (1955). This may account for the relationship of epinephrine to pigmentation. Meirowsky (1940) found that the production of pigment in human skin was highly increased under the influence of adrenochrome. Cells of the intestinal mucosa can produce melanin-like pigments from epinephrine and adrenochrome, Langemann and Koelle (1958). They yield yellow or yellow brown pigments.

f. Adrenochrome and Oxygen Toxicity

The oxidation of epinephrine to adrenochrome is accelerated by oxygen. This raises an interesting speculation about the role of oxygen poisoning in living animals which is relevant for studying deep sea divers and other humans exposed to high oxygen pressures. From the evidence presented this far, it is evident that excessive quantities of adrenochrome can effect the metabolic function of nearly all cells in the body. Gershenovich et al (1955) showed that under high oxygen tension, much epinephrine can be transformed into adrenochrome. Rabbits were placed in compression chambers filled with oxygen at 3.5 and 6 atmospheres pressure. With the latter pressure, the animals showed three distinct changes (a) a period of stimulation with motor restlessness 10-13 minutes after beginning the experiment, (b) a period of convulsions 20-25 minutes after the beginning, (c) a terminal period marked by coma, disturbed respiration and finally terminal convulsions. The epinephrine and oxidized epinephrine derivatives (expressed as adrenochrome although others were also formed) changed during these periods as shown below:

	Epinephrine	*Adrenochrome*
Brain	A. decreased 60%	increased 15%
	B. slight increase	slight decrease
	C. slight increase	increased 33%
Adrenal Medulla	A. increased 234%	increased 34%
	B. reduced 42%	slight decrease
	C. none detected	increase

Under 3.5 atmospheres pressure, the same changes occurred but more slowly. It is likely the toxic changes are due to adrenochrome and other oxidized derivatives of epinephrine. Laborit, Broussalle and Perrimond-Trouchet (1957, 1957a) found adrenochrome increased slightly the tendency of mice to have convulsions under pure oxygen. Serotonin in contrast was protective. Adrenoxyl also increased the frequency of convulsions. LSD did not increase the convulsive tendency. Bean and Johnson (1955) reported that unlike most stresses, high oxygen tension is less toxic to animals after adrenal medullation. In the absence of corticosteroids, epinephrine alone will increase toxicity to oxygen. In the intact animal, epinephrine also increases toxicity to oxygen. Adrenergic blocking agents increase survival time. Gerschman, Gilbert, Nye, Price and Fenn (1955) confirmed these observations. Taylor (1958) reported that adrenalectomy protected against the convulsing effect of 6 atmospheres O_2 pressure. Finally Perot and Stein (1956) found that peripheral nerve conduction block is produced by high O_2 pressure. Marrazzi and Hart (1956) have shown that adrenochrome can block synaptic transmission of stimuli.

Thus, it is possible mental changes induced the people exposed to high pressures of oxygen for prolonged periods of time, e.g. sea divers, may be due to the effect of slight increases in the adrenochrome in their brain. Cousteau and Dumas (1953) have given a vivid description of this folie des profondeurs in which the diver becomes enamoured of the depths around him and loses all sense of the danger of going deeper and deeper. This would be prevented by giving divers substances which counter the effect of adrenochrome on the brain. Nicotinic acid reverses the EEG abnormalities produced in epileptics by adrenochrome and its psychological effects. Perhaps divers should take adequate quantities of nicotinic acid.

g. Adrenochrome and Allergies

Hutcheon, Lowenthal and Eade (1956) reported that adrenochrome had weak antihistaminic properties. In concentrations of 2 to 10 x 10^{-6} mole, adrenochrome inhibited histamine induced concentration of the isolated guinea pig ileum. This is about 4%

of the activity of pyrilamine. Thus, although adrenochrome is weakly antihistaminic, it could by its continuous presence be as effective as much stronger antihistamines given sporadically. Alberty and Takkvnen (1956) found that adrenochrome monosemicarbazone prevented the increase in vascular permeability due to intradermal injections of histamine. It was equally effective as a specific antihistamine in suppressing the skin reaction to 48/80 (most potent histamine release substance). Intraperitoneally, it had the same order of magnitude as the antihistamines.

Adrenochrome may well counteract histamine in vivo. Halpern, Benacerraff and Briot (1952) reported that adrenalectomized mice have a much decreased tolerance to histamine. Cortisone or epinephrine alone gave protection against 5 to 10 times the lethal dose. Both together increased the tolerance 50 to 100 times. No increase in tolerance was produced in intact animals. Ingle and Nezamis (1953) reported that adrenalectomized rats were much more sensitive to histamine. With this species of animal, epinephrine restored normal histamine tolerance but the corticosteroid hormones did not.

3. Neurophysiological Properties

a. Effect on Electroencephalogram

Szatmari, Hoffer and Schneider (1955) injected adrenochrome intravenously into a few normals and a larger series of epileptic patients while they were having electroencephalograms recorded. There was no EEG change in the normals. The epileptic patients were divided into two groups (1) 5 cases with a history of grand mal seizures but without a clinical or EEG focus and (2) 21 cases of focal-cortical seizure epileptics. In the first group, there were marked increases in diffuse and paroxysmal abnormality and increased amplitude. In the second group there was a spontaneous increase in focal activity in four cases and an increase in focal activity on hyperventilation in all cases. Intravenous nicotinic acid normalized the adrenochrome-induced abnormality and in many instances after nicotinic acid the records were more normal than had been the original routine EEG.

Small quantities of adrenochrome placed in the lateral or third

ventricle of cats produced marked changes in behaviour and changes in the depth electroencephalogram. Schwarz, Wakim, Bickford and Lichtenheld (1956) found .125 to 1 mg. of adrenochrome induced a drowsy trance-like state. This was accompanied by occipital 4 CPS slow waves with low-voltage spike components which spread to the frontal regions and then diffusely over the brain. Diffuse slow waves and spindles were often noticeable when the cat was sitting with eyes open. These authors reported that the animals responded by blinking, yawning or retching a few minutes after they were given adrenochrome. They then went to sleep. However, they were readily aroused. With adrenolutin, the results were the same but they came on more quickly and were more pronounced. The cats also became very drowsy and assumed unusual positions.

Leimdorfer and Metzner (1949) found that large quantities of epinephrine, i.e. ½ to 1 mg./kg. caused dogs to become quiet within 10 to 11 minutes and 30 minutes after the injection into brain ventricles, they were asleep. Sleep lasted 1 to 2 hours. Surgical anesthesia was produced. These quantities of epinephrine did not produce EEG changes as measured by surface electrodes. However, with 2½ to 3 mg./kg., EEG waves were greatly depressed in voltage. Then the animals died. The epinephrine did not elevate the blood pressure but did induce hyperglycemia, Leimdorfer, Arana and Hack (1947). In contrast, a sympathomimetic amine which can not form adrenochrome-like metabolites, did not produce analgesia or sleep and the blood pressure was elevated.

Adrenochrome produces changes in the animal more quickly than does larger quantities of epinephrine. This suggests that perhaps epinephrine must be converted into adrenochrome for an effect to occur. Derouaux and Roskam (1949) similarly found that adrenochrome produced maximum hemostatic activity in a shorter period of time than epinephrine.

In addition, the inactivity of ephedrine which is closer to epinephrine than to adrenochrome in structure reinforces the suggestion that epinephrine per se is not as active as adrenochrome.

Adrenochrome produces changes in the EEG of animals comparable to LSD, serotonin, epinephrine and norepinephrine, Slo-

combe, Hoagland and Tozian (1956) reported that LSD, serotonin, adrenochrome and epinephrine all reduced spontaneous electrical activity in both frequency and amplitude in rats anesthesized with pentothal but not with ether. They suggested these substances may all work in the reticular formation. In terms of concentration, serotonin was most active followed by epinephrine, LSD norepinephrine and adrenochrome. They used 30-75 μg adrenochrome per animal. Slocombe (1956) also found that these substances reduced evoked electrical activity in albino rats under pentothal anesthesia. In anesthesized animals, there was no depression of spontaneous activity but in some cases an increase in slow wave amplitude superimposed on unchanged fast activity.

It is evident that adrenochrome does produce changes in cerebral function in intact animals. Marrazzi (1957) has indicated the site of activity. He found that adrenochrome resembled in activity the synaptic neurohormones, epinephrine and norepinephrine, as did serotonin. Serotonin was most active and adrenochrome least active.

It is possible lesser quantities of adrenochrome would have given similar activity if crystalline adrenochrome had been available to Marrazzi. Furthermore, since adrenochrome is rapidly removed from plasma, Hoffer (1959) and Hoffer and Payza (1958), less would effectively penetrate the synapses. However, it is not likely these two factors would alter the relative activities of the substance.

At this point, it might be useful to discuss the relationship of activity to dosage. At one time, we considered it likely that the essential schizophrenic factor might be present only in schizophrenics, i.e. resemble the all or none characteristic of specific poisoning. This implied that minute quantities of highly active substances resembling LSD were the most likely candidates. Our later analyses of the problem suggested that larger quantities of a less active substance might account for the illness. However, the recent finding that adrenochrome is present normally in concentrations of around 60 μg per liter indicates that even larger quantities of even less potent substances may be present. If adrenochrome by Marrazzi's test was as active as serotonin, brain activity would

undoubtedly cease. The living organism can not tolerate large quantities of highly active substances. It either binds them and releases them rapidly in minute bursts as it does with acetylcholine or provides many pathways for quickly destroying them as it does for epinephrine. If serotonin or epinephrine were present in large concentrations in the brain it seems likely that activity would cease. Adrenochrome, however, could accumulate slowly without producing a catastrophic reaction until subtle changes in cerebral function occurred. This makes it more reasonable to direct the search toward chrome indole substances. Finally, it is easy for the laboratory worker to forget that most schizophrenic patients do not die of their illness, i.e. only mild and subtle changes in cerebral function are induced. These need not be great to produce major disorders in perception and thought.

b. Hypothermia

Hutcheon, Lowenthal and Eade (1956) found that both adrenochrome and even more adrenolutin intraperitoneally markedly lowered body temperature of rats. 2.5 mg. per rat lowered temperature 1° C. at ½ hour with a return to normal temperature at 4 hours. 5 mg. per rat lowered the temperature 2½° C. at two hours with normality restored at 6 hours. Since adrenochrome has little or no effect on the oxygen consumption of rats, it seems adrenochrome produces hypothermia by a central effect on the temperature regulating system of the hypothalamus. Cerletti (1956) found that LSD and similar ergot derivatives also lowered temperature in rats. LSD was the most effective. Brom LSD was least active.

Hoffer (1958, 1959) reported that LSD increased adrenochrome levels in serum and urine in human subjects. It is therefore possible the hypothermic action of LSD is potentiated by the endogenous adrenochrome. Brom LSD does not increase adrenochrome levels in humans. This may account for the increased activity of LSD compared to brom LSD. Rabbits, on the other hand, respond to LSD with hyperthermia which suggests they either do not form adrenochrome or do not react to adrenochrome as do rats. Rinkel in discussing Cerletti's (1956) contribution re-

ported that skin temperatures of human subjects decreased slightly 2 hours after LSD.

c. Adrenochrome and Diuresis

Schizophrenic patients with ready and free access to water tend to secrete larger volumes of urine per day than non schizophrenic subjects. This was reported by Hoskins (1946), Hoagland, Pincus, Elmadjian, Ramonoff, Freeman, Hope, Ballan, Berkley and Carlo (1953), Hoagland, Rinkel and Hyde (1955) and has been observed by Hoffer and Osmond (1958). LSD is antidiuretic for humans, Kies, Horst, Evarts and Goldstein (1957), due these authors suggest to hypothalamic stimulation. However, with large series

TABLE 16

Effect of LSD, Adrenochrome or Both on Volume of Urine and Amount of Adrenochrome Excreted

Subject	*Treatment*	*Time*	*Volume Urine ml/hour*	*Total Adreno-chrome μg/hour*
Mrs. Y.	LSD 200 μg at 9:00 A.M.	7:00-9:00	40	9
	10 mg. adrenochrome I.V.	9:00-12:00	35	100
	at 11:40	12:00-2:30	160	30
		2:30-4:00	310	20
		4:00-5:00	205	11
Mr. B.	LSD 200 μg at 9:00	7:00-9:00	43	10
		9:00-11:00	56	28
		11:00-1:00	72	19
		1:00-3:00	83	17
Mr. Bl.	LSD 200 μg at 9:00	7:00-9:00	40	6
		9:00-11:00	130	27
		11:00-11:30	750	21
		11:30-12:45	157	6
Mr. D.	(a) Adrenochrome 10 mg. at 1:30	1:30-3:30	62	62
	(b) LSD 200 μg at 9:30	9:30-4:00	22	12

of patients our experience shows that antidiuresis which is usually observed in the first half of the experience may be replaced by diuresis and that this is apparently related to the production of adrenochrome.

This was studied by measuring urine volumes excreted for timed intervals and determining the concentration of adrenochrome in blood or urine or both. Subjects were given either LSD alone or adrenochrome alone or both combined, Hoffer (1959). The results are shown in Table 16.

After intravenous adrenochrome alone in one instance, urine excretion was normal. In two subjects (B and Bl) there was a three to four fold increase in urinary adrenochrome and a two to four fold increase in secretion of urine. In subject Mrs. Y. the injection intravenously of ten mg. adrenochrome caused a ten fold increase in urinary adrenochrome whereas urine excretion increased five fold. In subject Mr. D., LSD alone produced a slight psychological reaction and the urine rate was half of normal. There was no increase in urinary adrenochrome. On another occasion 10 mg. adrenochrome caused a five-fold increase in adrenochrome and about two fold increase in urine.

C. ADRENOCHROME, A NATURAL METABOLITE OF EPINEPHRINE

1. Assay Method

Harley-Mason and Bu'Lock (1950) found that zinc acetate catalyzed the conversion of adrenochrome into adrenolutin which could, they thought, chelate with the zinc. Fischer, Derouaux, Lambot and Lecomte (1950) reported that the adrenolutin complex which fluoresced could be used for measuring adrenochrome excretion in the urine of animals when it was given to them intravenously (Fischer and Lecomte, 1951). Payza and Mahon (1959) developed a method for measuring adrenochrome in blood, and cerebrospinal fluid based upon this reaction. This method modified may be used to measure adrenochrome in urine.

Freshly drawn heparinized blood is centrifuged. Zinc acetate-ascorbic acid reagent is added to an aliquot and to another aliquot containing a known quantity of crystalline adrenochrome (internal

standard). The zinc adrenolutin complex is taken into acetone containing ascorbic acid. The fluorescence is determined using 405 mμ for excitation and 500 mμ for maximum emission.

The mean plasma value for over 50 non schizophrenic subjects is 56 μg per liter ranging between 20 to 110. Some schizophrenics have values beyond this range. Cerebrospinal fluid contains similar concentrations. Urine contains about 250 μg per liter and non schizophrenic subjects excrete about 10 μg adrenochrome per hour.

2. *Does the Body Produce Sufficient Epinephrine to Account for the Adrenochrome?*

It has been hinted from time to time that while the adrenochrome hypothesis may be ingenious, unfortunately the body does not make enough epinephrine for it to be feasible. This is a serious and might be a fatal objection. Cannon certainly implied that epinephrine is only produced in emergencies and the fact that little of it is found in the plasma has made some investigators confident that there is equally little in the rest of the body.

While metabolic balance studies are not conclusive, there is much evidence suggesting that about 5 mg. of epinephrine can easily be produced per day under normal conditions. The total quantity present in the body may be considerably greater for epinephrine is stored in many tissues. Erythocytes may contain up to 1 μg per gram of sympathomimetic amines or about 5 mg. in total blood. Supporting evidence for these statements will now be reviewed.

a. Evidence from Concentration of Epinephrine in Plasma

Epinephrine is found chiefly in red cells and platelets, not in serum or plasma. In a colloidal system such as blood, the quantity of epinephrine held in whole blood can not be estimated from the quantity of plasma unless the adsorption isotherm[1] is known. Furthermore tissues, e.g. myocardium, remove epinephrine so quickly from blood that there is very little chance for a great increase in concentration unless the rate of production is excessive.

[1]The mathematical equation relating the amount of substance free and adsorbed in a colloidal system.

Richardson, Woods and Richardson (1958) reported that morphine increased epinephrine in plasma in dogs from 25 to 70 μg/liter within 10 minutes.

Furthermore, since fresh hemoglobin can so readily catalyze the oxidation of epinephrine to adrenochrome (about one percent of the red cells are destroyed each day), this contributes to the uncertainty of estimates based upon plasma levels. Finally biochemical assays measure both dextro and laevo epinephrine whereas biological tests measure primarily laevo epinephrine.

b. Evidence from Injection Intravenously of Epinephrine

Epinephrine cannot be given in large quantities because of its sympathomimetic activity. To counteract this animals are often protected by sympathomimetic agents. It is questionable whether one should draw conclusions about normal epinephrine metabolism from this admittedly abnormal state. When epinephrine is injected in smaller quantities, it more closely approximates the physiological state, but even then it does not necessarily compare with the release of epinephrine from the adrenal medulla into inferior vena cava blood or from autonomic ganglia into cell masses, Raab (1953).

Injected epinephrine does not produce a gradual build up in concentration. It is removed so quickly from plasma that a steady state develops, Watts and Poole (1957). The concentration of free epinephrine closely parallels the blood pressure. Only about one percent of any quantity given intravenously appears free in urine.

Chemists continue to examine the relationship between epinephrine metabolism and mental disease. This is done most frequently by injecting epinephrine intravenously. The dose is limited by its toxicity. These studies will eventually yield important data especially when a method for assaying epinephrine becomes generally used. But unless the epinephrine metabolites are studied simultaneously, the information will be difficult to interpret.

If one measures the loss of epinephrine from the plasma, it seems that schizophrenic patients use epinephrine in the same way

as do other people. Thus, it has been found that epinephrine was equally stable in plasma from normal and schizophrenic patients in vitro when certain conditions such as pH, buffers, etc. are used. However when conditions are altered to make them optimal for the oxidation of epinephrine by enzymes then there may be some differences. In this instance schizophrenic plasma tends to be more active. These findings suggest that oxidation of epinephrine normally does not proceed in plasma. Rather it is an intracellular process. This is not strange since epinephrine has a preference for cells, i.e. erythrocytes, myocardial cells, etc.

Hoffer (1957) and Payza and Hoffer (1960) showed that freshly hemolyzed erythrocytes accelerated the rate of oxidation of epinephrine. About one percent of human red cells are destroyed daily releasing about 0.7 grams of hemoglobin into 5 liters of blood. This may account for the ease with which epinephrine is oxidized in plasma under optimal conditions. Such optimal conditions should, we suggest, approximate to those found inside red cells rather than in plasma.

Although Holland et al (1958) reported that schizophrenics remove injected epinephrine at the same rate as other people, one cannot conclude from this that they metabolize it in the same manner. It can be removed from plasma by (a) being taken into cells, (b) by being converted to other substances. The first method is probably more important. Epinephrine is then either stored or changed into other compounds. Plasma can also convert some of it to adrenochrome and so to adrenolutin.

While the total rate for the loss or destruction of epinephrine is essential to establish the intermediary metabolism, this alone would result in a very crude approximation. If epinephrine is metabolized by two pathways, the normal one (a), and an abnormal one (b), what one must discover is not simply how much epinephrine is handled by (a) and how much by (b) but what proportion goes in each direction. Sulkowitch and Altschule (1959) have recently demonstrated that psychotic and neurotic (anxiety) patients have large quantities of "epinephrines" (these include epinephrine, norepinephrine and their indoles). In addition, schizophrenic patients have an unstable adrenolutin-like substance

in their urine. They suggest that these patients may make adrenolutin instead of epinephrine and not from it. Their reasoning is that the total quantity of epinephrines is much the same and injected epinephrine is mostly converted into methoxy derivatives.

We have examined these points elsewhere and believe that other interpretations of their findings are at least plausible. Shaw, McMillan and Armstrong (1956) demonstrated that methoxy derivatives of epinephrine were formed in the body. Axelrod has claimed that epinephrine is mostly changed into these methoxy derivatives. What his work in fact suggests is that this may well occur when epinephrine is injected by vein. It does not follow, of course, that epinephrine made in the body must follow the same pathway. But even if it did metepinephrine could form metadrenochrome or even, after demethylation, adrenochrome. Axelrod's contention, even if it were wholly correct, does not mean that adrenochrome cannot be present in the body.

A comprehensive study of epinephrine metabolism should include (a) the rate of removal of epinephrine from various depots, e.g. plasma, subcutaneous tissue, and lung tissue, (b) a measure of the metabolites formed which will account for 100% of the epinephrine without needing large correction factors which only mislead by attempting to disguise our ignorance. Chemists searching for adrenochrome must remember its great reactivity and use techniques which will not decompose it or its metabolites.

c. Evidence of Rates of Secretion from Adrenal Glands

Blood may be drawn directly from the adrenal vein. The difference in epinephrine concentration between the adrenal artery and vein allow one to estimate the quantity secreted by the gland. Kaindle and Von Euler (1951) reported that in a cat the resting secretion from a single adrenal gland was 0.073 μg/kg/minute of total catechol amines. This would be about 7 mg. daily for a human adult. Severe stress, e.g. carotid occlusion, increased the rate in cats to 0.23 μg/kg/minute (23 mg. per human per day). Epinephrine made up 15 to 40 percent of the total. Dogs have similar secretion rates. Houssay and Rapela (1953) found that one adrenal gland of a dog secreted 0.032 μg/kg/minute.

Splanchnic stimulation increased this to 0.39. Epinephrine made up 80 percent of the total. Carter and Hardy (1959) sampled adrenal vein blood from humans, undergoing abdominal surgery. They calculated that under these conditions the daily rate of secretion was 0.23 mg. per gland or 0.45 mg. per person. This may be an underestimate as anesthesia decreases epinephrine levels, Montagu (1958).

d. Evidence from Quantity of Epinephrine in Urine

The evidence here is very confused due perhaps to uncertainties in the chemical methods for assaying epinephrine. Only about one percent of injected epinephrine appears in urine so that a correction factor of 100 is used in estimating daily production. In addition, there may be considerable destruction in the bladder because especially in alkaline urine epinephrine is very unstable.

Diller and Kilpatrick (1958) reported a mean daily excretion in man of 2.8 μg. During hyperthyroidism this increased to 25 μg. Multiplying these by a factor of 100 yields estimates of 0.28 mg/day at rest and 2.5 mg. during hyperthyroidism. Helmer (1957) using a bioassay found an excretion of 80 μg/day (multiplied by 100 this yields an estimate of 8 mg.). Luft and von Euler (1956) reported the normal excretion of 18.9 μg/day in humans (multiplied by 100 the estimate is 1.80 mg/day). Insulin hypoglycemia increased this to 231 μg/day.

Crawford and Law (1958) measured the excretion of sympathin in rats as 2 μg per day which is equivalent to 5 mg./day per human.

Armstrong and McMillan (1957) reported that about 30 percent of administered norepinephrine is excreted as homovanillic acid. Normal humans excrete 2-4 mg. of this compound per day. Multiplied by 10/3 this yields an estimate of 10 mg/day. A summary of these estimates is given in Table 17.

Sundin (1958) found that tilting normal subjects from a prone position to a 75° tilt increased the secretion of sympathomimetic amines from 0.56 to 3.0 mg/day. Thus estimates made from urine collected while subjects are prone are liable to be under estimates.

TABLE 17

ESTIMATE OF SYMPATHOMIMETIC PRODUCTION

Authors	*Source of Epinephrine*	*Correction Factor*	*Final Estimate mg/day 70 kg. man*
1. Kaindl and von Euler	1. Secretion in adrenal vein blood of cat	None	7
	2. As above—under stress	—	23
2. Houssay and Rapela	1. As above—dog	—	3
	2. As above—under stress	—	39
3. Carter and Hardy	Human adrenal vein	—	0.5
4. Diller and Kilpatrick	1. Urine	100	0.3
	2. Urine (hyperthyroid)	100	2.5
5. Helmer	1. Urine	100	8
6. Luft and von Euler	1. Urine	100	1.9
	2. Urine—stress	100	23.1
7. Crawford and Law	1. Rat urine	100	5
8. McMillan and Armstrong	1. Human urine (homovanillic acid)	10/3	10

The best estimate from all these sources therefore shows the extreme range from 0.3 to 23.1 mg. per day for humans. Thus it seems reasonable to suppose that an average male weighing 70 kg. secretes at least 5 mg. of sympathomimetic amines daily.

3. Is Adrenochrome Present in the Body?

Neither adrenochrome nor any of its derivatives have been isolated and crystallized from living tissue. There is thus no absolute proof that it is a natural metabolite of epinephrine. This will be difficult because adrenochrome, if present, is in very low concentrations and since it is so chemically reactive very exact techniques will be required. The body produces ample quantities of both epinephrine and oxidizing enzymes so that one would expect adrenochrome to be formed.

Indeed Payza and Mahon (1959) found fluorescent substances in plasma and in whole blood which have properties remarkably like those of adrenochrome. They have not been able to find any other possible metabolite which has these properties. They therefore suggest it is adrenochrome or some chemical very similar in structure. Other workers have reported similar findings. Utevskii and Osinskaya (1957) found substances in heart and brain of rabbit similar in structure to the fluorescent oxidized derivatives of epinephrine. They were bound to protein.

4. Oxidation of Epinephrine to Adrenochrome

Bacq (1949) reviewed the evidence for the transformation of epinephrine to adrenochrome. This is theoretically possible because many enzyme systems which oxidize epinephrine to adrenochrome in vitro are present in vivo. Blaschko, Richter and Schlossman (1937) and Green and Richter (1937) found a cyanide insensitive system present in cardiac and skeletal muscle and indophenol oxidase present in all tissues. Other reported oxidases are tyrosinase, the phenolase system (Mason, 1955) and ferritin.

Leach and Heath (1956) renewed interest in the transformation products of epinephrine in plasma. It logically followed from the adrenochrome hypothesis of schizophrenia that such a change might be possible. They found that under specified conditions, plasma converted added epinephrine into a new substance which had an absorption band at 395 mμ in the DU Spectrophotometer. This was not adrenochrome. Adrenochrome was rapidly transformed into this substance by plasma. Leach, Cohen, Heath and Martens (1956) suggested that ceruloplasmin, a copper containing enzyme, was the oxidase.

Following this report, Hoffer and Kenyon (1957) found the new substance was adrenolutin. Adrenochrome is probably the first oxidation product but is transformed into adrenolutin. Both are present in the final reaction. Hoffer (1957) followed the formation of both adrenochrome and adrenolutin. Adrenolutin was estimated by the optical density at 395 mμ and adrenochrome by the increase in optical density at 460 mμ. The quantity formed from several groups of patients is shown in Table 18.

TABLE 18

FORMATION OF ADRENOCHROME AND ADRENOLUTIN FROM EPINEPHRINE BY PLASMA DRAWN FROM VARIOUS GROUPS OF SUBJECTS

Group	N	Optical Density		
		395	460	Ascorbic Acid Bleaching at 420
Normal and Neurotic	34	0.31	0.10	0.10
Surgical—Pre Op.	28	0.36	0.12	0.13
Surgical—During Op.	12	0.43	0.19	0.22
Schizophrenic—Before Treatment	13	0.35	0.12	0.21
Schizophrenic—After Treatment	11	0.35	0.13	0.06

Conversion of epinephrine to adrenolutin and adrenochrome was greatest in surgical patients during operation. Plasma from blood which was drawn before operation and from schizophrenic patients also converted more epinephrine into adrenolutin. Ascorbic acid converts adrenochrome into leuco derivatives and also bleaches plasma when the optical density is measured at 420 mμ. Hemoglobin is bleached in a similar manner. Blood drawn from patients undergoing surgery showed the greatest reduction of color by ascorbic acid. This was probably due to the presence of freshly liberated hemoglobin in the blood. Blood plasma drawn from schizophrenic patients who had not yet been treated was bleached to about the same degree. This may be due to the increased fragility and therefore greater hemolysis and to the presence of adrenochrome-like pigments in hemoglobin. After treatment, schizophrenic plasma was bleached much less by ascorbic acid.

5. *Epinephrine Oxidase*

Adrenochrome can accumulate in such a system only if the further transformation of adrenochrome into other substances was prevented. Payza and Hoffer (1958) used Richter's finding that semicarbazone combined with adrenochrome to trap adrenochrome as inactive adrenochrome semicarbazide.

The activity of plasma was determined by reacting 75 micromoles epinephrine with plasma in the presence of semicarbazone

at pH 6.8 (phosphate buffer) containing optimal concentrations of copper. The formation of adrenochrome monosemicarbazide was followed by measuring the increase in optical density at 360 mμ.

The oxidation of epinephrine was enzymatic and not due to auto-oxidation. Varene (1957) also found this reaction was enzymatic not auto-catalytic. Between 5 to 25 percent of the substrate, epinephrine, was converted. Maximum conversion occurred with 12.5 micromoles epinephrine. The total production of adrenochrome increased as more substrate was added. Both d- and l-epinephrine were oxidized equally but norepinephrine did not yield colored derivatives. Optimal pH was 6.8. The enzyme was inactivated by heating at 80° C. for 15 minutes. The following substances activated the reaction: semicarbazone, copper, fresh hemoglobin, marsilid and oxygen. Removal of copper by dialysis stopped activity which was restored when copper was returned. The reaction was inhibited by cysteine, NaCu, tris buffer, ascorbic acid, ethylene diamine tetraacetate. The following substances were inert: ephedrine, adrenochrome semicarbazide, heparin, nicotinic acid, LSD, l-tryptophane and mescaline.

These properties are not consistent with the known properties of ceruloplasmin. Payza and Zaleschuk (1959) concluded that epinephrine oxidase is not the same enzyme as paraphenylene diamine oxidase and therefore is not ceruloplasmin.

Payza and Hoffer (1959) studied the distribution of epinephrine oxidase in various tissues using acetone powdered extracts as the enzyme source. High concentrations were found in brain, followed by plasma, kidney, lung and spleen with lowest concentrations in liver.

6. Metabolism of Adrenochrome

Leach and Heath (1956) and Hoffer and Kenyon (1957) noted that adrenochrome is converted into adrenolutin by plasma. Ascorbic acid changes adrenochrome into leuco adrenochrome. However, neither adrenolutin nor leuco adrenochrome are changed appreciably by plasma, Melander (1957).

Fischer and Lecomte (1951) found that most of the injected

adrenochrome in some animals was converted into adrenolutin. Earlier Fisher and Landtsheer (1950) reported that adrenochrome rapidly disappeared from blood and was found in liver and kidney where it was changed to adrenolutin which was then excreted.

The metabolism of adrenochrome in vivo was followed by injecting 10 mg. intravenously and measuring plasma levels at 15, 30 and 60 minutes. Urine values were determined in some cases. This is an adrenochrome tolerance test and similar in principle to the intravenous glucose tolerance test.

In a series of nine subjects not schizophrenic, the mean initial level of 51 μg per liter in the plasma was increased 170 percent after 15 minutes but after 30 and 60 minutes the levels were lower than the initial value. These subjects destroyed the adrenochrome very rapidly and little was excreted in the urine. Thus subject Mr. D (Table 16) excreted 0.12 mg. adrenochrome in urine after 2 hours although the plasma level went up to 173 μg at 15 minutes from 102 μg/liter (about 1 percent of the injected quantity).

Pretreatment of subjects with LSD but not with Brom LSD markedly stabilized the adrenochrome in vivo. When 10 mg. of adrenochrome was injected by vein two hours after 35 μg LSD had been taken by mouth, it was found that an hour after this injection the adrenochrome level was still 67 percent above the initial level. When 100 micrograms of LSD was given and the same process repeated, the adrenochrome level one hour after injection was 170% above the initial level. In Mrs. Y's case where LSD and adrenochrome were combined the amount of adrenochrome in the urine was 0.37 mg. or 3.7 percent of the quantity injected as compared to 0.12 mg. for adrenochrome alone in subject Mr. D.

D. PSYCHOLOGICAL PROPERTIES OF ADRENOCHROME AND ADRENOLUTIN

Both adrenochrome and adrenolutin are psychotomimetic for animals and man. The evidence for this statement was reported by Hoffer, Osmond and Smythies (1954), Hoffer (1957). We have not seen many scientific accounts of experiments where these claims have been tested. Our first report was followed by a series

of curious errors. Rinkel (1954) used adrenoxyl (adrenochrome semicarbazide) and could find no psychological activity. This supports other reports that this substance is relatively inactive. Witt (1954) for instance found that, in strong contrast to adrenochrome, the semicarbazone does not affect web spinning spiders. This may be because both spiders and humans cannot hydrolyze this stable compound. Since Rinkel's account, other investigators have reported to each other that their adrenochrome was not active. But they did not publish their reports so that it is not possible to evaluate their claims. There has been ample confirmation that these substances are psychotomimetic for animals and two reports of activity in humans.

If adrenochrome is to produce psychological changes it must get to the brain centres where it acts. Many things may prevent it from getting there. Unless the adrenochrome used is pure, it may be auto-oxidized in solution, so that even a brief time lag between its preparation and use will decrease its activity. It is also possible that impure adrenochrome may be destroyed more quickly in vivo. Secondly, adrenochrome synthesized from l-epinephrine may be contaminated with its optical isomer. Both dextro and laevo adrenochrome have been synthesized, Heacock (1958). Preliminary studies suggest the isomer prepared from d-epinephrine is more potent, Hoffer (1958). Thirdly, even stable adrenochrome is very quickly removed from plasma. Some people can remove adrenochrome more quickly than others and if such people are used as experimental subjects the results may be misleading. Fourthly, the route of administration will determine response. Adrenochrome is active in smaller quantities when inhaled in aerosol, Hoffer (1957) or placed sublingually, von Taubmann and Jantz (1957). Osmond and Hoffer (1958) recorded in detail the history of one asthmatic who produced a psychosis in himself inadvertently by taking pink epinephrine. For these reasons, it is most important to specify the method of administration, the stability of adrenochrome and the optical isomer used.

a. Animal Response to Adrenochrome

Adrenochrome synthesized by C. Pfizer and Company, not crystalline, but the best preparation available at that time, was

placed in the ventricles of cats by Schwarz, Wakim, Bickford and Lichtenheld (1956). The EEG findings were discussed earlier. They examined the activity of serotonin, 75 to 500 μg; LSD, 15 μg; mescaline, 0.3 to 15 mg; adrenochrome, 0.125 to 1 mg.; adrenolutin, 0.3 to 0.65 mg. and ergotamine, 20 μg. Serotonin produced moderate changes. The cat lay down quietly, but was alert. There was some licking and occasional retching. One docile cat became hostile. Slight catalepsy and muscular incoordination was also present. LSD following serotonin did not alter this behavior.

LSD produced restlessness and retching followed by drowsiness. There was no motor impairment. Mescaline produced striking changes in EEG and behavior. After higher doses, animals cried and howled and had violent paroxysms of scratching. One cat developed convulsions and died.

Adrenochrome and adrenolutin both produced striking effects psychologically although less adrenolutin produced this change more quickly. Within a few minutes after adrenochrome, cats blinked, yawned, or retched, then sat or lay down or slept. They were readily roused. Gait was normal. After 20 minutes, the cats were moderately insensitive to painful stimulation (see analgesic action of epinephrine), Leimdorfer and Metzner (1949). The cats retained clear sensorium for they remained affectionate and responded to petting. Memory was intact. The cats would remain sitting on a chair for long periods of time without running away. One male cat became sexually excited and attempted to copulate first with a female cat and once with a comatose dog in the laboratory.

In summary, Schwarz *et al.* found that adrenochrome and adrenolutin produced marked changes in behavior as well as in the EEG. Mescaline produced chiefly epileptic type behavior. LSD produced slight effects less marked than did serotonin and similar in nature to those induced by ergotamine. It seems likely LSD placed in the ventricles does not cause an increase in central adrenochrome as it does when given to humans by mouth, Hoffer (1958).

Rice and McColl (1957) confirmed these results using pure crystalline adrenochrome as did Sherwood (1957). Sherwood gave

a cat .5 mg. of crystalline adrenochrome prepared in our laboratory. We were present and watched him inject the solution into the bung of the intraventricular cannula. We were able to watch this cat for the next three hours, while Sherwood demonstrated its inappropriate behaviour and we took photographs. This cat walked into its bowl of milk and did not lick its paws; let itself be placed in unusual positions without protest; tried to lie down all the time and was not interested in grooming itself. It remained affectionate and well disposed towards Sherwood and seemed fully aware of its surroundings.

Melander (1957) found that when monkeys were given large quantities of adrenochrome, they developed catatonia. One hundred mg. of adrenolutin per monkey was more effective. Other animals also responded to adrenochrome in a way which classes it with other psychotomimetic substances. Thus adrenochrome but not its semicarbazide produces marked distortion in spider web, Witt (1954). Adrenochrome and adrenolutin also produce disturbances in instinctual behavior of pigeons. They discontinue nesting, refuse to drive away interloping pigeons, cease cooing. Dosages between 10 to 20 mg. per adult pigeon produce catatonia, Wojcicki and Hoffer (1957). Wojcicki (1959) studied the action of crystalline adrenochrome on the behavior of racing and homing pigeons in their natural (man created) habitat. This appears to us to be more fruitful and informative than using artificial laboratory conditions. Adrenochrome (8 mg/pigeon) produced marked changes in behavior. A homing bird released three miles from home normally returns to its aviary very quickly. Pigeons treated with adrenochrome fly to the nearest resting place, a fence post, etc. and only fly home when they are vigorously chased away from where they have stopped. They are able to fly home however. When treated in their aviary they recognize their nest and fly to it but will not defend it against other pigeons. This shows that while adrenochrome does not produce disorientation in the birds for they can find their way home, they are unusually apathetic and disinterested about matters which normally concern them greatly. Adrenochrome does not alter certain functions such as flying, eating and drinking but markedly alters other functions

related to reproduction, i.e. nesting, fighting and mating. Wojcicki demonstrated pigeon catatonia by placing a pigeon on his head and walking up and down a corridor. This interesting method for demonstrating catatonia was developed by Baruk who found schizophrenic bile produced these changes, Baruk and Camus (1957), Baruk, Launay and Berges (1957), Baruk, Launay, Berges and Perles (1958) and Baruk, Launey, Berges, Perles and Conte (1958).

Adrenochrome produces changes in behavior of guppy fish, Abood (1957). This contrasts with Abramson's finding that discolored adrenaline (pink) does not alter behavior of Siamese fighting fish, Abramson (1955). Nor does it produce change in the guppy, Abood (1957). However, discolored adrenaline is known to contain many different colored compounds. Adrenochrome may be one of the minor components. The mixture of substances may have properties quite different from pure adrenochrome.

Adrenochrome produces changes in behavior in rats, Eade (1954), Noval, Brande and Sohler (1959). Noval *et al.* reported that 10 mg/kg of crystalline adrenochrome in saline injected intravenously caused convulsions and death in half the treated rats in less than 15 minutes. After 8 mg/kg their physical activity was greatly reduced for many hours. One of us (A.H.) observed some of the treated rats several hours after treatment. The rats did not appear sick but were disinclined to move about. When placed alongside a Bunsen burner (the de Jong test), the animals grasped the burner with their forelegs and clung until they sank slowly to the table, exhausted but still clinging. The catatonia was easily demonstrated. Pretreatment with LSD made the adrenochrome four times as effective.

b. Psychological Activity of Adrenochrome in Humans

For some years following Hoffer, Osmond and Smythies' (1954) initial report, no adrenochrome was available. Adrenolutin, derived from adrenochrome, was therefore studied and several reports released, Hoffer (1957). No further psychological studies with adrenochrome were made until crystalline adrenochrome became available late in 1957.

In the meantime, Taubmann and Jantz (1957) initiated a careful study of adrenochrome and confirmed its psychotomimetic

effect. They believed it produces a toxic psychosis but this is a matter of interpretation and definition, Hoffer and Osmond (1958), Osmond and Hoffer (1958).

Taubmann and Jantz reasoned that if adrenochrome was given under the tongue it would reach the brain with less destruction than by vein. They believed that it would get to the brain directly through the sublingual venous anastomosis, just as novocaine is believed to reach the brain more readily by this route. Many euphorients are commonly absorbed through the buccal mucosa, e.g. coca, betal nut, hashish. They therefore administered 3 mg. adrenochrome as a powder under the tongue. The adrenochrome produced a biting sensation. After ten minutes, the subject noted a slight feeling of facial warmth and tingling in the fingers. They often complained of mild pain about the heart region. All somatic feelings were gone within 30 minutes. Psychic changes occurred within 10 minutes. They varied from person to person and even from time to time in the same person. Depression was more frequent than euphoria.

Marked visual perceptual changes occurred. Colors of objects changed in quality and appeared peculiar or strange and disproportionate. Their perceptions of their own bodies were distorted. Distant objects appeared to be too close. Movement was observed in stationary objects. No disorders of thought or of consciousness were observed. All changes ceased after one half hour. They suggest that an active substance resembling adrenochrome is the psychotoxic agent and that activity apparently depended upon the type of chemical syntheses. Their adrenochrome crystallized very rapidly at the temperature of liquid carbon dioxide was less active than adrenochrome precipitated at higher temperatures.

Sublingual Adrenochrome

Following Taubmann and Jantz' observation, similar experiments were repeated with crystalline adrenochrome from l-epinephrine, d-epinephrine and dl-epinephrine, Hoffer (1958). In a couple of trials, 6 mg. of sublingual adrenochrome from l-epinephrine did not produce any change. However, the adrenochrome from d-epinephrine in 3 mg. quantities was active as was dl-adrenochrome in 6 mg. quantities.

With 3 mg. adrenochrome from d-epinephrine, subject one noted difficulty in reading and focussing after 7 minutes. After 12 minutes, far objects seemed very far away. At 24 minutes, he was euphoric and unable to estimate time. At 35 minutes, time appeared stationary. At 45 minutes, colors were bright and vivid. At 80 minutes, he was overtly active in movement and speech. At 5½ hours he subjectively felt normal but for the next 24 hours, far objects seemed too small and occasionally objects became alternately normal or too small in size. People walking toward him became large too quickly. Similar changes were observed by this subject two weeks later with 3 mg. dl-adrenochrome but these were less intense and of shorter duration.

Subject two received 6 mg. dl-adrenochrome sublingually. After 20 minutes, he appeared readily irritated and defensive. He felt euphoric and irritated. He estimated 88 seconds for a 30 second interval and would not believe he had been so far out. With eyes closed, visual changes became most interesting. The experience was as interesting as with LSD but lacked tension induced by LSD. At 45 minutes, he was able to see visual images with his eyes closed and was apathetic. At 1½ hours, distance perception was quite abnormal. He was driven home in a small car and was very nervous riding in the car. At home, the living room 28 feet long appeared at least 50 feet long. The face of an eight year old girl four feet from him appeared larger than that of an adult woman 6 feet away. At 4 hours, he was nearly normal but things still appeared odd. In summary, he suffered marked changes in estimation and perception of time, distance and size of objects. Constancy of perception was disturbed. His mood was irritable then flat. He was suspicious but showed no other evidence of thought disorder.

Subject three was given 6 mg. dl-adrenochrome sublingually. It tasted bitter. At 7 minutes, his upper lip felt anesthesized similar to that produced by dental injections. At 9 minutes, the area of anesthesia spread up both cheeks. At 12 minutes, his jaw muscles were very tense. He had some difficulty in focussing. The anesthetic feeling spread up to his ears. At 15 minutes, he was very quiet and felt sad. He began to cry. At 20 minutes, he was not able to estimate time. At 25 minutes, he felt he had been here all afternoon. His limbs were very light and he could not feel the weight of one crossed on the other. On suggestion, he was able to visualize one hand bigger or smaller than the other. At 30

minutes saw my face changing shape. Looking at a Van Gogh self portrait, he found him a very unhappy man and hostile. Van Gogh's left half of his face was desperate, the right side hostile. At 35 minutes, Van Gogh's face became first younger then older. He saw him looking dead and rotting away and finally he was replaced by another man. At 43 minutes, he saw the eyes close partially and saw a variety of faces of Franz Hals type but all distortions of Van Gogh. At 55 minutes, he had occipital headache and felt indifferent. At one hour, he was given 1 gram soluble nicotinic acid. Five minutes later, he was euphoric and normal. Ten minutes later, he flushed. Headache was gone. Fifteen minutes later felt nauseated and miserable. No visual changes. That night he had twilight sleep (half awake, half asleep).

Inhalant Adrenochrome

Crystalline adrenochrome was administered to several subjects in a freon spray kindly prepared by Cronheim of Riker Corporation, California.

Subject three above volunteered to inhale some six months before he took it sublingually. He was very skeptical of activity. He persuaded me to give him 300 μg. by spray which I did at 12:45 P.M. Saturday. A few minutes later there was a mild flush. At 6 minutes, the positive after image became prolonged. At 11 minutes ears felt plugged. Vision not normal. I swung my arm back and forth rapidly, he saw it as a series of stationary arms. It was difficult to concentrate visually. At 15 minutes, the after image still was prolonged but ears felt normal. Facial flush was still present. He had to concentrate very hard to read a book. When he moved the book the lines moved. At 19 minutes, vision began to become normal. At 37 minutes, he was visually normal. The facial flush began to fade. He reported he was now normal and believing this was so, I then left him.

At 4 P.M., I called his home. He seemed rather distant and quiet. He informed me that after I left him, he developed a type of over and irregular breathing similar to Cheyne Stokes. He felt quite relaxed after 30 minutes and decided to go home. He was riding away from the hospital on his bicycle toward a tree which suddenly became much larger in size as if it were blowing up.

His wife was not home when he arrived. He felt lonely and went to find her. Failing in this, he was depressed until just before four when his wife came home.

On Monday, he gave a more complete account of what had happened. Saturday morning, he had had a mild disagreement with his wife over a misplaced photograph. When he got home his wife was not in. He decided that she had left him and returned to her mother in a far distant city. In confirmation of this he found the missing photograph which his wife had placed for him in the living room before she went out. He construed this to mean that she was much more disturbed by their minor disagreement than he had supposed. He noticed that she had left the vacuum cleaner in the middle of the room and realized that this was another message for him, meaning that she was a neat and orderly person who did not misplace things. Shortly after this he decided that she might have gone shopping and looking for the shopping cart found it gone. He then visited two stores where she often shopped without success. On returning home he counted all the suitcases for if she had gone home, one would be missing. One was missing which increased his worry as he became more certain that she had left him. A little later, he found it behind a door with some clothing piled on it (they had recently moved into a new house). He then suspected that she had started packing, stopped in the middle of her packing to purchase her airline ticket. But he also concluded from this that she was still unsure about leaving him. After this, he became very depressed until a few minutes later when she returned home from shopping. When I called him at 4 P.M. he suddenly remembered he had taken the adrenochrome and became very angry with me for forcing him to take the chemical. At 5 P.M. he flushed. This was noted by his wife and he then told her about the experience he had undergone. He then recognized he had repeatedly asked to be given the adrenochrome. By that evening, he was normal.

The same freon preparation was given to Subject Two several months later. He expected it to be very active and inhaled up to 500 or more micrograms. There was no psychological change. On close examination, the freon solution appeared off color. Paper chromatography showed it contained melanin-like pigments.

Intravenous Adrenochrome

Crystalline adrenochrome, 10 mg., does not produce striking psychological changes in the majority of volunteers except during

the injection. Adrenochrome so administered is very rapidly removed from plasma as will be shown later. For this reason plasma levels do not remain high long enough. Melander (1957, 1959) noted that doses of LSD which in themselves had little effect on the behavior of cats and monkeys could potentiate the action of adrenochrome and adrenolutin. 100 mg. of adrenolutin is usually needed to produce catatonic changes in cats. Two hours after a dose of LSD which has little effect on the cat, 5 to 10 mg. of adrenochrome produced stronger catatonia than 100 mg. of adrenolutin.

Hoffer (1957, 1958) found that LSD potentiated the adrenochrome and adrenolutin experience in volunteers and stabilized adrenochrome in blood in vivo. Apparently the typical LSD experience, i.e. little tension, marked visual and/or psychological change, depends upon the formation of adequate quantities of adrenochrome, probably in the brain. Many subjects especially tense alcoholics show little psychological changes when given LSD apart from suffering from great tension. When this happens, the adrenochrome present in blood and urine increases little and may even decrease. If 10 mg. adrenochrome or adrenolutin is given this markedly alleviates the tension and the usual psychological changes of LSD follow.

If Brom LSD is given before adrenochrome, it does not intensify the experience, neither does it elevate adrenochrome levels nor increase the stability of adrenochrome in vivo.

In summary, small quantities of adrenochrome are not active when given intravenously partially because it is so rapidly removed. When this is controlled by giving LSD or by using other routes of administration, i.e. sublingually or by inhalation, smaller quantities produce psychological changes.

Schizophrenic patients do not as a rule react strongly to adrenochrome. However, in a few instances, the reaction is severe and prolonged.

> Thus one subject was given 10 mg. intravenously. He immediately felt relaxed but developed marked visual changes. When he looked at his hands, they alternately swelled and decreased in size as did faces. He was unable to estimate how far people were from him. One hour later while looking in the mirror, he saw his face dividing into a white half and a black half. He inter-

preted this to mean his white half was pure and good, whereas the black half was dirty and bad. The black half tried to crowd out the white. Eventually during discussion with his therapist, the two halves fused into one grey face. He reported, "I was scared of the black part at first. It was knowledge of some sort I tried to push away because I had the idea it was bad. There was something like a valley between them. The black seemed so powerful it could turn the white black but not vice versa." For the next six days these visual changes occurred when he became agitated or tense. He later reported that during his illness he had had similar visions but had been afraid to look at them. The adrenochrome reactivated the visual changes and brought them to the attention of the patient.

Schwarz et al (1956) found that intravenous adrenochrome produced changes in patients. They wrote "It was difficult to evaluate the effects of adrenochrome on the psyche. The epileptic appeared to be relaxed and became drowsy. One schizophrenic appeared to show loosening of associations and increase in disturbance of body image; for instance, he raised his hand, gazed at it and said 'my arm wiggles and waves, ha, ha.' The other schizophrenic who received adrenochrome experienced cataplexy on two occasions which persisted for more than 30 minutes. At these times his upper extremeties were held in unnatural positions which volunteers who served as controls could not maintain for long and was not his usual reaction and a similar state did not develop with either mescaline or LSD-25."

c. Potentiation of Adrenochrome Experience

The psychotomimetic experience induced by adrenochrome and adrenolutin does not resemble the usual LSD or mescaline experience. The changes occur primarily in thought and mood. Perceptual changes are subtle and not obvious. These are in sharp contrast with visual changes often found after consuming LSD.

Since pretreatment with LSD stabilized adrenochrome when injected into normal subjects, it is not surprising that pretreatment with LSD markedly potentiates the effect of adrenochrome, Noval, Brand and Sohler (1959), and adrenolutin, Melander and Martens (1958). The potentiation of the adrenochrome experience

by LSD was examined by giving normal volunteers 35 micrograms of LSD orally, followed one or more weeks later by 10 milligrams of adrenochrome intravenously and one or more weeks later by a combination of both, i.e. the adrenochrome was administered one and one half hours to two hours after the LSD. The same sequence was not used in all the experiments.

Subject One—First Experiment. After 35 micrograms of LSD, no change was noted in the first hour. During the second hour, the subject became nervous and complained of feeling jumpy similar to the feeling he had during examinations but more intense. During the injection with adrenochrome, two hours later, he blanched, began to breathe deeply and complained of air hunger and of feeling intensely nervous. There was no change in the pulse rate. Five minutes later, his normal color reappeared. After twenty minutes he was very nervous and felt quite chilly. He was markedly restless and irritable. He now noted some blurring of vision when looking at book titles a couple of yards from him. He was able to read but had difficulty comprehending what he read. He now reported he had completely lost any sensation of time and he could not estimate how long he had been in the experimental setting. On suggestion, he looked at his hands and noted momentarily that one was smaller. His movements were clumsy and fumbling. Fast moving objects appeared blurred. He was not as nervous now. On walking, his knees had a tendency to knock. Two hours later while walking downstairs he complained he had not realized how weak his legs were. Driving him home, he was less aware of surroundings and had difficulty in telling his driver how to get to his home. The next day he reported "I experienced very slight nervousness with LSD. For a short time after the adrenochrome injection I had difficulty getting enough air and could also feel my heart pounding quite hard. After the injection, I was intensely jumpy and could not move smoothly. With the picture tests in which I had to lay out the pictures myself, I experienced some confusion. I could have gone through them much faster normally. When I got home I had a letter waiting from a company. I had some trouble getting the drift of the letter. I could not remember what I had read before at times. Also I had a headache for approximately two hours during the evening after the experiment."

Subject One—Second Experiment. Two weeks later, he received the same quantity of LSD without adrenochrome. There was no change until one and one half hours when there was an increase in nervousness. There was no change in perception of passage of time. At two hours, he was a "bit jumpy." Dots tended to look smaller. Book titles at no time appeared blurred. On his way home, he noted no weakness and no other unusual changes. Two days later, he reported that since so little had happened he had no written report to submit. The experience was more pleasant than the first one.

Subject One—Third Experiment. Two weeks later, he was given 20 milligrams of adrenochrome intravenously. During the injection he blanched, became very pale and complained of marked air hunger and felt his heart pounding in his throat. He also developed a slight frontal headache. Ten minutes later, he felt physically normal and very relaxed. This was the first time during the three experiments he noted this relaxation. He remarked he was less interested in the situation. There were no visual changes. Time sense was changed and he estimated time since injection as ten minutes when it was twenty minutes. Thirty minutes later he was not able to estimate closely to thirty seconds as his mind wandered. One hour later, he felt entirely normal with normal awareness of the passage of time. He was relaxed, more so than during previous experiments.

Subject Two. Subject two received LSD followed by adrenochrome as above, followed one week later by 0.5 mg. brom LSD two hours before 10 milligrams of adrenochrome, and finally two weeks later 35 micrograms LSD followed three hours later by adrenolutin. His written report for the experiences follows:

"LSD and Adrenochrome. I reported at 9 A.M., am in good spirits. Following the ingestion of LSD I tried to find changes in my mental and physical state but was hard pressed to do so. Eventually about an hour after I thought I detected a very slight increase in intracranial pressure in the frontal region and a slight feeling of warmth in my abdomen. Looking back on this, I am suspicious that these findings may have been only because I wanted to be able to report something. I know that my general mental and physical state was well within the range of my own normal.

"At about 10:30 I was injected with the adrenochrome and within a minute I felt a marked tightness about the midsternal region of my chest which passed off very shortly and increased difficulty in sufficiently ventilating my lungs which diminished as time passed but did not completely abate until after the ingestion of nicotinic acid at about 3:30.

"Within half an hour I had an increasing feeling that there was little or nothing in the world for which I would profitably live. Nothing interested me and though I ordinarily have a very good appetite I was completely apathetic toward the mention of food. However during the experiment the extreme lowness of spirit and physical lethargy which came in waves abated and allowed me to eat when food was brought in. Shortly after I was asked to do a short test. I didn't want to do so, not because I didn't want to cooperate but because I felt so physically and mentally weak and exhausted that I actually felt that I could hardly do it. With extreme effort I was able to do as I was told.

"During my time of depression I felt they were watching me (the investigators) quite keenly and I felt much more apart from them than I had at the beginning of the experiment. During the midafternoon coffee break (six hours after taking LSD), I felt that people were watching me and would think I was acting a bit odd but I did not mind because I was with the investigators and I thought that people would realize that I was a psychiatric research 'guinea pig.' Although people were laughing and singing carols and I ordinarily enjoy trying to sing, I had absolutely no desire to join in the festivities. I think my feeling during my periods of depression could best be described by saying that I couldn't care less about anything that happened as long as it entailed no physical and mental effort. During the period 10:30 to 3:30 while I had brief periods in which I felt normal or close to normal my characteristic feeling was one of depression, flatness and lethargy. During the day time passed very quickly and looking back on it, it seems remarkable that I put in a whole eight hour day. One other thing I should mention is my judgment of size. Often small things looked very large to me and relatively large things generally looked larger and what to me was the most important observation was that I was perfectly confident that I could judge size without difficulty. I was completely astonished when I found out how bad my judgment was.

"LSD Alone. I reported for the experiment shortly after 4:30 P.M. in good spirits although a wee bit apprehensive that the combination of drugs would produce the same effect in me that LSD and adrenochrome had about three weeks ago. That experience was invaluable to me but nevertheless something that I have no desire to repeat. Shortly after taking the LSD I noted a very odd feeling in the parietal region of my cranium. I felt quite dizzy and yet neither the room nor I seemed to be going round in circles. I have felt slightly similar things before but never in the same intensity. It did not bother me but after it continued for some time became annoying. I was very surprised at this since the previous time I had taken LSD there had been virtually no effect. This and some difficulty in visual judgment were my only findings until after the injection of adrenolutin."

Subject Three. This female alcoholic subject was given 200 micrograms of LSD by mouth. She became extremely tense with a minimal visual reaction to the drug. Her adrenochrome levels four hours after were much lower than the baseline sample. This has happened only to her out of twelve subjects. Five hours after she was still very tense and had not experienced visual changes of note. She was then given 10 mg. of adrenochrome by vein. Within five minutes she lost her tension and for the next two hours had a normal LSD reaction. One hour after the injection, the adrenochrome level was 144 μg/liter compared to 44 before the injection.

The psychological experience induced by adrenochrome following LSD is similar to changes we have reported before for adrenochrome alone but more clearly demonstrated and in each instance were clearly known to the subject. The combination of these two substances produced more pronounced changes than that of either compound alone.

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Chapter 11

THE TARAXEIN HYPOTHESIS

(Substances Related to Epinephrine Enzymes)

Heath and his co-workers were able to isolate taraxein because they were interested in both (1) the analyses of electrical changes which occur deep in the brain, and (2) in epinephrine metabolism. The taraxein hypothesis is strongly opposed, not it seems on theoretical grounds, but because it could not be confirmed at first in some other laboratories, Siegel, Niswander, Sachs and Stavros (1959), have encountered technical difficulties in isolating this substance. Confirmatory reports from Sweden, Melander and Martens (1958), and from Russia, Mekler, Lapteva and Lozovskii (1958) will probably renew interest in Heath's reports. It is not uncommon for experimenters to blame their failure to reproduce another's work not on their own incompetence but on their predecessors' over lively imagination. In this chapter, we shall trace the development of the taraxein hypothesis and show its relationship to the adrenochrome hypothesis.

EXTRACTION OF TARAXEIN

When Heath and Leach (1956) summarized the research of the Tulane group into the neurophysiology of schizophrenia, they postulated some defect in the function of subcortical centers and located this defect particularly in the septal regions. The technique for implanting permanent deep electrodes was first developed in monkeys and later applied to human subjects. Chronic schizophrenic patients showed unusual electrical abnormalities in the septal region.

Heath believed that it might be possible to correct this abnormality by suitable stimulation through the implanted electrodes.

When this was done some patients became more alert and showed greater clarity of thought. After repeated stimulation, some were improved enough to leave hospital. However, in a recent report Heath and Leach doubt whether the therapeutic results warrant this type of surgical intervention. Because of this work the Tulane group have been able to study the electrophysiological changes produced by psychotomimetics deep in the brain. They found that when monkeys were given mescaline or LSD the peculiar EEG abnormality found in chronic schizophrenia occurred.

When the adrenochrome hypothesis was reported in 1954 some of the Tulane workers expressed an interest in it and since then we have kept each other informed. Leach and Heath (1956) recognized that there might be enzymes in blood plasma which could change epinephrine into indolic metabolites. In 1956, they reported that if epinephrine was added to plasma buffered at alkaline pH, it was converted into a substance which when its optical density was measured in a DU Spectrophotometer absorbed maximally at 395 mμ. This substance was not adrenochrome which absorbs maximally at 460 to 480 mμ. Indeed, when adrenochrome was added to this system, it was quickly transformed into the new substance. Leach and Heath further reported that schizophrenic patients oxidized more epinephrine into this new substance than did normal subjects. This was not specific for schizophrenics as plasma from pregnant women and from patients with organic disease also produced more of this factor. Shortly afterwards Hoffer and Kenyon (1957) reported the new substance was adrenolutin. This was confirmed by Harley-Mason and Smythies in 1957. Thus it was shown plasma could change epinephrine to adrenolutin. In such a system, adrenochrome must be a transient intermediary because epinephrine is first oxidized to adrenochrome which then rearranges to adrenolutin. Leach, Cohen, Heath and Martens (1956) studied the system which oxidized epinephrine into adrenolutin and concluded it was ceruloplasmin. This is the copper containing enzyme first described by Holmberg and Laurell (1948). It occurs in large quantities in the plasma of pregnant females. A major source is placenta. Heath et al suggested that if the ceruloplasmin level was raised in schizophrenic plasma then this might

account for an increased conversion of epinephrine into adrenolutin. Akerfeldt (1957) using the oxidation of a dye to measure ceruloplasmin levels apparently confirmed this. In 1956, Heath and Leach extracted ceruloplasmin from both schizophrenics and normals and compared their effects on monkeys. They found that the ceruloplasmin from schizophrenics produced mild behavioral changes in their monkeys accompanied by schizophrenic-like EEG changes in the septal region. They found that in schizophrenic plasma there was a globulin fraction bound to ceruloplasmin which could however be separated from it. When this globulin fraction was injected into monkeys or man, it produced marked changes both in behavior and, where this could be used, in the depth encephalogram. They called this new substance taraxein. In 1957 and 1958, Heath and his colleagues reported that taraxein produced symptoms in normal volunteers closely resembling those seen in schizophrenia but only for one to two hours.

Taraxein has never been extracted from the blood of those not suffering from schizophrenia. Its effects do not seem to be related to the clinical subtype of the sick person from whose blood it was taken. They seem to depend less on the personality of the volunteer than the amount of taraxein injected. So far, Heath and Leach use as a standard dose the amount of taraxein which they can extract from 400 ml. of schizophrenic serum. They inject this rapidly by vein for it seems that taraxein is quickly destroyed in normal blood. Heath, Leach, Martens, Cohen and Feigley (1958) also found that when schizophrenic serum is injected very rapidly (400 ml. in 4 minutes), it too produced a short schizophrenic experience in volunteers. With a slow injection, the serum is inactive.

Although the taraxein reports were received with suspicion and hostility, Heath and his colleagues have continued their work and this has now been confirmed by two independent groups. Melander and Martens (1958) extracted taraxein from schizophrenic plasma and with it produced catatonic changes in Rhesus monkeys. Mekler, Lapteva and Lozovskii (1958) using an extraction method similar to Heath's isolated taraxein from schizophrenic serum and produced catatonia in mice. They concluded that schizo-

phrenic plasma contained taraxein. Benjamin (1958) and Siegel, Niswander, Sachs, and Stavros (1959) recently reported the taraxein work remained unconfirmed. Apparently these authors were not well acquainted with the literature.

Heath, Leach, Byers, Martens and Feigley (1958) have elaborated their hypothesis. They suggest that in schizophrenia there is a qualitative difference in serum oxidases resulting in a defective metabolism of amines and a faulty breakdown in catecholamines. The products of this faulty metabolism can affect certain parts of the brain. By increasing the output of epinephrine stress plays a non specific part in this process. Heath et al have attempted to remedy the defect in schizophrenia by giving injections of ceruloplasmin to restore normal amine metabolism. They claim some success for this although ceruloplasmin is difficult to obtain in quantity. Following the report of Altschule, Siegel, Goncz and Murmane (1954) and Altschule (1957) that pineal extract changes the carbohydrate chemistry of schizophrenics, they have been using an extract of septal tissue to counteract the effects of taraxein in animals and of schizophrenia in humans. Patients who have been given this extract which is a polypeptide show an increased level of glutathione and a decrease in serum copper. The excretion of cathecholamines in urine was reduced to normal levels.

According to the Tulane group taraxein provides evidence for a difference in the oxidizing enzyme system which acts upon epinephrine and related compounds. (This leads according to the adrenochrome hypothesis to indoles derived from adrenochrome.) Sulkovitch, Perrin and Altschule (1957) have recently found large quantities of "epinephrines" in the urine of psychotic patients (see chapter on depression). Heath and Leach have confirmed these excretion studies. They also reported that epinephrine which has been injected subcutaneously is recovered in much higher quantities from the urine of schizophrenics than from that of normals. Chronic schizophrenics do not respond physiologically to epinephrine and this may be due to abnormalities in its metabolism. They found that when the septal region is stimulated in monkeys there is a prompt reduction in the rate at which epinephrine is oxidized by plasma.

This establishes a relationship between schizophrenia, the septal region, epinephrine and the oxidizing enzymes, including ceruloplasmin and taraxein. Recent work shows this is even more intricate than it seemed at first. Heath et al assumed initially ceruloplasmin was the enzyme which oxidized epinephrine to adrenochrome. This would be inconsistent with their use of ceruloplasmin as a treatment for schizophrenia. To account for this they suggested that there was qualitatively a difference from normals.

The identity of the enzymes in plasma which oxidized epinephrine to adrenolutin and the dye paraphenylenediamine is not established. It was suggested by the high correlation in the ability of various plasma samples to oxidize both substrates and by the inhibitor action of ascorbic acid on both. In contrast Payza and Hoffer (1959) and Payza and Zaleschuk (1959) found that they were not identical. Epinephrine and adrenolutin markedly inhibited the action of ceruloplasmin but not of epinephrine oxidase. The acidity, molarity and buffer requirements were quite different. Eiduson (1959) also found that ceruloplasmin does not oxidize epinephrine. However, he believes the oxidation may be due to copper ions present in plasma. In any event, it appears doubtful whether ceruloplasmin is the specific epinephrine oxidase.

Melander (1957) found that ceruloplasmin can bind adrenolutin irreversibly whereas other globulins do not do so. Adrenochrome is not bound. Payza (1959) has confirmed this observation. A small portion of ceruloplasmin placed in a semi permeable membrane removed adrenolutin from solution when the sac was placed therein. The affinity of adrenolutin for ceruloplasmin is further suggested by the powerful inhibition adrenolutin has on ceruloplasmin as an oxidase for paraphenylene diamine.

Thus it seems clear ceruloplasmin protects against adrenolutin by binding it. This could explain why ceruloplasmin levels are increased during stress and in schizophrenia. It is no longer necessary to postulate a qualitative difference in the ceruloplasmin of schizophrenics and normals. Melander suggested taraxein (also LSD) allowed certain brain centers to react to compounds in

plasma which normally do not reach them. Both these substances markedly potentiate the action of adrenolutin. This seems a reasonable suggestion and may account for the action of taraxein. It may also interfere with ceruloplasmin ability to bind adrenolutin. Perhaps taraxein is simply an aberrant ceruloplasmin and this may prove to be the genetic defect in schizophrenia.

If ceruloplasmin protects the brain by binding adrenolutin then taraxein may be toxic by both (1) making the brain more permeable to adrenolutin or some other epinephrine metabolite, and by (2) increasing the amount of adrenolutin free in the plasma.

Taraxein is destroyed quickly by normals but not by schizophrenics. This indicates that schizophrenics may have a defect in an enzyme which normally destroys taraxein.

The taraxein and adrenochrome (epinephrine metabolite) hypotheses may be united thus:

1) In schizophrenics, the septal region is abnormally sensitive to certain substances in the blood (taraxein and adrenolutin).

2) Ceruloplasmin absorbs epinephrine and so protects the brain. It does not oxidize epinephrine.

3) Taraxein may both sensitize the brain to adrenolutin and decrease the absorption of adrenolutin on ceruloplasmin, if it is correct that it can displace adrenolutin.

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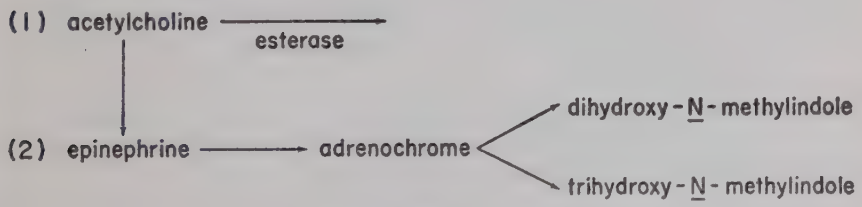
Chapter 12

HOW DO PSYCHOTOMIMETICS WORK?

In chapter five we divided the substances used for the treatment of anxiety and depression into three groups: (1) those resembling epinephrine or which interfere with its metabolism, (2) those resembling adrenochrome, and (3) those which either resemble acetylcholine or increased the level of acetylcholine. This same classification will be applied to the known psychotomimetics. The autonomic nervous system with its system of chemical mediators is closely related both to mood and to the regulation of perception and thinking.

The parasympathetic and sympathetic nervous systems function in close harmony. The former being more primitive is perhaps of greater importance and more fundamental. Certainly substances which interfere with parasympathetic function generally disturb physiology to a greater degree. The production of the sympathomimetic amines is controlled by the secretion of acetylcholine. When atropinized animals receive repeated injections of acetylcholine their adrenal medullas were found to be depleted of amines in seven days, Butterworth and Mann (1957). Any increase in the account of acetylcholine present usually increases the output of epinephrine. Therefore psychotomimetic drugs are substances which increase the concentration of acetylcholine (or similar substances), of epinephrine (or similar substances and some of its indole derivatives.

The known psychotomimetics can be related by the following equation:



It appears to be true that "all substances which increase the concentration of acetylcholine, epinephrine, adrenochrome and adrenolutin or combinations of these in brain are psychotomimetic." The relationship of these to the equation is shown in Table 19.

The most potent in terms of dosage is LSD. It is the only compound which interferes with parasympathetic function, increases adrenochrome levels and is also an anti serotonin. The first property may be due to the inhibition of an enzyme which converts adrenochrome into leuco adrenochrome. This accounts for the increase in the levels of adrenochrome in both plasma and urine, for the decreased rate of destruction of adrenochrome after LSD administration, for the lack of psychological response to LSD

TABLE 19

Relation of Psychotomimetic Activity to Autonomic Activity

		Property		
Psychotomimetic	*Structure*	*Increased Acetylcholine*	*Increased Adrenochrome*	*Anti Serotonin*
Abood's compounds[1]	Atropine-like	Probably	?	?
Esterase inhibitors	Variable	Yes	?	?
Mescaline	Epinephrine-like	?	No	?
Adrenochrome	Indole	Yes	Yes	Yes
d-LSD-25	Indole	Yes	Yes	Yes
Methyl LSD	Indole	Yes	Yes	Yes
Brom LSD*	Indole	Yes	No	Yes
Dimethyl tryptamine	Indole	?	?	?
Harmine[2]	Indole	Probably	?	?
Ibogaine[3]	Indole	Yes	?	?
Psilocybin[4]	Indole	?	?	?
Taraxein	Protein	?	Perhaps	?

[1]Ostfeld, Abood and Marcus (1958).
[2]Pennes and Hoch (1957).
[3]Schneider and Sigg (1957).
[4]Hoffmann, Heim, Brack and Kobel (1958).
*Brom LSD is not psychotomimetic but is included in this table in order to show its relationship to the other ergot derivatives.

if adrenochrome does not increase, and for the inactivity of Brom LSD. Brom LSD would be active if it increased adrenochrome. If BOL was combined with a continuous infusion of adrenochrome until the plasma levels were elevated a marked LSD-like experience should result.

According to the adrenochrome hypothesis psychotomimetics are substances which increase acetylcholine activity and adrenochrome and/or adrenolutin concentrations in certain areas of the brain.

Psychotomimetics which do not increase adrenochrome levels will either replace and react as does adrenochrome or will be metabolised into substances which can do so.

Of nine such substances, two (atropine like compounds and esterase inhibitors) apparently have only parasympathomimetic activity. Their effects on adrenochrome levels is not known.

Brom LSD does not elevate adrenochrome levels. Six of them (bufotenine, ibogaine, harmine, dimethyl tryptamine, psilocybin) are indole (resemble adrenolutin) or epinephrine-like in structure (mescaline) or may form endogenous indoles. Mescaline must be given in large quantities whereas the indoles are active in much smaller concentration.

LSD and methyl LSD are indoles, have parasympathomimetic activity and elevate adrenochrome. They are in terms of quantity the most active psychotomimetics. Brom LSD does not elevate adrenochrome and is not psychotomimetic. It appears then that psychotomimetic activity is related to the indole nucleus. The compound itself may be an indole or it may increase the production of other indoles such as adrenochrome. Atropine in large dosages does sometimes induce psychosis which are difficult to distinguish from schizophrenia but more often produces states of confusion and delirium. In smaller quantities atropine markedly potentiates psychotomimesis and has been used to convert the experience induced by cannabis into something more like schizophrenia, Johnson (1953) and Smartt (1956).

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Chapter 13

THE ADRENOCHROME MODEL AND SCHIZOPHRENIA

So far medical research has met with little success in its attempts to discover biological mechanisms underlying schizophrenia. It is sometimes forgotten by those who glibly refer to schizophrenia as a faulty psycho-social reaction, a way of life, etc., that if their contentions were true, then it would be outside medicine and our speculations would be simply impertinent. Psychiatrists have seldom been prepared to relinquish this group of major illnesses but baffled by its complexity they have resorted to the dubious ruse of proclaiming under a specious holism, inherited from Adolph Meyer that all factors are or may be of equal importance. This has allowed them to avoid the danger of being wrong while ensuring that they will never be right. Unfortunately as a prescription for scientific research, this is poisonous because the researcher is bound to select those variables which he considers more important, or if not more important, at least more susceptible to study. A medical researcher must be alert to factors which are likely to be changed for the better by means available to his profession. A medical man may reasonably be expected to consider first the means of medicine and surgery.

A theory of schizophrenia must not only account for what we already know about it from both clinical observation and investigation; but it must also be testable. Untestable theories however attractive are not of scientific interest. The attempt to define schizophrenia chemically has bogged down due to the fact that biochemists are unable to isolate or identify toxic (and presumably psychotomimetic) substances unless they know what they are looking for. It appears that this limitation of chemistry has not been fully appreciated by psychiatrists or, if appreciated, no

one recognized that an essential task was to define the sort of substances which should be got as accurately as possible.

The adrenochrome hypothesis of schizophrenia was developed by the Saskatchewan group to remedy this and to guide biochemists. Chemicals were studied which were termed hallucinogenic and more recently have been called psychotomimetic. Adrenochrome and adrenolutin might now be called schizogenic substances. When they are given they produce an experience which more closely resembles early schizophrenia than that induced by LSD or mescaline.

It has been suggested by some colleagues that a simple demonstration that the body fluids of schizophrenic people contain more adrenolutin and adrenochrome than do those of normal people or mentally ill suffering from other illnesses will substantiate our hypothesis. In our view, the matter is not as simple. Four different steps are necessary to achieve this end: (1) adrenochrome, adrenolutin and/or other immediate derivatives of them must not only be present but must be shown to have some relationship to schizophrenia, (2) these epinephrine derivatives must reproduce some of the psychological and clinical features of schizophrenia, (3) adrenochrome and adrenolutin must reproduce some of the biochemical features of schizophrenia, (4) the hypothesis must be useful in developing new treatments.

We shall discuss these crucial experiments using data already recorded and presenting new data from our own laboratory which relates to them.

A. BIOCHEMICAL DIFFERENTIATION OF SCHIZOPHRENIC FLUIDS FROM NON SCHIZOPHRENIC FLUIDS

1. Introduction

One advantage of the early indole theory of mental disease first proposed was simplicity. The bowel toxins were supposed to accumulate in the blood especially of the constipated. With greater sophistication in medicine generally and the development of biochemistry, this was slowly disproved. Early toxic hypotheses implicated vast groups of compounds such as amines, nitrogenous

compounds, etc. and so were impossible to test. Later this was narrowed to indoles but this still leaves tens or even hundreds of compounds. If, however, one decides to look for indoles related to epinephrine and tryptophan, then the problem becomes much smaller.

From our knowledge of the properties of adrenochrome and adrenolutin, we should be able to predict the sort of differences there would be between body fluids taken from schizophrenic patients and those of other people. If we then add adrenochrome and adrenolutin to normal serum and this then becomes more like schizophrenic serum, this will suggest that something similar is present in schizophrenic serum. We have therefore examined the effect of schizophrenic fluids in biological assays compared to psychotomimetic substances and to search them for the presence of indoles related to epinephrine.

2. Biological Assays

There is ample evidence that schizophrenic plasma contains substances not found as a rule in patients who do not suffer from the illness. Reviewing this evidence Hoffer and Osmond (1959) include: (1) the 1-strain fibroblast toxicity factor, Fedoroff (1955, 1956, 1958), Fedoroff and Hoffer (1956); (2) the toxic factor for the climbing rats, Winter and Flataker (1956), Bergen, Pennell, Hoagland and Freeman (1959); (3) the toxic factor for spore germination, Schwarzenbach (1957); (4) the toxic factor for spinning webs of spiders, Witt (1954), Rieder (1957); (5) the toxic factor for pigeons, Baruk and Camus (1957), Baruk, Launay, Berges, Perles and Conte (1958); (6) the toxic factor for lupin root, Macht and Kremen (1956); (7) the hemolytic factor in schizophrenics, Sjovall (1947); (8) the toxic factor on glucose utilization by rat diaphragm, Walaas, Lingjaerde, Loken and Hundevadt (1954); (9) the toxic factor for rat retina, Striefler (1957); (10) the toxic factor which increases norepinephrine and epinephrine markedly in rabbit brain, Walaszek and Minz (1958), Minz and Walaszek (1958); (11) taraxein, Heath, Martens, Leach, Cohen and Angel (1957), Heath and Leach (1956), Heath, Leach, Byers, Martens and Fiegley (1958), Lief (1957).

This formidable array of biological indicators provide substantial support to the hypothesis that schizophrenic plasma contains some toxic factor. Perhaps one or more of these is the factor which inhibits the conversion of adrenochrome into leuco adrenochrome.

(a) L-Strain Fibroblast Toxicity. In this test, serum taken from patients in the morning before breakfast is added to tissue cultures of L-strain cells, Fedoroff (1958). Schizophrenic serum markedly inhibits cell growth whereas this occurs much less frequently when normal serum is used. Blood serum from patients undergoing surgery is also toxic but that from neurotic patients is similar to the normal group. Some neurotic patients high in toxicity show many schizophrenic features.

Adrenochrome and adrenolutin are antimitotic and thus toxic for some cells. However, Fedoroff's work shows that at least two factors are involved in the toxicity test which cannot with certainty be ascribed to adrenochrome and adrenolutin alone.

(b) Rat Climbing Test. When trained climbing rats are injected with a standard quantity of schizophrenic serum, performance is greatly impaired. Normal serum does not have this effect. Serum from about 90 percent of schizophrenic patients have this property and from only about 10 percent of normals. This distribution of toxicity is very similar to that found by the fibroblast test.

LSD and adrenochrome also impair rat performance and certain urinary derivatives from schizophrenics have a similar effect.

(c) Spore Germination Test. When suitable extracts from the serum or urine of schizophrenics are added to the spore of certain fungi their germination is inhibited, Schwarzenbach (1957). Similar extracts from normal people do not do this. From a variety of substances tested so far, LSD, mescaline and adrenochrome semicarbazone and adrenochrome inhibited germination in concentrations of one in a million. Serotonin and bufotenine inhibit germination at concentrations of one in a thousand. Schizophrenic serum contains substances which are more toxic for these spores than any chemical tested so far.

(d) Spider Web Test. When the extract from schizophrenic urine is fed to certain spiders, there is an impairment in the quality of the web, Rieder (1957). Mescaline, LSD and adrenochrome are also very active in this respect whereas adrenochrome semicarbazone does not distort the web, Witt (1954).

(e) Catatonizing Effect on Pigeons. Schizophrenic bile produces a form of disinterest and indifference in pigeons which has been called catatonia, Baruk and Camus (1957). Normal bile has no effect. The administration of 5 to 10 mg. per pigeon of adrenochrome and of adrenolutin produces a similar reaction, Hoffer and Wojcicki (1957). LSD (½ mg.) has little effect on pigeon behavior, Blough (1957).

The results of the five biological tests are summarized in Table 20.

On these tests, adrenochrome has very similar effects to those of extracts of schizophrenic fluids. Mescaline and LSD do not resemble the schizophrenic so closely. The only substances tested so far which are likely to be present in the body are adrenochrome and adrenolutin. But they alone are required in dosages larger than one would expect to find in serum. However, schizophrenic serum contains taraxein, Heath, Martens, Leach, Cohen and Angel (1957) which can markedly potentiate the activity of adrenochrome and adrenolutin, Melander and Martens (1958), and thus small

TABLE 20

TOXICITY OF NORMAL AND SCHIZOPHRENIC PLASMA AND OF SOME PSYCHOTOMIMETIC SUBSTANCES

	Body Fluids		*Chemicals*		
Assay	*Normal*	*Schizophrenic*	*Adrenochrome*	*Mescaline*	*LSD*
L strain fibroblasts	No	Yes	Yes	?	No
Rat climbing	No	Yes	Yes	Yes	Yes
Spore germination	No	Yes	Yes	Yes	Yes
Spider web	No	Yes	Yes	Yes	Yes
Pigeon catatonia	No	Yes	Yes	?	No

quantities will be more effective than larger quantities of pure compound.

3. Adrenochrome Levels and Schizophrenia

Biological assays often precede more accurate biochemical methods. Payza and Mahon (1959) developed a method for measuring adrenochrome in plasma, cerebrospinal fluid and urine. The method is specific for nor adrenochrome and adrenochrome.

The method is based upon the conversion of adrenochrome to a zinc complex of adrenolutin. This is extracted into acetone and its fluorescence determined. Recovery experiments are satisfactory and reproducibility is good.

The mean plasma adrenochrome values for a series of fifty seven normals was 56 μg/liter, ranging from 10 to 106. Means for thirty three schizophrenics, sixteen depressed patients and ten alcoholics were 55, 50 and 52 μg/liter. These values do not differ from those found in plasma drawn from normal subjects.

Adrenochrome levels in plasma compared to cerebrospinal fluid are shown in Table 21.

The levels in cerebrospinal fluid of medical and surgical patients is nearly the same as for plasma, i.e. about 65 μg/liter with a ratio close to 1.0. With schizophrenic patients, this ratio is closer to 2.0. This data indicates that the brain may be the source of adrenochrome and that there is more in the schizophrenic brain. High oxygen tension increased brain adrenochrome, Gershenovich (1955). As adrenochrome is more stable in cerebro-

TABLE 21

ADRENOCHROME LEVELS IN PLASMA AND CEREBROSPINAL FLUID, μG/LITER

Group	*N*	*Plasma*	*CSF*	*Ratio*
Schizophrenic	15	43	82	1.9
Possibly Schizophrenic[1]	5	85	104	1.2
Depression or Anxiety	7	50	47	0.9
Means for Normals	—	66	68	1.0

[1]These patients would be classed as pseudoneurotic schizophrenic patients by some authors.

spinal fluid than in plasma, it is not surprising that cerebrospinal fluid levels can be higher whereas in plasma the high rate of destruction would equalize the values.

4. Adrenochrome Tolerance

Since there was no difference between various groups of patients and as adrenochrome is apparently rapidly destroyed by blood in vitro, Hoffer and Kenyon (1957), and in vivo, Fischer and Lecomte (1951), the ability of groups of patients to destroy adrenochrome was determined. The patients were injected by vein with 10 mg. crystalline adrenochrome, Heacock, Nerenberg and Payza (1958), and plasma adrenochrome determined at one quarter, one half and one hour after injection. The results are shown in Table 22.

Much of the injection adrenochrome is very rapidly converted into adrenolutin and the fluorescence of the acetone blank is markedly increased.

The plasma adrenochrome values fifteen minutes after injection with adrenochrome are between three and four times the pre-injection value for the schizophrenic and possibly schizophrenic group. After one hour, the values are twice as high in the first group but have returned to normal in the second. In the schizophrenics who had received large quantities of nicotinic acid before the test, little increase was noted and after one hour levels had

TABLE 22

TOLERANCE FOR TEN MILLIGRAMS INTRAVENOUS ADRENOCHROME

Group	*Treatment*	*N*	*Initial Level*	*Percent Change at*		
				15 min.	*30 min.*	*60 min.*
Schizophrenic	None	6	43	+280	+ 75	+107
Possibly Schizophrenic	None	5	68	+220	+ 10	− 6
Schizophrenic	Niacin	5	50	+100	0	− 44
Not Schizophrenic	None	9	51	+170	− 45	− 23
Not Schizophrenic	35 μg LSD*	6	43	+260	+100	+ 67
Not Schizophrenic	100 μg LSD*	2	46	—	—	+170

*2 hours before adrenochrome tolerance.

decreased below the initial level. A similar pattern is seen for non schizophrenic subjects.

The schizophrenics were not able to remove adrenochrome as rapidly from plasma as non schizophrenic subjects. However, after nicotinic acid treatment the removal of adrenochrome was increased even though these patients were not clinically improved. The schizophrenic adrenochrome tolerance curve resembles that in normals pretreated with LSD, Hoffer (1959). Pretreatment with brom LSD does not produce abnormal adrenochrome tolerance curves.

5. Conversion of Adrenochrome to Adrenolutin

The adrenochrome is quickly converted into adrenolutin, Hoffer (1957) and leuco adrenochrome. Adrenolutin is readily extracted by the acetone which shows a distinct peak at the specific fluorescence area for adrenolutin. The increase in the acetone blank over the value before injection is therefore a measure of the amount of adrenochrome converted into adrenolutin. The blank went up 3 fluorescence units for eleven schizophrenic patients one half hour after injection and 4 units for eleven non schizophrenic patients. These changes are not significantly different. However, at this time, non schizophrenics had destroyed all the injected adrenochrome whereas in schizophrenics the levels were still elevated. This indicates that schizophrenics convert a greater proportion of adrenochrome into adrenolutin.

Payza and Hoffer (1958) examined the in vitro conversion of adrenochrome into adrenolutin by adding adrenochrome to plasma buffered at pH 4.0. Disappearance of adrenochrome was measured by the decrease in optical density at 480 mμ. Formation of adrenolutin was followed by the increase in optical density at 410 mμ. The quantity of adrenolutin formed relative to adrenochrome lost was determined by dividing the optical density decrease at 480 by the increase in optical density at 410. High ratios indicate small conversion of adrenochrome into adrenolutin.

The ratios for schizophrenic and non schizophrenic patients are shown in Table 23.

Thus schizophrenic plasma in vitro also converts more adrenochrome into adrenolutin. The ratio 0.91 differentiates the schizo-

TABLE 23

SHOWING RELATIVE IN VITRO CONVERSION OF ADRENOCHROME TO ADRENOLUTIN. RATIO IS THE DECREASE IN OPTICAL DENSITY AT 480 mμ DIVIDED BY INCREASE IN OPTICAL DENSITY AT 410

Group	*N*	*Mean*	*Range*	*Number under 0.91*	*Number 0.91 and over*
Schizophrenic	11	0.78	.36-1.12	10	1
Other Patients[1]	10	1.04	.54-1.40	3	7
Normals	10	1.25	.55-2.05	1	9

[1]Four are non psychiatric cases undergoing surgery. Blood drawn during operation.

phrenic group from the other patients (Chi Sq=4.8). Other patients and normals have similar distributions. Similar studies have been reported with alcoholic psychoses, Jantz (1956).

6. Discussion

Adrenochrome is converted in plasma into adrenolutin in vivo and in vitro and perhaps into a series of leuco substances. The evidence outlined suggests that adrenochrome is formed in the brain and is converted there and in blood into these other substances. This suggests that chemical substances are present in the bodies of schizophrenic patients which inhibit the conversion of adrenochrome into substances which are not psychotomimetic, and thus increase the amount available to be made into adrenolutin which is. With this assumption, it is possible to account for: (1) the higher levels of adrenochrome in cerebrospinal fluid where it is slowly destroyed, while the blood levels remain normal; (2) a decreased tolerance for adrenochrome administered intraveniously, and (3) the increased conversion of adrenochrome to adrenolutin in vivo and in vitro. It may be assumed that LSD too inhibits the production of the non psychotomimetic substances and this reproduces a schizophrenic-like reaction whereas BOL does not.

The increase in the production of indole substances derived from epinephrine may account partially for the findings recently reviewed by McGeer *et al.* (1957) and Buscaino (1958) for aromaturia in schizophrenia.

The possibility that schizophrenic fluids contain substances which interfere with metabolism of adrenochrome and thus perhaps of epinephrine is strongly supported by recent studies of Walaszek and Minz (1958). They found that when hypothalamuses taken from rabbits which had been treated with schizophrenic serum were examined they contained the following quantities of nor epinephrine and epinephrine.

	Normal Serum	*Schizophrenic Serum*
Nor epinephrine	3.3 μg/gram	7.0 μg/gram
Epinephrine	0.11 μg/gram	0.90 μg/gram

Schizophrenic serum apparently contains factors which interfere with the utilization of epinephrine.

Fellman's finding (1958) that epinephrine may form some of the pigments of substantia nigra through oxidative polymerization, i.e. through adrenochrome to melanin-like pigments, supports the suggestion that adrenochrome plays a role in brain metabolism.

7. Conclusion

Adrenochrome metabolism is disturbed in schizophrenia and in normal subjects given LSD. The first crucial experiment receives substantial support. It is likely that the bodies of schizophrenics contain substances which inhibit the transformation of adrenochrome into leuco adrenochrome thereby increasing the relative production of adrenolutin.

B. SIMILARITY OF THE ADRENOCHROME INDUCED EXPERIENCE AND SCHIZOPHRENIA

The similarity between the adrenochrome induced experience and schizophrenia can be inferred from the work we have reviewed in the previous chapter. There is no doubt this similarity corroborates the basic hypothesis.

C. THE SIMILARITY BETWEEN EXPERIMENTAL PSYCHOSES AND SCHIZOPHRENIA

1. Introduction

In normal volunteers, LSD and mescaline produce psychological changes which have much in common with schizophrenia, Osmond and Smythies (1952), Osmond (1957), Rinkel, DeShon, Hyde and Solomon (1952), Rinkel, Hyde, Solomon and Hoagland (1955) and Stockings (1940). Investigators working with these compounds and more recently with adrenochrome and adrenolutin have been challenged to prove that there is some similarity between these two experiences. Bleuler (1956) terms these experiences a toxic psychosis whereas Denber (1955) suggests the experience is neither a toxic psychosis nor schizophrenia. While it is true that one might support either contention both neglect theoretical principles in the use of models.

Scientists often have to discover ways of producing natural phenomena in the laboratory where they can be studied at leisure. A model is not a reproduction of an original. If it were, it would not be a model. A model is required to clarify certain aspects of an original. This the psychotomimetic substances do reasonably well. There undoubtedly is more similarity between the mescaline experience and schizophrenia than between a simple deteriorated schizophrenic without hallucinations and delusions and a wildly excited catatonic schizophrenic with vivid visual and auditory hallucinations. There is less similarity between toxic confusional states and schizophrenia.

Toxic confusional states are characterized by the presence of one or more of the following (1) disorientation, (2) some disturbance in consciousness, (3) and some memory difficulty. These are usually found in deleria produced by fever, bromide, etc. Even then it is sometimes difficult to be sure of the diagnosis which depends upon the presence of an infection (fever) or the knowledge that the patient has been taking some noxious substance. A rapid recovery when the patient no longer has access to the drug supports the inference.

As normally used, the psychotomimetic drugs do not produce the confusion or clouding found in toxic states. They therefore

are "toxic" only because they have been produced by a chemical substance given by the investigator. Unless this semantic trap is recognized for what it is, we may one day be forced to call schizophrenia a toxic psychosis.

To compare a model psychosis with schizophrenia, the clinical and biochemical responses of normal subjects given the particular psychotomimetic substances under investigation are compared. If these substances really are models, the similarities should be more striking than the differences.

2. *Psychotomimetic Antagonists and Schizophrenic Therapeutic Agents*

For many years, barbiturates have been an important weapon in treating schizophrenia. Intravenous amytal will often dramatically relieve a psychosis but unfortunately this is fleeting. Similarly amytal will remove the LSD psychosis but when the amytal is excreted it returns.

Chlorpromazine is considered helpful for many excited schizophrenics especially those in chronic mental hospitals and it too will remove most of the features of the psychotomimetic drugs, Hoch (1956) and Schwarz, Bickford and Rome (1955). The value of reserpine, which depletes brain of serotonin, norepinephrine, and epinephrine, Carlsson, Rosengren, Bertler and Nolsson (1957), in treatment of schizophrenia is as disputed as is its capacity for antagonizing LSD. The effects of Frenquel in both schizophrenia and as an LSD antagonist are equally vague, Fabing (1955). Succinic acid was originally used to abort the mescaline experience, Schueler (1948) and Stevensen and Sanchez (1957), and this has led to its use in the treatment of schizophrenia, Burrell (1956).

Nicotinic acid (3 grams per day) given for three days before LSD altered the experience by preventing most of the visual perceptual changes. Given intravenously, 200 to 400 mg. quickly antagonized the experience, Agnew and Hoffer (1953), Ruiz-Ogara et al (1956). Both substances are useful for the treatment of early schizophrenia. Nicotinic acid removes EEG dysrhythmia produced by intravenous adrenochrome and terminates the adrenolutin experience in humans. In contrast Miller, Williams and Murphree

(1957) giving 600 mg. by mouth of nicotinic acid and nicotinamide found no modification of an LSD experience following a dose of 75 μg. In our experience oral doses of between one and two grams of nicotinic acid are required for modification. We have not found nicotinamide very effective.

Anxiety which intensifies the schizophrenic panic also markedly intensifies the LSD experience. An experience which is pleasant and euphoriant may easily be converted into a state of panic.

Thus, it may generally be said that both conditions are aggravated by similar drugs and similar situations.

3. Psychotomimetic Potentiators

Atropine can produce psychotic reactions that are very difficult to distinguish from schizophrenia. Datura which contains atropine has long been used in both India and Africa to intensify the hashish psychosis, Johnson (1953).

Forrer and Goldner (1951) in a study of LSD pretreated some subjects with atropine. An examination of their protocols suggest there was some intensification. However, more recently it has been shown that atropine did not increase the intensity of the LSD experience, Miller, Williams and Murphree (1957).

Benzedrine derivatives either in very large single doses or when taken for prolonged periods produces a schizophrenic-like condition, Connell (1958). It reactivates the LSD psychosis after the experience has waned, Hubbard (1957).

4. Autonomic Changes

In both schizophrenia and model psychoses, changes in blood pressure, pulse rate and other indices of autonomic activity occur, Rothlin (1957). Mayer-Gross, McAdams and Walker (1951) found thatLSD tended to elevate blood sugar slightly. A proportion of schizophrenics have abnormal sugar tolerance tests, Meduna and McCullough (1945). This has not yet been studied in model psychoses. Temperature changes in humans were not significant. In animals, where larger dosages are permissable, it has been found that adrenochrome and trihydroxy-*N*-methylindole produce a marked lowering of body temperature, Hutcheon, Lowenthal and

Eade (1956), concommitant with an increase in oxygen consumption (hypothalamic activity) and that LSD has a pyretogenic action on rabbits, Cerletti (1956).

5. Biochemical Changes

Phosphate excretion is shown in Table 24. There was no significant variance at each time period for the various groups. However, schizophrenics and subjects given 50 mg. of adrenolutin retained more during the night. The values found for the night sample are mean values of the entire sleeping period. Values at 10 P.M. are different. It is therefore possible to calculate the excretion per minute toward the end of the collection period using the 10 P.M. value as representative of the rate for the first part of this collection period and the mean value for the entire period. These are shown in Table 24. Calculated schizophrenic excretions for the last interval are much lower than for all other groups followed by the normals receiving the most adrenolutin.

In order to check the validity of this calculation, urines were collected between 7 and 10 A.M. for twenty eight schizophrenic patients and thirteen mentally ill non schizophrenic patients residing in the same hospital. The mean phosphate excretion mg. per minute was 0.32 for schizophrenics and 0.53 for the other group. This difference in means is statistically significant ($k=2.10$, $p=0.03$).

Using the 6 or 8 P.M. values or their mean when both are

TABLE 24

PHOSPHATE EXCRETION, MG/MINUTE

	4-6 P.M.	*6-8 P.M.*	*8-10 P.M.*	*Night Sample*	*A.M. Calc.*
Schizophrenics	—	.83	.83	.52	.21
Adrenolutin—50 mg.	.81	.76	.61	.51	.41
Adrenolutin—25 mg.	—	.78	.68	.63	.58
Placebo	.79	.70	.70	.68	.66
Control	.82	.94	.84	.70	.56

available as a baseline, the following retention of phosphate was found:

Schizophrenics	37%
Adrenolutin 50 mg.	35%
Adrenolutin 25 mg.	19%
Placebo	9%
Control	20%

The excretion of phosphorus per unit of creatinine for the period 6 to 10 P.M. is compared with the night excretion.

The adrenolutin effect of phosphate excretion is quite different from any placebo (anxiety) effect and adrenolutinized subjects show changes in phosphate excretion very similar to those seen in schizophrenia.

Phosphate retention was not affected by anxiety. However, retention of phosphate was greater for schizophrenics and for adrenolutin at 50 mg. level. The other adrenolutin group showed little displacement from controls. Comparing the evening rate and morning rate it is seen that the excretion of phosphate per unit of creatinine is quite different separating placebo and controls on one hand from the other three groups.

The retention of phosphate following administration of adrenolutin resembles similar retention induced by LSD in humans, Hoagland, Rinkel and Hyde (1955) and in animals, Bergen and Beisaw (1956). Similarly the calculated morning excretion rates for schizophrenics which are about forty percent of

TABLE 25

PHOSPHATE EXCRETION, MG. PER MG. CREATININE

	6-10 P.M. Mean	*Night*	*Change %*
Schizophrenic	0.90	0.82	− 9
Adrenolutin 50 mg.	0.49	0.43	−12
Adrenolutin 25 mg.	0.59	0.56	− 5
Placebo	0.47	0.60	+28
Control	0.59	0.64	+ 8

normal for the calculated late night rates (see Table 23) and sixty percent for the collection period 7 to 10 A.M. are similar to those reported by Hoagland et al.

6. Conclusion

Some substances which aggravate or produce schizophrenic-like reactions act similarly with model psychosis. Conversely antagonists to model psychosis tend to be therapeutic for schizophrenia.

Similar autonomic disturbances are found in both states. Finally, adrenolutin and LSD produces changes in phosphate similar to those found in schizophrenia. The third crucial experiment thus receives support.

D. TREATMENT OF SCHIZOPHRENIA

Treatment according to the adrenochrome hypothesis should be directed toward (1) decreasing adrenaline production, (2) decreasing the conversion of adrenaline into adrenochrome, (3) preventing the toxic action of adrenochrome and adrenolutin, and (4) removing or destroying adrenochrome and adrenolutin.

1. Reduction in Production of Adrenaline

Barbiturates and tranquilizers may decrease the production of adrenaline by decreasing sensory input. Psychotherapy and other environmental therapy may similarly reduce epinephrine production by decreasing fear and anxiety. Chemical control is often easier.

Few substances are known which decrease the production of epinephrine. Adrenolytic agents do not decrease adrenaline output nor "lyse" circulating epinephrine but reduce the sensitivity of the receptors. They may even increase the amount of epinephrine and so make matters worse.

Nicotinic Acid.* Nicotinic acid and nicotinamide are both methyl acceptors. Hoffer, Osmond, Callbeck and Kahan (1957) found these compounds useful in the treatment of early schizophrenia. They suggested that in large quantities, these substances would pick up methyl groups and thus decrease the production of epinephrine by competition with norepinephrine. Nicotinic acid

*A complete report on the usefulness of giving nicotinic acid as a treatment will be published (Charles C Thomas, Publisher) in the near future.

must have other properties not depending solely on methylation. When administered intravenously to epileptic subjects who had previously been given adrenochrome, it quickly reversed the changes induced in the electroencephalogram as well as the epileptic dysrhythmia.

2. Decreasing Production of Adrenochrome

Ascorbic Acid. Ascorbic acid may restore proper epinephrine metabolism due to three known properties: (1) It inhibits the oxidation of epinephrine to adrenochrome, Angel, Leach, Martens, Cohen and Heath (1957), Payza and Hoffer (1958), Hoffer (1957). As a result, LSD does not increase plasma adrenochrome levels when large quantities of ascorbic acid are given. (2) It changes adrenochrome to leuco adrenochrome which is not psychotomimetic for animals, Melander (1957), nor, according to our findings, for man. This change occurs more rapidly with the free base at acid pH than at the pH of blood (7.3) as the sodium salt. (3) It deaminates beta phenylisopropyl amine (amphetamine) in vitro and in dogs given amphetamine decreases the quantity excreted in urine, Beyer (1941). It thus may also deaminate norepinephrine and epinephrine in vivo. Lucksch (1940) found ascorbic acid useful in the treatment of schizophrenia. We have also found this in a few priliminary trials with early schizophrenia. The combination of ascorbic acid and sodium chloride suggested by Lea (1955) may be even more effective.

Conversely decreased levels of ascorbic acid are probably detrimental. Lowered levels are not necessarily due to inadequate dietary intake although unfortunately this may occur in mental hospitals. Urbach, Hickman and Harris (1952) using normal controls on adequate diets found remarkable variations in plasma ascorbic acid levels. Almost any disturbance of body or mind altered ascorbic acid levels. Colds, respiratory infections and any elevation of body temperature lowered Vitamin C sometimes to zero but always by at least 50%. Most dramatic was the effect of emotional stress. Whenever some subjects were angry or truculent at the time blood was taken, ascorbic acid was low. If they were happy and carefree (unlikely in a mental hospital), ascorbic acid

was high. After severe physical exertion, blood ascorbic acid was drastically reduced.

Ascorbic acid does not prevent the LSD reaction, Hoffer (1958c) although it is modified which suggests it does not completely block adrenochrome production in the brain. It may therefore be useful only in very early schizophrenia. Because of its safety, it might be useful to treat all early and borderline schizophrenics with ascorbic acid as an adjunct by using at least 3 grams per day by mouth.

Glutathione. Glutathione also converts adrenochrome to leuco adrenochrome and thus may resemble ascorbic acid and might be useful in the treatment of schizophrenia. Schizophrenics also have below normal levels, Martens, Leach, Heath and Cohen (1956), Altschule, Henneman and Goncz (1957). Indeed Surikov, Ushakov, Verblivnskaia and Khokhlov (1957) found intravenous glutathione (1% in 40% glucose—0.2 to 0.6 mg. per dose) quite useful in psychiatric therapy. Four out of nine schizophrenics and four out of five seniles were improved. Out of four involutional depressions none were improved.

3. Neutralizing Adrenolutin

Ceruloplasmin. Ceruloplasmin, a copper protein enzyme, normally present in serum oxidizes catechol, epinephrine, serotonin and other amines. Leach, Cohen, Heath and Martens (1956) believed it was the catalyst in the oxidation of epinephrine to adrenochrome. Akerfeldt (1957) found that N,N-diethyl-p-phenylene diamine was a useful substrate for measuring ceruloplasmin levels. Akerfeldt reported that schizophrenic patients generally were higher in ceruloplasmin thus supporting the suggestion of Angel, Leach, Martens, Cohen and Heath (1957) that schizophrenic serum converted more epinephrine into adrenolutin. Since then, conflicting reports have appeared regarding the relationship of ceruloplasmin concentration and schizophrenia. However, it now appears that schizophrenics as a group do have higher levels of ceruloplasmin although there is considerable overlap with other types of patients, Abood, Gibbs, and Gibbs (1957), Scheinberg, Morell, Harris and Berger (1957). Abood (1957) and Ostfeld, Abood and

Marcus (1958) reported that a new series of atropine-like compounds (e.g. N-ethyl-3-piperidyl benzilate) are psychotomimetic and also elevate ceruloplasmin levels. Ceruloplasmin levels were also elevated in psychiatric patients who were excited compared to patients not excited.

The epinephrine oxidase activity of ceruloplasmin and its increase in schizophrenia as well as in other physical illnesses apparently provides support for the adrenochrome hypothesis. However, other findings throw doubt on ceruloplasmin as a major pathological factor: (a) Payza and Zaleschuk (1960) and Payza and Hoffer (1960) compared the enzymatic properties of the enzyme oxidizing epinephrine and p-phenylenediamine. The properties were so markedly different that it was unlikely they were the same. They suggested that epinephrine oxidase in tissues is not ceruloplasmin although it may play a role. (b) Ceruloplasmin is elevated in physical illnesses and during excitement without the production of schizophrenia. (c) Ceruloplasmin has been used in the treatment of schizophrenia. (d) Schizophrenics with increased ceruloplasmin levels have a better prognosis, Heath, Leach, Byers, Martens and Feigley (1958). They suggested that the ceruloplasmin response might be an important part of the mechanism for counteracting the psychotic process.

Martens, Vallbo and Melander (1958) support this hypothesis, i.e. that ceruloplasmin is part of a protective mechanism which may be faulty in schizophrenia. Heath et al (1958) showed that injected ceruloplasmin has a half life of 5 days. In four patients, they doubled serum ceruloplasmin. There were indications that their epinephrine metabolism had become more normal and these patients responded clinically to subcutaneous epinephrine more like normal subjects.

Martens, Vallbo and Melander (1958) administered ceruloplasmin to 22 schizophrenic patients. Nineteen were improved. Usually clinical improvement occurred ¾ to 2 hours after the injection and sometimes was very dramatic. Of the 19 patients, 9 remitted completely and 6 have remained well. In all cases, serum copper levels increased and remained high for one week after last treatment. Epinephrine oxidation by serum also increased.

Ascorbic acid levels were decreased. Administration of ascorbic acid decreased epinephrine oxidation but copper levels remained high. Since clinical improvement did occur, they suggested maintenance of high copper is more important than maintaining a high rate of epinephrine oxidation.

The ability of ceruloplasmin to protect against schizophrenia may account for the interesting relationship between pregnancy and schizophrenia. During pregnancy, especially in the last trimester, ceruloplasmin levels are markedly elevated. Two weeks after parturition, serum ceruloplasmin levels have decreased appreciably. During pregnancy, some schizophrenic patients became clinically improved. Recently we have seen a young schizophrenic patient become normal during pregnancy and at present this has been maintained for two and a half years. She had been treated with nicotinic acid and electroconvulsive therapy over a year before pregnancy with moderate improvement. However, her adjustment to the community was most tenous. During the third trimester, a dramatic change in the schizophrenia occurred.

Wiedorn (1954) found that the incidence of toxemia is greater in schizophrenic women than in controls. Before term, epinephrine levels are elevated and very quickly decrease during labor. Ritzel, Staub and Hunzinger (1957). Puerperal psychosis occur following birth, at a time when ceruloplasmin levels are falling quickly.

Melander (1957) found that ceruloplasmin absorbs adrenolutin. Adrenolutin readily dialyzes through a semipermeable membrane. When ceruloplasmin is added, no further dialysis occurs. Other globulins do not bind adrenolutin. Payza and Zaleschuk (1960) showed that adrenolutin strongly inhibits ceruloplasmin activity on p-phenylenediamine. Adrenochrome does not. Ceruloplasmin also protects animals against catatonic dosages of adrenolutin. Perhaps it is the role of ceruloplasmin to bind adrenolutin and thus protect against excessive quantities. Under stress, epinephrine and adrenochrome production may increase. Ceruloplasmin would also increase and the ratio of epinephrine metabolites to ceruloplasmin remain normal. Pathological changes could occur when this ratio is unbalanced by excessive production of

epinephrine metabolites or by defective formation of ceruloplasmin. With this hypothesis, it will follow that:

(1) Ceruloplasmin will increase in conditions of stress and excitement.

(2) Deficiency in ceruloplasmin will be harmful and may be responsible for some toxemias of pregnancy and for puerperal psychosis.

(3) Ceruloplasmin will be therapeutic. If not available, transfusions from pregnant women in third trimester may be therapeutic.

(4) Schizophrenics, lacking ceruloplasmin, will not bind adrenolutin and thus by some chemical mass action may decrease oxidation of hypodermically administered epinephrine. Administration of ceruloplasmin will thus allow more rapid metabolism of epinephrine.

4. Destroying Adrenochrome

Penicillamine. In 1953, one of us (A.H.) observed an unusual therapeutic response of a schizophrenic patient to penicillin. This patient, ill for nearly eight years in the community, had failed to show any response to a combination of nicotinic acid (3 grams per day) and ECT. Some weeks after ECT was discontinued, she slipped and cut her wrist. This soon became infected and she was given 0.4 gram penicillin per day for five days. At the end of this time there was a remarkable clinical improvement. She was discharged shortly after, much improved and has remained in the community on nicotinic acid. She is still paranoid but able to support herself as a stenographer. This sudden response which occurred while she was given penicillin concentrated our attention on this compound. Two similar responses were noted since then. However, we did no more although we had once formulated plans for a large scale therapeutic trial. There was then no adequate rationale for using penicillin.

Subsequently, it was shown that a derivative of penicillin called penicillamine ($\beta\beta$-dimethyl cysteine) was a chelating agent and could bind copper. It is therefore used as a treatment for Wilsons disease. Shortly after giving penicillamine there is a several fold increase in urinary excretion of copper.

Copper ions catalyze the oxidation of epinephrine to adrenochrome in vitro. If this also occurred in vivo it might be useful to reduce copper ions in order to decrease the conversion of epinephrine through adrenochrome to adrenolutin. For this reason it appeared rational to use this copper binding substance as a treatment for schizophrenia. Dr. J. Webb of Upjohn and Company in the United States kindly provided us with penicillamine with which to start these trials. When the penicillamine became available, Heacock and Scott (1959) found that in common with other sulfhydril containing compounds, it reduced adrenochrome to 5,6-dihydroxy-*N*-methylindole and other substances. Compared to other such substances it produces a greater proportion of the non toxic dihydroxy indoles. This is therefore another rationale for treating schizophrenia.

Four patients who had not responded to a combination of ECT and nicotinic acid were given ECT; nicotinic acid; 3 grams per day; ascorbic acid, 3 grams per day and penicillamine, 2 grams per day for up to two weeks. All four patients have become normal (3) or markedly improved (1) and remain well on nicotinic acid and ascorbic acid. The following is a brief account of one patient:

Subject M. Age twenty. Had been seriously ill for two years. He had hallucinations, delusions, serious thought disorder, mannerisms, posturings, etc. He received 20 ECT and nicotinic acid, 6 grams per day. There was a moderate improvement followed a few days after the last ECT by a reversion to the admission state. He was then given 3 more ECT, nicotinic acid as above, ascorbic acid, 3 grams per day, and penicillamine, 2 grams per day for ten days and discharged unimproved. To our surprise he began to improve within about two weeks at home which continued for six months at which time he was seen. He then appeared physically healthy, had no thought disorder, no hallucinations and was able to engage in conversation. He was working with his father on his farm, played hockey and became interested in completing his senior matriculation by correspondence. He has remained at this level about one year. During this time he has received 3 grams of nicotinic acid per day. This is the subject classed as much improved. His was the most striking response as he had been so sick. The

other three patients are now well and living normally in the community. They are maintained on nicotinic acid.

The four patients treated had been ill several years and had failed all other treatment. Improvement followed immediately after they started receiving penicillamine. By chance alone it is not likely any one of them would have recovered. Penicillamine may therefore be a useful additional treatment when ECT and nicotinic acid have failed.

The first rationale seems unlikely to be correct. On the contrary excessive excretion of copper may be detrimental. Two of the patients after improving while on penicillamine lost their affect much as did the subject described earlier who had received LSD and penicillamine. However, a few days after a penicillamine was stopped they showed marked improvement. The dosage will have to be controlled not to produce copper depletion. The second rationale seems the most likely.

It may be that the response of Wilson's disease to penicillamine is due to both factors. Perhaps the mental abnormality of Wilson's disease is due to excess adrenochrome and adrenolutin. They have (1) excess copper, (2) little ceruloplasmin. They should therefore suffer from schizophrenic-like psychosis. Knehr and Bearn (1956) reported Wilson's disease patients had a decreased capacity for conceptual thinking. They also had a lowered critical flicker fusion frequency and a prolonged after image, as do many schizophrenics.

E. SOME PHYSIOLOGICAL CORRELATES OF SCHIZOPHRENIA WHICH FOLLOWS FROM THE ADRENOCHROME HYPOTHESIS

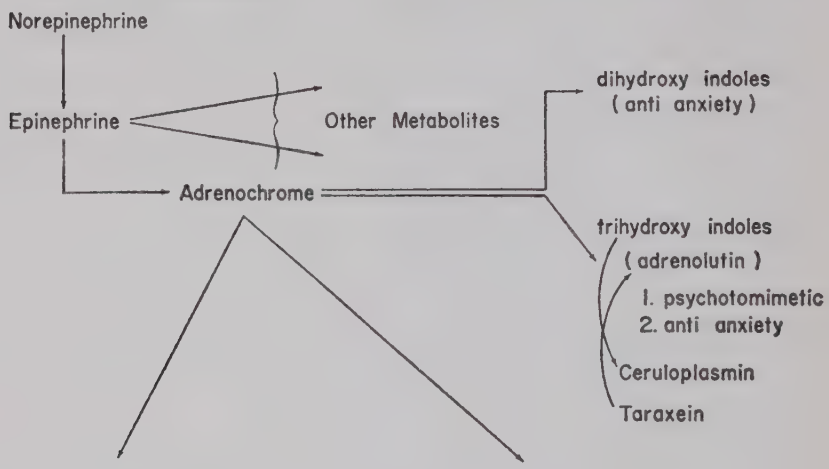
Many physiological and biochemical properties of adrenochrome are known. The presence of this substance in the body in greater than normal quantities in schizophrenic should give them certain predictable properties. The properties of adrenochrome and the expected clinical findings in schizophrenia are shown in Table 26.

1. Antihistaminic

One would expect that people who have large amounts of adrenochrome either in tissues or fluids would show a tolerance

TABLE 26

PHYSIOLOGICAL AND BIOCHEMICALS OF ADRENOCHROME AND RESULTING CLINICAL PROPERTIES IF IT IS PRESENT IN SCHIZOPHRENIA



Properties	*Clinical Findings Predicted*
1. Psychotomimetic	Schizophrenia.
2. Antihistaminic	Few allergies. Tolerant to histamine.
3. Polymerizes to brain pigments	Increased pigmentation.
4. Anti thyroid	Increased tolerance to thyroid.
5. Diuretic	Increased diuresis.
6. Indole	Indoles in urine.
7. Inhibits glutamic acid decarboxylase	Deficiency in GABA, i.e. increased susceptibility to convulsions.
8. Oxidizes ascorbic acid	Deficiency of ascorbic acid, glutathione.
9. Interference in oxidative phosphorylation	Disturbances in glucose metabolism.
10. Intracellular	Alteration of rapidly growing cells.
11. Accumulation during day	Schizophrenia clinically worse in evening or after prolonged sleeplessness.
12. Insulinase inhibitor	Incompatibility of diabetes mellitus and schizophrenia.

toward histamine. Sackler, Sackler, Van Ophuijsen, Co Tui and Sackler (1951) and Sackler, Sackler, Sackler, La Burt, Van Ophuijsen and Co Tui (1951) found that schizophrenic patients could tolerate increased quantities of histamine. This was confirmed by Lucy (1954) who showed that the histamine tolerance increased with the chronicity of the illness. Weckowicz and Hall (1958) further found that the wheal produced by schizophrenic patients after intradermal injection of histamine came on more slowly than in normals. This simple test satisfactorily differentiated blind between a chronic group of schizophrenic patients and non schizophrenic subjects. Finally, Doust, Husdan and Salna (1956) found that a series of schizophrenic patients had 106 μg/liter histamine in their blood compared with 88 μg/liter for normals. This difference was significant and indicates again that schizophrenics can tolerate more histamine.

Since antihistaminics are useful in the treatment of allergies thought to be mediated by the presence of too much histamine, one would expect that if schizophrenics have more adrenochrome available than other people then they would be less likely to develop allergies. It has been observed by Lea (1955), Sackler, Sackler, Marti-Ibanez and Sackler (1956) as well as others that allergic states do seem to be rare among schizophrenic patients. Lea found one allergic condition in a carefully studied series of five hundred schizophrenics. There were twenty-two cases in five hundred head injury controls. This finding is most significant. That this is not simply a characteristic of those who become schizophrenic, but of schizophrenia itself, is suggested by the fact that they develop allergies when freed of schizophrenia. Funkenstein (1950) reported a small series of psychotic patients who had alternately asthma or psychosis (most frequently schizophrenia) but never both together. He also reviewed the literature showing the scarcity of allergies in psychotic patients. Rheumatoid arthritis is also very rare, Trevathan and Tatum (1954).

Using the adrenochrome hypothesis, it is possible to understand these apparently unrelated findings. During periods of mental health, there would be normal adrenochrome production and therefore a normal probability for allergy reactions. During schizophrenic episodes, the increased production of adrenochrome would

prevent the allergy. Since epinephrine is a standard treatment for asthma, it is possible that asthmatics who take large quantities of epinephrine may develop schizophrenic states, Hoffer (1957), as has occurred after inhalation of discolored epinephrine, Osmond and Hoffer (1958).

2. *Formation of Pigments*

Lea (1955) deduced that if there were indeed an over production of adrenochrome in schizophrenia, then more melanin-like pigments should be deposed in schizophrenia. Melanin pigments come from tyrosine either by way of dihydroxy phenylalanine (dopa) leading to dark brown or black pigments or by way of epinephrine and adrenochrome leading to yellow or yellow brown pig-

TABLE 27

RELATIONSHIP OF SCHIZOPHRENIA TO HAIR COLOR

	N	*Hair Color*				
		Blond	*Grey*	*Brown*	*Black*	*% Brown and Black*
		Age 10-29				
Schizophrenia	123	33	0	66	24	73
All Others	217	60	1	110	46	72
		Age 30-49				
Schizophernia	175	25	26	81	43	71
All Others	339	37	74	156	72	70
		Age 50 and over				
Schizophrenia						
Munroe Wing Sask. Hospital[1]	21	2	12	5	2	34
North Battleford Sask. Hospital[2]	100	8	24	56	12	68
Weyburn	100	1	51	32	16	48
Total	221	11	87	93	30	58
All Others[3]	307	6	246	32	23	15

[1]Mean Age 56.
[2]Mean Age 61.
[3]Mean Age 61.

ments. Langemann and Koelle (1958) reported that cells of the intestinal mucosa polymerize epinephrine and adrenochrome in vitro into these brownish pigments. The increase in adrenochrome in the body would therefore lead to an increase in brown coloration rather than of black pigmentation. Lea compared the eye and hair colors of 1008 schizophrenics against 5127 cases of injury. Eye color did not discriminate between these groups. But in the age group 15 to 19 years there were 241 dark haired subjects and 58 fair haired whereas in the injury group there were 1066 dark and 426 fair, i.e. 80 percent of the schizophrenics and 71 percent of the controls had dark hair (Chi Sq—over 10.58). There was no significant difference in the age group 20 to 24.

We have made a similar study of 1182 patients admitted to a psychiatric ward of a General Hospital over a three year period (Munroe Wing). The hair and eye color was recorded by the receiving psychiatric nurse, for a routine data admission sheet. The evaluation of hair color was subjective but probably sufficiently accurate. It corresponds to the data reported by Lea. The distribution of eye color was the same for both groups. The distribution of hair color for the two younger age groups was also similar. However, in the age group 50 and over, a greater proportion of schizophrenic patients retained their hair color, i.e. did not turn grey. Unfortunately there were very few schizophrenics in the group. We therefore examined the hair color of 200 schizophrenics in our mental hospitals, many of whom have grown old there. Out of this group 56 percent still had dark hair.

The lack of differentiation in the age groups reported here confirms Lea's finding. Too few patients in our group fall into this 15 to 19 age group. Combining the data gathered by Lea and reported here, it is apparent that schizophrenic patients develop darker hair more quickly and retain it longer than non schizophrenics. This is shown in Table 28. The 15 to 19 age data is from Lea.

This data may be explained on the basis of two assumptions: (1) that every person has a genetic potential for his maximum hair darkening, and (2) that the rate of pigment deposition is increased in people who become schizophrenic. Thus the differences would show up in the younger age group, would not be altered in the

TABLE 28

PERCENT OF GROUP HAVING DARK HAIR

	Age			
	15-19	*20-29*	*30-49*	*Over 49*
Schizophrenic	80	73	71	58
Others	71	72	70	15

middle age group and be maintained longer since the extra pigmentation would compensate the factors leading to greying. That is schizophrenia can be considered as a catalyst which hastens the rate of maximum color development but not the final end point. It also counteracts natural greying processes. The schizophrenic group over age 49 have proportionately more brown than black haired subjects (Chi Sq = 5.0). This suggests that the black haired subjects have suffered more depigmentation. Perhaps the black melanin pigments are removed whereas the brownish adrenochrome pigments which continue to be formed maintain the brown color.

The pronounced difference in greying of the non schizophrenic population is not due to the greater age. The mean age of the non schizophrenic group was only 5 years more than the mean age of the schizophrenic group. If all non schizophrenic patients older than 60 are excluded from the non schizophrenic group, the proportion grey remains about the same. It may be said that life in a mental hospital is less stressful for schizophrenics than it is for other types of mental disease. Those who suggest this must prove this is so. In our opinion there is no evidence for this concept. On the contrary our observations lead us to believe that modern mental hospitals are more stressful on their patients. Furthermore, there is no clear association between stress (whatever that is) and rate of greying.

Pigmentation in skin has not been studied as thoroughly. Harris (1942) described a schizophrenic-like psychosis associated with generalized brownish yellow pigmentation (adrenochrome

pigments) of skin, much deeper in the areola and nipples which were nearly black. We have observed many chronic patients whose skin was brown as if they had been tanned by sun but had not been in the sun for months.

Internal pigmentation of brain may be similarly related to epinephrine metabolism. Fellman (1958) observed argentophillic granules in the substantia nigra not unlike those observed in the adrenal medulla and other chromaffin sites. He suggested the pigments in substantia nigra may come from oxidative polymerization of epinephrine. They would of necessity have to go through some quinone intermediate.

3. Antithyroid

Quinones are antagonistic to thyroxin. Adrenochrome is a quinone. Thus the presence of more adrenochrome might account for the increased tolerance of schizophrenic patients for thyroid, Hoskins (1946), Danziger and Kindwall (1954), Danziger (1958). Perhaps it may be related to the periodicity of thyroid function in periodic catatonia.

4. Diuresis

Hoagland *et al.* (1955) and others have reported that schizophrenics excrete more water per day than other patients. We have observed the same, Hoffer and Osmond (1958). Steven, Mojka and Humoiler (1959) showed that when schizophrenics were given one liter of water they excreted more than other patients. Thus increased consumption of liquid as well as diuresic appear to be factors. Adrenochrome is diuretic which may account for this increased diuresis. Groenendijk (1959) has recently reported one catatonic schizophrenic who had three relapses following a series of ECT. About three days before each relapse before there were any clinical changes there was a marked increase in excretion of urine and a marked decrease in weight. When he was finally cured and remained well, his excretion of urine and his weight remained stable.

5. Indole Excretion

The source of indoles in mammalian urine is not yet well known. Adrenochrome leads to two types of indoles: (1) dihydroxy

and (2) trihydroxy indoles. These indoles have been found in urine and can come from either dopa through dopachrome or from epinephrine via adrenochrome. Many biochemical abnormalities have been reported for schizophrenia. Of these, an increase in the quantity and difference in quality in indoles is one of the most constant.

6. Effect on GABA

Adrenochrome by inhibiting decarboxylase will decrease the formation of gamma amino butyric acid (GABA). This may be the major component of inhibitor factor of the brain. There is apparently an inverse relationship between the concentration of GABA and the convulsive threshold. Thus the decrease in the convulsive threshold and the non specific EEG abnormalities reported by many authors for schizophrenia may be due to increased quantities of adrenochrome in the brain.

7. Oxidation of Ascorbic Acid

According to Angel, Leach, Martens, Cohen and Heath (1957) schizophrenics have less ascorbic acid in their blood than do other patients. This is ascribed to a low dietary intake. Some of the deficiency may be due to an increased consumption and need for ascorbic acid. While it is interesting that giving schizophrenic patients large quantities of ascorbic acid corrects these oxidative abnormalities in blood this does not alter the fact that the initial values are low. We still need to know whether the blood oxidation of schizophrenics, as compared with others, remains normal after ascorbic acid has been given. Perhaps for the same reason glutathione also appears to be decreased in the red cells of schizophrenics. With low levels of glutathione one would expect increased pigmentation. Kohn (1955) found that glutathione combines with some product of tyrosine before it forms dopachrome to yield a compound which absorbs at 375 mμ.

8. Phosphorylation

Adrenochrome by interfering in phosphorylation could readily produce those alterations that have been found in schizophrenic tissues.

Boszormenyi-Nagy and Gerty (1955) found that with normal

erythrocytes, insulin pretreatment decreases the formation of adenosine triphosphate by hemolyzed cells. They suggest this may be due to an increased rate of consumption of high energy phosphate. Insulin did not interfere with this process in the red cells of schizophrenics, which appear to be resistant to insulin in this regard. They further suggested the insulin disrupted some energy transfer in the citric acid cycle.

Streifler and Kornblueth (1958) used rat retina as a biological test for the presence of toxins in serum by measuring the consumption of oxygen. They found that serum from schizophrenic patients decreased the consumption of glucose by rat retina. The decrease was less than that produced by serum from patients suffering from organic nervous system disease.

Rieder (1954) reported schizophrenic serum interfered with the respiration of yeast. Walaas, Lingjaerde, Laken and Hundevadt (1954) found rat diaphragm utilized less glucose in the presence of schizophrenic serum. Bullough (1952) showed that adrenochrome inhibited mitosis in mouse epidermis both in vitro and in vivo. He suggested that the inhibition of mitosis in mice observed during stress was due to the endogenous conversion of epinephrine into adrenochrome.

Henneman, Altschule and Goncz (1955) found disturbances in carbohydrate metabolism of psychotic patients. Most of these patients were probably schizophrenic.

This evidence suggests that cell multiplication ought to be inhibited, at least in severe illnesses. One would expect that more rapidly growing tissues would be more noticeably inhibited. We suggest that the growth rate of the following tissues would be reduced: (a) hair, (b) nails, (c) epidermis, (d) fibrous tissue, (e) spermatogenesis, (f) erythropoeisis. There is evidence which suggests such an interference with growth. Brodny (1955) found a high incidence of spermatic abnormalities in the semen of schizophrenics. He suggested that schizophrenics produced an X substance which both decreased spermatogenesis and encouraged abnormal spermatozoa.

If antimitosis is a factor, it should be more pathological in children before puberty. It follows from this that any general interference with growth would only be observed in people whose

growth was not completed. As with diabetes mellitus and with tuberculosis, the order in which the event occurs is vital. Those who look for an effect of schizophrenia on body build will therefore find it in those patients where the illness has first expressed itself at an age before growth is complete. Two lines of evidence support this proposition: (1) schizophrenic children in general according to the work of Bender are slightly more deformed or asymmetrical than normal children and (2) schizophrenics in whom the illness has been present a long time are more ectomorphic than those in whom the illness came on late. Rees (1957) reviewed the evidence which shows a relationship between physical type and this illness. In general schizophrenics are smaller and have shorter antero posterior diameters. There is still much controversy about this. Perhaps if the data were re-examined and the patients classified by the age of onset this controversy might be resolved. Rees states, "the work of (various authors) suggests that schizophrenics with a leptomorphic body build tend to have an early age of onset, show a greater degree of withdrawal, apathy and scattered thinking, whereas schizophrenics of eurymorphic body build tend to have a later age of onset and to show a better preservation of personality and better affective relations with the environment." This could be rewritten "suggests that schizophrenics with an early age of onset tend to have a leptomorphic body build, etc." Wittman (1948) compared a group of shut-in personality schizophrenics ill since childhood with an early and insidious onset against a group where onset was acute in response to some situational stress. The first group was largely ectomorphic. The second group was less ectomorphic with more mesomorphy. There was a high association between schizophrenia and tuberculosis, according to Appel, Myers and Morris (1959). The mortality from tuberculosis among schizophrenics and their relatives is higher than average. A main variable for the control of pulmonary tuberculosis is the ability to enclose a lesion with fibrous tissue. If the rate of fibrosis (growth or mitosis) is defective one would expect some defect in dealing with tuberculosis. This means that in the presence of schizophrenia tuberculosis is more malignant, i.e. more schizophrenics will have more severe tuberculosis. However, the converse need not apply. The presence of tuberculosis does not imply adrenochrome is present in excess.

One must not disregard the order in which two diseases develop when they coexist. Bleuler and Zurgilgen (1949) found no increase in prevalence of schizophrenia among tuberculotic patients and therefore concluded the increased incidence of tuberculosis was due to greater exposure to infection only. They assumed that a coexistence should be present in both illnesses. Ordered events are common in medicine and in life. Thus all pregnancies occur in women but not all women are pregnant. Similarly schizophrenics are unusually susceptible to tuberculosis but tuberculotics are not unusually susceptible to schizophrenia. This is easily accounted for by the adrenochrome hypothesis.

9. Relation to Iron and Copper

There may be an important relationship between adrenochrome, adrenolutin, copper, iron and hemoglobin.

Ovshinsky (1957) suggested that epinephrine acting as an iron binding substance can remove iron from ferritin stored in liver and spleen and in so doing is oxidized to adrenochrome.

Since adrenochrome is not a vaso constrictor, epinephrine would be continuously removed and replaced resulting in a self stimulating cycle which might account for the very long sustained nature of chronic schizophrenia. In a small series of schizophrenic patients, Ovshinsky (1958) reported a sixteen percent decrease in transferrin levels compared to normals. This would fit in with the above hypothesis because if iron was being bound by epinephrine, there would be less available for the formation of transferrin.

Lehmann and Kral (1951) and Kral and Lehman (1952) found decreased levels of iron in the cerebrospinal fluid of acute schizophrenic patients and higher values in chronic schizophrenics. Perhaps the same mechanism is at work in the cerebrospinal fluid of acute schizophrenics.

This relationship of epinephrine to iron metabolism may also involve erythrocyte function. Thus Scheid (1938) found changes in hemoglobin metabolism during febrile episodes in schizophrenic psychoses. There was an increased excretion of urobilinogen in the urine and an increased destruction of erythrocytes. Scheid and Baumer (1937) noted that some schizophrenic-like psychoses

even seemed to be related to febrile episodes. These patients were usually catatonic. Before the febrile episode, there was increased hemolysis and hemoglobin was low. Hemoglobin later rose above normal and finally decreased. They suggested the increased hemolysis led to the intoxication.

There is other evidence that the red cells of schizophrenics are peculiar. Ansley, Sheldon, Tenney and Elderkin (1957) found that they were more variable in diameter compared to normal erythrocytes. The standard deviation of diameter distribution was 1.023 for schizophrenics and 0.546 for others. There was little overlap. Hoffer (1958) found that schizophrenic erythrocytes were more fragile to hypotonic solutions of saline and appeared to be more readily ruptured by mechanical activity. In addition, the fresh hemoglobin was optically more dense per unit of iron between 410 and 420 mμ on the DU Spectrophotometer. This might be due to the presence of substances in the red cells of schizophrenics which absorb light at this wave length. Hoffer (1957) also reported that the addition of adrenochrome or epinephrine to plasma increased the optical density at this absorption frequency.

Bain, Gaunt and Suffolk (1937) reported that erythrocytes hold epinephrine in equilibrium with serum. The quantity of epinephrine held within or on the cells depended upon the equilibrium concentration in the serum as it does for adsorption reactions. The epinephrine bound by erythrocytes can be partially recovered by laking separated cells or the equilibrium mixture or in less amounts by placing separated cells in fresh plasma, serum or Lockes solution. About twenty percent of the epinephrine was not recovered which the authors suggest was either due to destruction or to irreversible adsorption on some constituent of the red cells.

Boszormenyi-Nagy and Gerty's observation that schizophrenic red cells have unusual metabolism may be accounted for by their relationship to epinephrine and adrenochrome. Thus (1) epinephrine and adrenochrome are bound in the cell, (2) adrenochrome interferes in the citric acid cycle of carbohydrate metabolism and uncouples phosphorylation. This would also be an explanation for the increased optical density of hemoglobin at 410 mμ per mg. iron,

the increased fragility of hypotonic saline and the increased variability of cell size.

Sjovall (1947) reported that mice which had been injected with serum from schizophrenics showed marked hemoglobinuria one hour after the injection. He did not find this with serum from normal controls.

It is not likely serotonin is directly involved in the production of schizophrenia. However recent information suggests that hemoglobin may unite serotonin and adrenochrome. It would not be surprising if serotonin played some subsidiary role. Ling and Blum (1958) reported that when serotonin was incubated with whole blood, washed red cells, hemolyzed red cells or hemoglobin there was a rapid loss of fluorescence. At the same time a pink substance developed which was a dihydro indole. Carbon monoxide and ascorbic acid prevented this reaction but glutathione did not. Rodnight (1958) also found that hemoglobin destroyed serotonin. This was inhibited by carbon monoxide saturation. He believed this oxidation was due to oxy hemoglobin.

Thus serotonin might be transformed into adrenochrome-like compounds. Porter, Titus, Sanders and Smith (1957) suggested ceruloplasmin could catalyze the transformation of serotonin to paraquinone imines which on further oxidation would lead to adrenochrome like compounds. Finally Martin, Eriksen and Bendett (1958) reported serum oxidized serotonin to colored compounds. They suggested the enzyme was ceruloplasmin as the reaction was inhibited 80 percent by 0.003 Molar iproniazid.

10. Diurnal Rhythm

The rate of production of epinephrine is increased on awakening in the morning and continues thus until the subject once more sleeps. Thus the products of epinephrine metabolism must come after the increase in epinephrine. In the case of schizophrenia adrenochrome, adrenolutin should build up during the day. The most lucid or normal period of the day should be the morning. This appears to be the case for schizophrenia. We have observed many schizophrenic patients who are relatively well in the morning and very disturbed in the evening. Naumova (1939)

reported that of 63 catatonic patients who were questioned immediately after awakening from a nights sleep, 25 responded normally. This lucid period lasted for less than two hours after awakening.

While this type of rhythm is not uncommon in organic illnesses, it is in striking contrast to many depressed patients who usually feel much better in the evening. This again can be accounted for by using our hypothesis because anti tension substances made from epinephrine via adrenochrome are likely to accumulate during the day when the sick person is erect and moving about.

Lack of sleep should and does aggravate schizophrenia. Indeed sleep deprivation alone can produce schizophrenic-like conditions, Tyler (1955) and markedly sensitizes normal volunteers to LSD, Bliss, Clark and West (1959).

11. Relationship of Schizophrenia to Diabetes Mellitus

Schizophrenia and diabetes mellitus seem to be relatively incompatible one with the other. Bellak in his first review referred to published accounts of this relationship. Between 1930 and 1939 the death rate from diabetes in schizophrenia was 11.9 per 100,000 compared to the death rate of other patients by diabetes of 89.8 in New York general hospitals. Many others have noted this unusual occurrence of diabetes in mental hospitals. Both Saskatchewan Hospitals (population of 3300) have less than five diabetics. Dynamic psychiatrists have explained this by stating that one defence mechanism removes the need for a second. But is this any more enlightening than merely noting that they are seen together infrequently?

Insulinase, the enzyme which destroys insulin, is believed to play a part in the genesis of diabetes. Substances which inhibit insulinase decrease demand on the pancreas and help control some mild diabetes. With this in mind, we sent Dr. B. Witkop at the National Institutes of Health some adrenolutin in mid 1956. This was our best preparation but not as good as crystalline adrenolutin. Dr. M. Vaughan, National Heart Institute, found adrenolutin at a concentration of 3×10^{-4} Molar caused 40 percent inhibition of insulinase. It was ten times stronger than 5 hydroxy indole. This inhibition is not far from those oral insulinase inhibitors used

clinically. If then adrenolutin plays some part in schizophrenia, it would act as an anti diabetic substance, and one would expect that once schizophrenia is established diabetes should be seen only infrequently if at all. In addition, mild diabetes should become less troublesome if the patient should become schizophrenic. Well established diabetes can be followed by schizophrenia. Once again, then, it is important when establishing coincidence between two conditions, one of which is schizophrenia, to know which came first. Where the two are associated, we would predict that the diabetes was present first. Naturally diabetes not due to primary insufficiency of insulin must be excluded from this prediction.

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Chapter 14

THE WAY AHEAD

Almost a decade ago Gillis (1951) wrote unhopefully, "The time worn search for a toxic factor in schizophrenia has been resumed." M. Bleuler ended on the melancholy note which we have quoted earlier, "It is possible that as a consequence of these negative results the search for a specific somatic basis for schizophrenia will be given up for a long time to come if not permanently." Prediction is always risky, but we think that the work we have discussed here shows that Bleuler was too pessimistic, furthermore we are now several steps closer to "a definable, specific, pathological somatic schizophrenia." If this is so we should perhaps look at the likely results of this new way of approaching schizophrenia and seek hints for the direction in which the hunt for epinephrine metabolites will probably take us. For there seems enough evidence to suggest there are many unusual, powerful and very interesting substances awaiting our attention.

So far we have stuck mainly to chemistry and have dealt only incidentally with clinical matters—the title of this series shows why. And indeed we are not sorry to make a small attempt to redress the balance a little in literature heavily biased in favor of the descriptive, the psychopathological, the social and the anecdotal aspects of psychiatry. Not that we think these aspects unimportant, for the pharmacologist and the chemist have seldom been of much use to medicine until their attention has been drawn to the nature of the clinical illness. It is indeed true that clinicians are often blind, prejudiced, habit ridden, capricious and unscientific, but they are also very well acquainted with patients' suffering. Fleming (Maurois, 1959) who was both laboratory worker and clinician, although fully aware of the extraordinary potentialities of penicillin, waited for a decade before chemists and pharmacologists took his work seriously. Clinicians were no more stubborn than the scientists.

In recent years, psychiatrists have written rich, though rather muddled and disorganized accounts of the phenomenology of schizophrenia, as the work of Binswanger, Van der Berg (1955) and Sechehaye (1956) shows. The social aspects of schizophrenia has had close attention from psychiatrists, sociologists and anthropologists. One does not doubt the value of these efforts, but they have done little more than underline Kraepelin's observation that the gravely ill schizophrenic looks much the same whether he is seen in Manhattan, Manchester, Munich or Malaya. It should surely have been possible by now to coordinate these social derangements with the psychological changes which patients describe, and to relate both to chemical changes in the body which might disorganize the workings of the mind and brain.

It is curious that even less has been done for illnesses characterized by anxiety and mood swing, which are rather easier to think about as models, for they are not so protean, bizarre and insidious as schizophrenia. Possibly it is the, to us, highly dubious belief that psychopathology of a dynamic sort is analogous to physical pathology that has played some part at least in making our present muddle.

With schizophrenia, every new sort of specialist who comes to it goes away with some interesting and illuminating discovery. The books which pour from the presses show that none leaves empty handed, but so small has the benefit been to the myriad sick that in 1950 E. Bleuler's great text book still seemed extremely up to date not only in its brilliant descriptions but in its therapeutic suggestions—even though it had been published forty years before. In few other branches of medicine has time stood still so unenviably.

It is only recently that attempts have been made by Weckowicz and Sommer (1960), Rausch (1956), Crooke, (1957) and others to reassess the nature of the patients' experiences and measure some of these in a systematic manner. Nearly sixty years ago Kraepelin (1919) stated that there were no perceptual changes in schizophrenia and those who copied this statement from textbook to textbook omitted to say what Kraepelin meant by this remark. Kraepelin subscribed to the German school of psychology and

was a pupil of Wundt who followed Hebart in distinguishing between perception and apperception. William James noted in his great Principles of Psychology (1950) as long ago as 1902 that this distinction was valueless, but for those who held that it meant something, perception was apparently the raw data which reached end organ and was processed in the brain by an "apperceiving" mass of ideas already in the brain. James objected that one could never distinguish satisfactorily between the end organ response and the "apperceiving" mass and that one should therefore not pretend to do so. Kraepelin and the German school did not agree. According to their view schizophrenics had no disturbances of perception but did have disturbances in apperception. Apparently they were either not interested enough or able to measure these apperceptive changes.

Any discussion with schizophrenic people about their illness, especially if it is of recent onset, often evokes the quite spontaneous remark that the world and the people in it seem to have changed. One of the very few attempts to study schizophrenics own published writings (collectively), Sommer and Osmond (1959), supports these clinical impressions. Books written during the last seventy years or so with hardly any evidence of cross-reference, are extremely similar. It seems at least possible that the peculiar behavior of schizophrenic people and their consequent social difficulties arise in part at least from misperceptions sometimes quite gross, but usually subtle enough to be undetected except in their effects. Weckowicz and Sommer (1960) believe that the main and possibly central difficulty lies in a failure to maintain constancy of perception which leaves the schizophrenic more or less at the mercy of his environment. Such a person afflicted in this way is likely to be too distressed to think clearly. Our capacity for social relationships depends upon a rapid and accurate recognition not only of the signals that people send us but of the people themselves. For, on reflection, it is obvious that unless we can be sure about the signaller we cannot pay undivided attention to what he is signalling. Minor impairments of these two capacities are enough to set in motion an ever widening series of social disasters, each of which will make the sick person and his relatives

and friends more anxious, puzzled, afraid, hostile and probably guilty too. In such circumstances it is hardly surprising that social communication quickly disintegrates. There are now a variety of psychotomimetic agents available which let those who are not completely confident that their intuitive and empathic gifts give them access to the world of the mad, go and see for themselves. We are not implying that these experiences are or need be identical with schizophrenia, only that they are proving a useful education and suggest that the mentally ill, far from exaggerating their plight, are unusually stoical, as indeed are most people when completely overwhelmed.

Psychopharmacology seems at last to be about to take the place which Louis Lewin predicted for it so many years ago and which is hinted in Claude Bernard's words: "Les poisons constituent un moyen d'analyse des propriétés nerveuses des sortes de scalpels physiologiques beaucoup plus délicats et plus subtils que les scalpels ordinaries." We believe that psychotomimetics and psychedelics are, to deploy Bernard's apt metaphor "des sortes de scalpels psychiques"—valuable instruments which have so far seldom found craftsmen skilled enough to use them properly. During the last century psychiatry, once a leading specialty in medicine, has declined into dogmatism, schism and empiricism, smothering in its own profuse and often redundant verbiage. Perhaps it is now waking again and will take its place once more in medical science.

Some immediate results are already being seen in the treatment of schizophrenia. For although the phenothiazines and similar compounds are empiricals about whose mode of action no one is clear, they have benefitted and are benefitting many sick people. Further, their existence has been a cause for hope and greater exertion. But they would be of no more importance than the barbiturates, bromides and chloral without the developing hypotheses which we have discussed earlier. If these succeed then within the foreseeable future schizophrenia will be definable in biological, psychological and social terms. The consequences of such a biological definition will be far reaching. Presently most of our patients and their relatives suffer at least as much from our vague, indefinite and often secretive diagnosis and our uncertain and obscure

instructions and prognosis as they do from the unpleasantness of the illness itself. Many patients would be greatly helped by being told unequivocally and in a way which they could understand, "You have this sort of illness. Here is the laboratory report and this is what it means. You must do this." Such information alone would be very beneficial both to our patients and to us as doctors, for it is part of the medical role to give unequivocal advice of this sort. A doctor who feels unable to advise his patients is not a doctor at all, and at times psychiatrists have come carelessly near to abandoning their medical authority. But a definable, specific, pathological, somatic schizophrenia would have other valuable social repercussions. At present the mentally ill, particularly schizophrenics, are third class citizens medically. Largely, we suspect, because neither doctors nor the public are absolutely sure that they are sick. For in our society part of the definition of sickness implies that the doctor knows what is wrong and that it is something over which the sick person has less control than the socially acknowledged expert; here the psychiatrist. Since the social role of the mentally ill is not clear, society's responsibility towards them is equally uncertain. At the present time it would be far harder to justify the almost universally shabby care of mentally ill people if they could be shown to be the victims of a specific and recognisable sort of metabolic illness. Consciences are more easily pricked by clear cut appeals of this sort.

Exact and therefore earlier diagnosis leads naturally to protection for susceptible people. Kallman (1953) and Slater (1953) have shown that inheritance plays a part. Our work with nicotinic acid therapy strongly suggests that early treatment is effective. With an accurate diagnostic method an inherited factor need not necessarily be cause for gloom. Once we can be fairly certain that schizophrenia is brought about by a toxic substance or substances which affect the brain a true "animal schizophrenia" can be developed and rational treatments devised in the laboratory.

Schizophrenia must, at present, seem very important, yet it is not the most widespread of psychiatric ailments although one of the most serious. The most widespread illnesses are those in which mood is disordered and inappropriate anxiety, depression or far

less often, elation develops. These may have secondary but extremely serious repercussions in addictions such as those to alcohol and various drugs. There are now strong hints that answers to at least some of these matters lie in the study of epinephrine derivatives which have been neglected so far. Our own cursory studies have shown that the dihydroxyindoles appear to play some part in reducing the tension associated with the presence of epinephrine and the anxiety which goes with it. There are doubtless several families of these substances with specific psychopharmacological actions awaiting investigations. While the devotees of psychosomatic medicine have often been rash and dogmatic in their statements, and while their interpretations have been more bizarre than useful, for centuries physicians who have studied these illnesses have observed that in some way or other anxiety and certain bodily upsets are very closely linked. It is quite unnecessary at present to insist upon rigidly schematized psychopathologies which only mislead the ignorant. Mens sana in corpore sano was an excellent slogan but surely we should be able to discuss it with greater precision now? Our psychosomatic economy seems to depend upon the delicate interplay of at least three great systems. A neuronal system for rapid response; an epinephrine-acetylcholine system for intermediate responses; and the ductless glands for long term changes. It may be that we shall soon be in a position to understand this relationship between short term and long term hormones more clearly. When we do we can predict that we shall have a clearer understanding of the way in which mood change affects and is affected by physical illness.

Man is a gregarious creature that preys upon his own kind. Perhaps he is not yet fully domesticated. As Lorenz (1952) observed, he is far more ferocious to his own kind than many canines. In the headlong rush involving, biologically speaking, very few generations during which he has been catapulted from being a marginal survivor to a dominant species, he has not yet learned to recognize and understand many of his own inadequacies and shortcomings. These may indeed be only the remnants of qualities which a few generations ago would have helped him to survive. We cannot now depend upon natural selection because our own

actions have destroyed the conditions in which it operates. It does not seem likely that we can expect the science of genetics to help us much for a long time to come, at least in this respect. It may be that psychopharmacology will provide us with enough knowledge about the functioning of the body and brain to allow us to obtain more frequently that most valuable gift, a calm and tranquil mind. For it is only such a mind unhampered by terrors from the past and undismayed by apprehensions for the future, which can think both kindly enough and detachedly enough to act for the best with despatch and compassion. In the past men so endowed have been rare and their gifts have not always lasted for their lifetime. We believe that psychopharmacology can help to release men and women from those storms of fear and panic which have so often made us a danger to other members of our species. The beast of prey who lurks inside each of us derives his energy and terrified destructiveness from ill directed epinephrine metabolism. In the section on psychedelics we noted that substances which derive from these same epinephrine metabolites and others which have a similar action, can, when conditions are suitable, produce unhabitual perception. The chief danger that faces a calm and tranquil mankind is stagnation. Psychopharmacology may help us to learn how to think clearly however distracting personal and other calls may be, without however preventing us from indulging, when we need it, in the boldest imaginings. Such capacities developed in an increasing number of our species would be as effective as a beneficial mutation, and we think, far more easily achieved. We dedicate this book to those who can read it not as a guide, but as a challenge.

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INDEX

A

Abood, L. G., 101, 105, 110, 126, 135, 148, 173, 183, 200, 220, 239, 245
Abood's compounds
  properties of, 200
  structure of, 200
Abramson, H. A., 72, 138, 139, 143, 145, 148, 173, 183
Acetylcholine
  action of LSD on, 135
  effect of Deaner on, 123
  effect on brain function, 122
  enzymes of, 123
  factors regarding concentration of, 123
  hydrolyzation of, 123
  interference with brain activity of, 123
  main activities of, 124
  psychotomimetics which interfere with function of, 122-126
  relation to known psychotomimetics, 199
  result of too little on brain function, 122-123
  results of too much on brain function, 122
  role of in body, 122
Acetylcholine antagonists
  action of, 124
  atropine, *See* Atropine
  benactyzine, *See* Benactyzine
  piperidyl benzilates, *See* Piperidyl benzilates
Acetylcholine esterase inhibitors, 124
  classes of compounds, 124
  types of, 124
Acetylcholine-like substances, 84-86
  arecoline, *See* Arecoline
  Deaner, *See* Deaner
Aconitum alkaloids, effect on function of central nervous system, 119
Adrenal glands, study of rate of secretion from, 163-164
Adrenalectomy, effect on blood pressure and pressor amines, 35
Adrenaline, reduction in production of in treatment of schizophrenia, 218-219
Adrenergic compounds, 116
  confusion with paranoid schizophrenia, 116
  effect on animals, 116
  effect on man, 116
  production of psychoses by, 116
Adrenochrome, 39-42, 147-183, *See also* Adrenoxyl
  a natural metabolite of spinephrine, 159-169
  amount in urine in psychiatric patients, 70
  and allergies, 153-154
  and amino acids, 151
  and brain inhibitor factor, 150-151
  and diuresis, 158-159
  and GABA, 232
  and histamine tolerance, 225, 227-228
  and hypothermia and LSD, 157-158
  and inhibition of histamine, 153-154
  and iron metabolism, 151
  and melanin pigmentation, 152
  and mental changes with high pressures of oxygen, 153
  and oxygen toxicity, 152-153
  and phosphorylation and schizophrenia, 232-235
  and thyroid tolerance, 231
  animal response to, 170-173
    of cats, 170-172
    of fish, 173
    of monkeys, 172
    of pigeons, 172-173
    of rats, 173
  as a diuretic, 231

as schizogenic substances, 204
assay method, 159-160
  mean plasma value, 160
  technique of, 159-160
assay of, 207
biochemical properties, 149-154
  adrenochrome and allergies, 153-154
  adrenochrome and brain inhibitor factor, 150-151
  adrenochrome and amino acids, 151
  adrenochrome and iron metabolism, 151
  adrenochrome and melanin pigmentation, 152
  adrenochrome and oxygen toxicity, 152-153
  carbohydrate metabolism, 149-150
  in schizophrenia, 226
carbohydrate metabolism, 149-150
change of to adrenolutin, 80-81
changes in cerebral function produced by, 156
changes in electroencephalogram of animals produced by, 155-156
changes induced in patient by, 40-41
changes with epinephrine oxidation to, 152
changes with reducing agents, 149
ceruloplasmin and hypothesis of, 221
chemical properties of, 149
conversion of by reducing materials, 81
conversion of to adrenolutin, 210-211
decolorization by penicillamine of, 137
decolorization with ascorbic acid, 136-137
decomposition of, 149
decreasing production of in treatment of schizophrenia, 219-220
description of, 149
destroying of in treatment of schizophrenia, 223-225
early studies with on epileptics, 39-40
effect of administering under tongue, 174
effect of iproniazid on levels of, 81
effect of on anxiety, 40-41
effect of on electroencephalogram, 154-157
effect of on volume of urine, 158
first preparation of, 147
formation of from epinephrine, 167
hypothermia due to, 157-158
hypothesis of schizophrenia, 204
inhalant, 176-177
  case study, 176-177
instability of preparations, 147-148
intravenous, 177-179
  case history, 178-179
isolation of, 147
leading to indoles, 231-232
levels in plasma and cerebrospinal fluid, 208
metabolism and tension, 46-48
metabolism of, 168-169
method of measurement, 46, 208-209
neurophysiological properties, 154-159
oxidation of epinephrine to, 166-167
physiological correlates of from hypothesis of, 225-239
physiological properties in schizophrenia, 226
plasma adrenochrome values during tolerance test, 41
potentiation of experience, 179-183
  case histories, 180-183
presence in the body, 165-166
producing psychological changes, 170
production of stable, 148
properties of, 148-159, 200, 201
  biochemical, 149-154
  chemical, 149
  neurophysiological, 154-159
psychological activity of in humans, 173-183
psychological properties of, 169-183
reaction to, 63
relation to known psychotomimetics, 199
relationship of activity to dosage, 156-157
relative in vitro conversion of to adrenolutin, 211
restoration of levels of, 139-140

results of adrenochrome tolerance test, 41-42
similarity of schizophrenia and experience induced by, 212
structure of, 200
studies of on cats and dogs, 154-155
study of, 147-148
study of on epileptics, 154
sublingual, 174-176
case study, 175-176
substantiation of hypothesis of schizophrenia, 204
synthesis of, 147-148
tolerance of some diagnostic groups to, 47, 209, 210
results of, 209-210
tolerance test, 46-47
use of nicotinic acid to reverse effects of, 153
Adrenochrome hypothesis, 192-197
and uniting of teraxein hypotheses, 197
Adrenochrome model, and schizophrenia, 203-239
Adrenolutin, 42-46, 147-183
and ceruloplasmin, 222-223
as schizogenic substances, 204
conversion of adrenochrome to, 80-81, 210-211
discovery of, 166
excerpts from accounts of patients who took, 42-46
formation of from epinephrine, 167
neutralizing of in treatment of schizophrenia, 220-223
properties of, 148-159
biochemical, 149-154
chemical, 149
neurophysiological, 154-159
psychological properties of, 169-183
reaction to, 63
relative in vitro conversion of adrenochrome to, 211
results of use of, 45
Adrenoxyl
euphorient activity of, 49
reasons for use of, 48-49
use of, 48
use of as hemostatic substance, 48
Agnew, J. N., 214, 239
Akerfeldt, S., 194, 197, 220, 239
Alberty, J., 154, 183
Alcohol, use to decrease epinephrine production, 92
Alcoholics
and LSD, 47
changes induced by adrenochrome, 41
relationship of adrenochrome levels to LSD intensity, 48
Allergies, in schizophrenic patients, 227-228
Altschule, M. D., 33, 39, 70, 71, 72, 74, 162, 190, 195, 197, 198, 220, 233, 239, 242
Ames, 108
Andel, H., 85, 92
Amines
relationship between sympathetic nervous system, anxiety, mood and, 63-72
synthesis of, 64
Amphetamine
action of, 20
use for anergic depression, 76
Anderson, E. G., 78, 92
Andrade, E. N. daC., 6, 15
Anergic depression
acetylcholine-like substances, 84-86
arecoline, 84-85, *See also* Arecoline
Deaner, 85-86, *See also* Deaner
inhibitors of acetylcholine esterase, 86
use of epinephrine-like compounds for, 76-77
Benzoquinolizines, 77
Piperidines, 76
sympathomimetic amines, 76
Tofranil, 76
use of substances which inhibit enzymes which act on epinephrine, 77-84
cocaine, 82-84, *See also* Cocaine
marsilid, 77-82, *See also* Marsilid
use of sympathomimetic amines, 76
Angel, C., 205, 207, 219, 232, 239

Anhalonidine
effect of, 118
production of hallucinations by, 118
structure of, 117
Ansley, H. R., 236, 239
Anxiety
adsorption equilibrium of epinephrine in, 35
and biochemical process, 30
as response to variety of events, 29
biochemical types of, 64-72
changes induced by adrenochrome, 41
chemical treatment of, 75-92
effect of in emergency, 38-39
epinephrine as mediator of, 31-32
evoking, 30
groups of substances used for treatment of, 199
produced by epinephrine, 32
produced by sympathomimetic amines, 33-34
relationship between amine hormones, sympathetic nervous system and, 63-72
relationship of to epinephrine, 90
relationship of to hydroxy tyramine, 90
relationship of to norepinephrine, 90
relationship of to ratio of epinephrine, 64
relationship of to serotonin, 90
results of adrenochrome tolerance test, 47
use of nicotinic acid in treatment of, 68
Anxiety depression
indoles, 86-91
substances decreasing epinephrine production, 92
substances reducing reactivity of receptors to epinephrine, 91
Aporphines, effect of function of central nervous system, 119
Appel, K. E., 234, 239
Arana, 155
Arecoline
effect of in humans, 84
effect of on rats, 85
effect of on schizophrenic patients, 85
in Betel, 85
use in treatment of anergic depression, 84-85
Armstrong, M. D., 34, 74, 163, 164, 165, 184, 190
Ascorbic acid
decolorization of adrenochrome with, 136, 317
effect of decreased levels of, 219-220
effect of LSD on, 87
effect of LSD on plasma adrenochrome levels with, 136
effect of LSD on plasma adrenochrome levels without, 136
in serum during infections, 87
oxidation of in schizophrenics, 232
properties of, 219
relationship to mood, 86-87
source of in body, 87
use in treatment of schizophrenia, 219-220
use to protect epinephrine, 90-91
Ashby, R., 113, 119
Atropine
action of, 125
as a psychotomimetic potentiator, 215
description of psychoses, 125
effect of on catatonia, 85
psychosis due to, 125
source of, 125
Austin, J., 147, 190
Autonomic activity, relation of to psychotomimetic activity, 200
Axelrod, J., 34, 72, 80, 92, 94, 163, 184
Ayd, F. J., 68, 72, 88, 89, 92, 125, 126

B

Bachtold, H. P., 118, 120
Bacon, 8
Bacq, Z. M., 148, 166, 184
Bailey, Percival, 18, 26
Bain, J. A., 113, 119
Bain, W. A., 35, 72, 236, 239
Baker, J. P., 125, 126
Ballan, J., 158, 186
Banerjee, S., 87, 93
Baron, M. O., 138, 143

Barsel, N., 148, 190
Barsky, J., 77, 96
Baruk, Henry, 23, 26, 173, 184, 205, 240
Bateman, J. F., 27
Baumer, L., 235, 246
Bazemore, A., 150, 184
Bean, J. W., 153, 184
Bearn, A. G., 225, 243
Beckett, D. G. S., 235, 241
Bein, H. J., 38, 73
Beisaw, N. E., 217, 240
Bellac, L., 74
Bellak, L., 238, 239
Belleville, R. E., 138, 145
Benacerraf, B., 154, 186
Benactyzine
  study of, 125-126
  use of, 125
Bender, 234
Benditt, E. P., 237, 244
Benjamin, J. D., 195, 197
Benzedrine
  as a psychotomimetic potentiator, 215
  structure of, 117
Benzoquinolizines
  action of on brain serotonin levels, 79
  as non hypnotic sedative, 118
  effect on function of central nervous system, 119
  effect on man, 77
  use for anergic depressions, 77
Bergen, J. R., 205, 217, 240
Berger, A., 220, 246
Berger, H., 22, 26
Berger, J., 173, 184, 205, 240
Berkeley, A., 158, 186
Bernard, Claude, 5, 7, 10, 12, 13, 15, 252, 255
Bertler, A., 214, 241
Besendorf, H., 79, 95, 118, 120
Betel
  active ingredient of, 85
  use as an euphorient, 85
Beyer, K. H., 91, 92, 219, 240
Bickford, R. G., 111, 121, 134, 146, 155, 171, 189, 214, 246
Binswanger, 250
Bischoff, F., 184
Bismarck, 17
Blaschko, H., 166, 184
Bleuler, Eugene, 18, 19, 25, 26, 97, 250
Bleuler, M., 25, 27, 213, 235, 240, 249
Blewett, D. B., 45, 53, 72, 109
Bliss, E. L., 238, 240
Block, W., 114, 115, 119
Blough, D. S., 240
Blum, J. J., 237, 244
Bogdanski, D. F., 79, 96
BOL-148
  effect with ascorbic acid upon plasma adrenochrome levels, 136
  effect without ascorbic acid upon plasma adrenochrome levels, 136
Bollman, J. L., 35, 73
Bone, A. D., 139, 146
Bonnycastle, D. D., 78, 79, 92, 93
Born, G. V. R., 35, 72
Boszormenyi, Z., 141, 143
Boszormenyi-Nagy, I., 232, 236, 240
Bozeman, R. F., 34, 74
Brack, A., 141, 145, 200
Bradley, P. B., 115, 119, 131, 132, 143
Bragg, 6
Brande, B. L., 138, 145, 173, 179, 188
Briot, M., 154, 186
Brodie, B. B., 89, 93, 95, 132
Brodny, M. L., 233, 240
Brom LSD, *See* LSD
Brooks, V. B., 86, 93
Broussolle, B., 153, 187, 188
Brown, W. T., 244
Bruce, L. C., 22, 27
Bruer, Joseph, 17
Brunecker, G., 141, 143
Buchler, J., 8, 15
Bufotenine
  effect on humans, 141-142
  properties of, 201
Bulbocapnine
  effect on function of central nervous system, 119
  effect on man, 118
  production of catatonia, with, 118

structure of, 117
use for schizophrenia, 23
Bullough, W. B., 150, 184
Bullough, W. S., 233, 240
Bu'lock, J. D., 159, 186
Bumpus, F. M., 129, 143
Burns, J. H., 37, 72
Burrell, R. H., 214, 240
Burton, R. M., 92, 95
Buscaino, V. M., 23, 27, 211, 240
Butterworth, K. R., 84, 93, 199, 202
Buzard, J. A., 118, 119
Byers, L. W., 193, 195, 196, 198, 221

C

Callbeck, M. J., 68, 73, 80, 92, 94, 137, 218, 243
Cameron, E., 65, 72
Campbell, J. D., 20, 27
Camus, L., 173, 184, 205, 240
Cannon, W. B., 19, 29, 31, 32, 72, 160
Cantril, H., 32, 72, 108, 109
Carlo, J., 158, 186
Carlsson, A., 78, 89, 93, 95, 214, 241
Carnegine, effect of, 118
Carter, T. E., 164, 165, 184
Catatonia
description of animal, 118
effect of atropine on, 85
Cetechol amines, relationship of mood to, 31-72
Cerletti, A., 133, 143, 157, 184, 216, 241
Ceruloplasmin
and adrenolutin, 222-223
as a factor in adrenochrome hypothesis, 221
description of, 193-194, 220
hypothesis regarding, 221
levels of in psychiatric patients, 220-221
properties of, 221
study of use with schizophrenia patients, 221-222
Chakrabarti, B., 87, 93
Chanley, J. D., 148, 190
Chapman, L. F., 37, 38, 60, 73
Chlorpromazine, use with schizophrenics, 214
Cholden, L., 144, 119, 242
Chwelos, N., 53, 72, 80, 94, 106, 109
Cinci, 4
Clark, L. D., 238, 240
Clinical psychiatry, chemical basis of
acceptance of theory of, 22
historical background, 17-26
theory of Thudichum, 17-18
Crawford, T. B. B., 164, 165, 185
Cocaine
effect on nervous system, 84
history of use of, 82-83
kinds of addicts to, 83-84
mode of action, 84
use of as an euphorient, 82-83
Cohen, G., 35, 72, 162, 187
Cohen, I., 4, 15
Cohen, M., 166, 188, 193, 194, 198, 205, 207, 219, 220, 232, 239, 242, 243, 244
Connell, P. H., 116, 119, 215, 241
Conte, C., 173, 184, 205, 240
Copper, relation of to schizophrenia, 235-237
Costa, E., 87, 93, 138, 144
Cotton, H. A., 22, 27
Co Tui, 227, 246
Cousteau, J. Y., 153, 185
Creveling, C. R., 92, 96
Cronheim, 176
Crooke, T. G., 250, 255

D

Daly, J. W., 92, 96
Danziger, L., 231, 241
Darwin, Charles, 6
Davis, P., 242
Deaner
composition of, 85
effect on synthesis of acetylcholine, 123
use of, 85-86
deJong, Hermann H., 23, 27, 118, 120, 173
Delay, J., 90, 93
de le Vega, Garcilasco, 82
Deltour, 48, 49
Denber, H. C. B., 26, 39, 72, 110, 119, 143, 184, 213, 241, 247
Deniker, P., 90, 93

Derouaux, G., 155, 159, 185
De Shon, 213
Desmedt, J. E., 123, 126
Devine, H., 22, 27
Dews, P. B., 87, 93
DFP
  effect on cats, 124
  effect on humans, 124
Delphinium alkaloids
  effect on function of central nervous system, 119
  lethal dose of, 119
Depression
  and body activity, 79
  anergic, *See* Anergic depression
  anxiety, *See* Anxiety depression
  changes induced by adrenochrome, 41
  chemical treatment of, 75-92
  classification of anti-depression drugs, 75
  defined, 75
  effect of Iproniazide on, 82
  explanation of diurnal rhythm of, 65
  groups of substances used for treatment of, 199
  logical sequence of diagnosis, 103
  response of patients to DNMI, 51-59
  use ofMarsilid in treatment of, 75
  use of nicotinic acid in treatment of, 68
  use of Tofranil for, 91
Dexamyl, use for anergic depression, 76
Dexedrine, use for anergic depression, 76
DIN, *See* Isopropylnorepinephrine
d-LSD-25, *See* LSD
Diabetes mellitus, relationship of schizophrenia to, 238-239
Dibenamine, as adrenolytic or adrenergic blocking agent, 91
Dibenzyline, as adrenolytic or adrenergic blocking agent, 91
Diethelm, O., 37, 72, 92, 93
Diethyl Tryptamine
  as a psychotomimetic, 141
  dosage used, 141
  source of, 141
Dihydroxy-N-methylindole
  amount in urine in psychiatric patients, 70
  case histories of response to
    of depressed individuals, 51-59
    of normal individuals, 50-51
    of schizophrenic patients, 59-60
  properties of, 49
  reaction to, 64
  reactions of normal individuals to, 50-51
  relation to known psychotomimetics, 199
  study of, 49-60
  table of responses to, 52
Dihydroxy phenylalanine, substances which may be derived from, 117-119
Diller, W. F., 164, 165, 185
Dimethyl Typtamine
  as a psychotomimetic, 141
  dosage used, 141
  properties of, 200, 201
  source of, 141
  structure of, 200
Dingle, Herbert, 3, 4, 5, 15
DNMI, *See* Dihydroxy-N-methylindole
Dorland, 102
Doust, J. W. L., 227, 241
Drill, V. A., 93, 96
Dumas, F., 153, 185

E

Eade, N. R., 147, 153, 157, 173, 185, 187, 216, 243
Eccles, O., 42, 72
Ehrlich, 18
Eiduson, S., 78, 93, 196, 197
Eiseley, L., 6, 15
Elderkin, R. D., 236, 239
Elkes, C., 115, 119
Elkes, J., 115, 119, 122, 126
Elliott, J. A. C., 122, 127
Elliott, K. A. C., 151, 180, 184, 185
Ellis, Havelock, 106, 109
Elmadjian, F., 48, 72, 80, 95, 158, 186
Ephedrin, structure of, 117
Epinephrine
  adsorption equilibrium, 35
  adsorption within cells, 36

amount in urine in psychiatric patients, 70
amount produced daily by man, 160
and intensity of anxiety, 34
biochemical effects of, 33-37
changes in body produced by, 33
changes of in plasma with methamphetamine, 34
changes with oxidation of to adrenochrome, 152
classes of epinephrine-like substances, 76
concentration of in blood, 37
concentration of in plasma, 160-161
concentration of in red cells and plasma, 36
effect on brain, 33
effect on diurnal rhythm, 237-238
estimate of sympathomimetic production, 165
evidence of as mediator of anxiety, 31-32
excess production of and anxiety ratio, 64-66
and inadequate conversion to DNMI, 64-65
and oversecretion of epinephrine and adequate conversion to DNMI, 65-66
formation of adrenochrome and adrenolutin from, 167
in cells in serum, 236-237
in normal serum, 212
in schizophrenic serum, 212
injection of intravenously, 161-163
internal pigmentation of brain and metabolism of, 231
levels of in plasma, 34
normal production of, 66-67
and adequate conversion to DNMI, 66
and excess conversion to DNMI, 66-67
and inadequate conversion to DNMI, 66
oxidation of to adrenochrome, 166-167
pathways of metabolism, 162
physiological effects of, 32
psychological effects of, 32
reaction to insufficient, 67
over utilization, 68-72
under production, 67-68
relationship of anxiety to, 90
relationship of iron metabolism to, 235-236
relationship of ratio of to level of anxiety, 64
relationship to known psychotomimetics, 199
relationship to mood, 77
role of in synthesis, 64
source of, 160
structure of, 117
study of adsorption by Fleetwood, 36
study of metabolism, 163
study of quantity of in urine, 164-165
study of secretion from adrenal glands, 163-164
study of values of in urine, 71-72
use of ascorbic acid to protect, 90-91
use of by schizophrenics, 161-162
use of to control vomiting of pregnancy, 42
Epinephrine metabolism, indirect action of LSD on, 135-140
Epinephrine oxidase
cause of, 167
distribution of, 168
study of, 167-168
Ergot alkaloid
as adrenolytic or adrenergic blocking agent, 91
use of, 91
Ergot psychotomimetics, *See* LSD
Eriksen, N., 237, 244
Eserine
effect of on rats, 85
effect on catatonia, 85
effect on cats, 124
Esterase, relation to known psychotomimetics, 199
Esterase inhibitors
properties of, 200, 201
structure of, 200

Euphoria, and epinephrine, 80
Eurieult, M., 90, 91, 93
Evarts, E. V., 131, 144, 158, 187
Everett, G. M., 78, 93

F

Fabing, H. D., 141, 144, 214, 241
Farley, J. D., 125, 126
Fedoroff, S., 205, 206, 241
Feigley, C. A., 193, 194, 195, 196, 198
Fellman, J. H., 212, 231, 241
Fenn, W. O., 153, 185
Fenton, 151
Ferguson, 91
Fiegley, C. A., 205, 221, 242
Fields, W. S., 120, 145
Fischer, P., 80, 93, 159, 168, 169, 185
Fish, M. S., 141, 145
Fisher, P., 209, 241
Flataker, L., 205, 247
Fleetwood, M. F., 36, 37, 72
Fleming, G. W. T. H., 249, 255
Florey, E., 150, 151, 184, 185
Forrer, G. R., 215, 241
Fourment, J., 90, 93
Fraser, H. F., 138, 145
Freeman, H., 80, 95, 158, 186, 205, 240
Freemont-Smith, N., 138, 143
Frenquel, use in treatment of schizophrenia, 214
Freud, Sigmund, 10, 11, 17, 18, 19, 25, 27, 83
Friend, D., 78, 94
Frohman, C. E., 235, 241
Fulcher, J. H., 85, 94
Funkenstein, D. H., 227, 242
Furness, P., 78, 95

G

GABA, and adrenochrome, 232
Gaddum, J. H., 132, 144
Galileo, 4, 6, 15
Gallagher, W. J., 85, 94
Garb, S., 37, 38, 60, 73
Garattini, S., 143, 146, 184, 186, 241, 246
Gaunt, W. E., 35, 72, 236, 239
Gardes, M. A., 125, 126
Gerard, R. W., 86, 93, 105
Gerschman, R., 153, 185
Gershenovich, Z. S., 152, 185, 208, 242
Gerty, F. J., 232, 236, 240
Gey, K. F., 79, 95
Ghetti, V., 143, 146, 184, 186, 241, 246
Giarman, N. J., 78, 93
Gibbons, A. J., 151, 186
Gibbs, E., 220, 239
Gibbs, F. A., 94, 186, 220, 239
Giberti, F., 139, 144
Gibson, W. C., 115, 120, 244
Gigee, W., 36, 74
Gilbert, D. L., 153, 185
Gillies, H., 255
Gillis, 249
Gilman, A., 140, 144
Gjessing, R., 12, 15
Glutathione, use in treatment of schizophrenia, 220
Goldenberg, M., 162, 187
Goldner, R. D., 215, 241
Goldstein, N. P., 158, 187
Golterman, H. L., 150, 189
Goncz, R. M., 195, 197, 220, 233, 239, 242
Gonzalez-Monclus, E., 214, 246
Goodman, L. S., 140, 144
Goodman, M., 235, 241
Gray, C. L., 184
Green, D. E., 147, 149, 166, 185
Green, H. C., 5, 15
Green, S., 151, 185
Gregoretti, L., 139, 144
Greig, M. E., 151, 186
Groenendijk, J., 231, 242

H

Haag, H. B., 84, 96
Hack, 155
Hall, R., 227, 247
Halpern, B. N., 154, 186
Hals, Franz, 176
Hanson, N. R., 6, 15
Hardy, J. D., 164, 165, 184
Harley-Mason, J., 115, 119, 159, 186, 193, 198

Harmine
effect on man, 142
properties of, 200, 201
source of, 142
structure of, 200
use by South American natives, 142
Harris, A., 230, 242
Harris, P. L., 219, 247
Harris, R. S., 220, 246
Hart, E. R., 153, 188
Hawkins, J. R., 141, 144
Heacock, R. A., 39, 49, 69, 73, 81, 87, 94, 137, 144, 147, 148, 149, 150, 170, 186, 209, 224, 242
Heath, R. G., 114, 120, 138, 144, 166, 168, 188, 192, 193, 194, 195, 196, 198, 205, 207, 219, 220, 221, 232, 239, 242, 243, 244
Hebart, 251
Heffter, 111
Heim, R., 141, 145, 200
Hellstrom, 48
Helmer, O. M., 164, 165, 186
Henneman, D. H., 220, 233, 239, 242
Hickman, K., 219, 247
Hippocrates, 21
Histamine
adrenochrome and tolerance of, 225, 227-228
inhibited by adrenochrome, 153-154
Hoagland, H., 135, 139, 144, 156, 158, 186, 190, 205, 213, 217, 231, 240, 242, 245
Hoch, P. H., 30, 112, 119, 128, 139, 142, 144, 145, 200, 214, 242
Hoffer, A., 33, 40, 41, 53, 68, 72, 73, 74, 80, 81, 92, 94, 100, 110 112 115, 120, 128, 137, 145, 154, 156, 157, 158, 159, 162, 166, 167, 168, 169, 170, 171, 172, 173, 174, 178, 186, 187, 189, 190, 191, 193, 196, 198, 205, 207, 209, 210, 214, 218, 219, 220, 221, 228, 231, 236, 239, 241, 242, 243, 245
Hoffmann, 24, 200
Hofmann, A., 28, 141, 145
Holland, B., 162, 187
Holmberg, C. G., 193, 198
Holmes, H. L., 120
Holtz, P., 151, 187
Holzbauer, M., 78, 94
Hope, J. M., 48, 72, 158, 186
Horning, E. C., 141, 145
Hornykiewicz, O., 35, 72
Horst, D., 158, 187
Hoskins, R. G., 158, 187, 231, 243
Houssay, B. A., 163, 165, 187
Hubbard, A. M., 108, 109, 215, 243
Humoller, F. L., 231, 246
Hundevadt, E., 205, 233, 247
Hungzinger, W. A., 222, 245
Hunt, W. A., 32, 72, 73
Hunter, 110
Husdan, H., 227, 241
Hutcheon, D. E., 79, 92, 153, 157, 187, 215, 243
Huxley, T. H., 108
Huxly, Aldous, 106, 108, 109
Hyde, R. W., 135, 139, 144, 158, 186, 189, 213, 217, 231, 242, 245
Hydroxy tyramine, relationship of anxiety to, 90
Hypothermia
and LSD and adrenochrome, 157-158
caused by adrenochrome, 157-158
Hypothesis
and empirical system, 13-14
and science, 7-9
criteria for, 8-9
defined, 8

I

Ibogaine
properties of, 200, 201
response to, 143
source of, 13
structure of, 200
Indoles
indolylethylpyridines, *See* Indolylethylpyridines
measurement of dihydroxy, 39
relationship of mood to, 38-39
reserpine, *See* Reserpine
types of and adrenochrome, 231-232
Indolylethylpyridines, effect of, 91

Ingle, D. J., 154, 187
Inscoe, J., 80, 92
Iproniazide
  action of antidepressive activity of, 82
  effect of on adrenochrome levels, 81
  effect on adrenochrome tolerance, 80
  effect of on reactive depression, 82
  effect of on schizophrenics, 82
  positive reward self-stimulation experiments with, 78
  relationship of to methoxy epinephrine, 80
  use for anergic depressions, 77-82
  use for treatment of depression, 75
Iron, relation of to schizophrenia, 235-237
Isbell, H., 138, 139, 145
Isocorydine
  effect on cats, 118
  effect on function of central nervous system, 119
  structure of, 117
Isoquinolines, effect on function of central nervous system, 119
Isopropylnorepinephrine
  effect on ganglionic cells, 38
  formation of, 60
  presence of in body, 60
  reaction to, 64
  reactions of normal subjects to, 60-63
  role in mediating anxiety, 37-38
  role of, 37-38
  study of, 60-63

J

James, William, 107, 109, 251
Jantz, H., 170, 173, 174, 190, 211, 243
Jacques, R., 38, 73
Jarvik, M. E., 140, 145
Jasper, H. H., 122, 127, 143
Jenney, E. H., 85, 95
Johnson, 215
Johnson, D. M., 201, 202, 243
Johnson, P. C., 153, 184
Jones, E., 17, 27
Jung, Carl G., 19, 128, 145

K

Kahan, I., 92, 94, 218, 243
Kaindl, F., 163, 165, 187
Kallman, Franz, G., 13, 15, 253
Kalnitsky, G., 152, 185, 242
Kaufmann, H., 39, 73, 80, 94
Kayahan, S., 87, 94
Kekule, 6
Kenyon, M., 80, 94, 166, 168, 187, 193, 198, 209, 243
Kety, S. S., 26, 27, 80, 94, 105, 109
Khokhlov, L. K., 220, 247
Kies, M. W., 158, 187
Kilpatrick, R., 164, 165, 185
Kindwall, 231
Kingsley, Charles, 108
Kirkbride, Thomas, 22, 27
Kisch, B., 147, 187
Knehr, C. A., 225, 243
Kobel, H., 141, 145, 200
Koch, E., 39, 73, 80, 94
Koelle, G. B., 152, 188, 229, 243
Kohn, R. R., 232, 243
Kornblueth, W., 233, 247
Kraepelin, 9, 18, 19, 97, 250, 251
Kral, V. A., 235, 243
Kreman, D., 205, 244
Krichevskaya, A. A., 152, 185, 242
Krivoy, W. A., 132, 144
Kropa, E. L., 141, 144
Kuntzman, R., 89, 95

L

Laborit, H., 153, 187, 188
Labrosse, E. H., 80, 94
La Burt, H. A., 227, 246
Lagrutta, G., 123, 126
Laidlow, B. D., 73, 81, 94
Laird, A. H., 115, 119
Lambot, H., 159, 185
Landis, C., 32, 73
Landtsheer, L., 80, 93, 169, 185
Langemann, H., 152, 188, 229, 243
Lapteva, N. N., 192, 194, 198
Laulon, M., 125, 126
Launay, J., 173, 184, 205, 240

Laurell, C. B., 193, 198
Laverty, G., 132, 144
Law W., 164, 165, 185
Lea, A. J., 219, 227, 228, 229, 243
Leach, B. E., 138, 144, 166, 168, 188, 192, 193, 194, 195, 196, 198, 205, 207, 219, 220, 221, 232, 239, 242, 243, 244
Leake, C. D., 141, 144
Lebovitz, B. Z., 110
Lecomte, J., 80, 159, 168, 185, 209, 241
Lehmann, H. E., 20, 235, 243
Leifer, L., 162, 187
Leimdorfer, A., 33, 73, 80, 95, 155, 171, 188
Leucoadrenochrome, *See also* DNMI
  production of, 81
  properties of, 49
  study of, 49
Lewin, Louis, 19, 27, 83, 85, 95, 104, 105, 106, 109, 118, 142, 145, 252
  discoverer of cactus Anhalonium Lewinii, 19
  work with Peyote and Mescaline, 19
Lewis, J. L., 113, 120
Libovitz, 101
Lichtenheld, F. R., 111, 121, 134, 146, 155, 171, 189
Liddell, D. W., 34, 73
Lief, H. I., 205, 244
Lindeman, E., 24, 27
Lindquist, M., 78, 93
Ling, Nan-Sing, 237, 244
Lingjaerde, O., 205, 233, 247
Lipmann, F., 150, 189
Lister, 10
Llewellyn, R., 114, 120
Logan, C. R., 139, 145
Loken, F., 205, 233, 247
Lorenz, 254
Lowenstein, E., 22, 27
Lowenthal, J., 153, 157, 187, 215, 243
Lozovskii, D. V., 192, 194, 198
LSD
  action as own antagonist, 139
  action of, 130
  and adrenochrome tolerance, 47
  and hypothermia and adrenochrome, 157-158
  antagonism to Serotonin, 132-134
  assay of, 207
  comparison with Mescaline, 112
  direct effects of, 130
  discoverer of psychotomimetic properties of, 141
  dosage given, 129
  dosage required for typical experience, 136
  effect on ascorbic acid, 87
  effect on cerebral circulation, 130
  effect on electroencephalogram, 131
  effect on production of energy in brain, 130
  effect on stimuli to optic nerve, 131
  effect on transmission of stimuli, 131
    in cats, 131
  effect on volume of urine, 158
  effect with ascorbic acid upon plasma adrenochrome levels, 136
  effect without ascorbic acid upon plasma adrenochrome levels, 136
  evidence of antagonism of serotonin, 133
  indirect action on acetylcholine, 135
  indirect action on epinephrine metabolism, 135-140
  mode of action, 130-140
    direct, 130-134
    indirect, 135-140
  properties of, 200, 201
  relationship of increase in adrenochrome levels to intensity of, 48
  response to and adrenochrome, 47
  structure of, 200
  tolerance of man to, 138-139
  use in treatment of schizophrenia, 214-215
  visual changes with, 99
L-strain fibroblast toxicity test, 206
Luby, E. D., 235, 241
Lucksch, F., 219, 244
Lucy, J., 227, 244
Luft, R., 164, 165, 188

M
Macalpine, 110
Macht, D. I., 205, 244
Maffezzoni, G., 123, 127
Magnusson, T., 78, 93
Mahon, M. E., 46, 74, 80, 94, 129, 145, 159, 166, 189, 208, 245
Majka, F. A., 231, 246
Manger, W. M., 34, 73
Mann, M., 84, 93
Mann, N., 199, 202
Manning, R. J., 147, 191
Manske, R. H. F., 118, 120
Marcus, D. A., 101, 110, 126, 200, 220, 245
Marrazzi, A. S., 33, 73, 113, 120, 131, 133, 134, 145, 153, 156, 188
Marsilid, *See* Iproniazide
Martens, S., 138, 145, 166, 179, 188, 192, 193, 194, 195, 196, 198, 205, 207, 219, 220, 221, 232, 239, 242, 243, 244
Marti-Ibanez, F., 246
Martin, G., 237, 244
Marti-Tusquets, J. L., 214, 246
Mason, H. S., 152, 166, 188
Masserman, J. H., 93, 244
Matthews, R. J., 38, 73
Maurois, 249
Maxwell, R. A., 78, 95
Mayer-Gross, W., 215, 244
Mayhew, Christopher, 106, 110
Mazur, A., 151, 185
McAdam, W., 215, 244
McColl, J. D., 171, 189
McColloch, W. S., 244
McCullough, 215
McGeer, E. G., 23, 24, 27, 211, 244
McGeer, P. L., 23, 24, 27, 211, 244
McIlwain, H., 113, 120
McKellar, P., 6, 15
McMillan, A., 34, 74, 163, 164, 165, 184, 190
McNair, F. E., 244
Meduna, L. J., 126, 215, 244
Meier, R., 38, 73
Meirowsky, E., 152, 188
Mekler, L. B., 192, 194, 198
Melander, B., 47, 48, 49, 74, 138, 145, 168, 172, 178, 179, 188, 192, 194, 196, 198, 207, 219, 221, 222, 244
Meratran, use for anergic depression, 76
Meriwether, B. P., 150, 189
Merlis, S., 39, 72, 141, 147
Mescaline
  action on brain, 112
  administration of, 111
  and electroencephalogram changes, 113-114
  and metabolism of brain tissue, 112
  and oxidation of succinate, 112-113
  and production of vitro inhibition, 113
  as inducer of anxiety, 33-34
  assay of, 207
  change in electroencephalogram with, 39-40
  comparison with LSD, 112
  conversion into dihydroxyindole, 115
  direct action of, 112-114
  effect of on humans, 111
  effect of on levels of adrenochrome in plasma, 115
  incorporation into body proteins, 114
  indirect action of, 114-115
  mode of action, 112-115
    direct, 112-114
    indirect, 114-115
  properties of, 200-201
  source of, 111
  structure of, 200
  TMA, 115-116
  visual changes with, 99
Methamphetamine
  effect of on level of epinephrine in plasma, 34
  structure of, 117
Methedrine, use for anergic depression, 76
Methodology
  approach of psychiatry to, 10-15
  defined, 3-4
  opinions on, 4-5
  use of, 3-4
Methyl LSD, *See* LSD
Metzner, W. R. T., 33, 73, 80, 95, 155, 171, 188

Meyer, Adolph, 10, 11, 24, 27, 197, 203
holistic approach of, 24-25
Meyerhoff, O., 149, 188
Michaux, H., 106, 110
Mickle, W. A., 114, 120
Mill, John Stuart, 44
Miller, A. I., 214, 215, 244
Minz, B., 205, 212, 244, 247
Mirsky, J. H., 91, 95
Mitchell, S. Weir, 9
Model psychoses
and cause of, 101-104
autonomic changes, 215-216
visual changes in, 98-99
Models
auditory hallucinations, 100-101
objections to model psychoses, 97-104
use of, 97
visual changes noted, 98-100
Montagu, J. D., 164, 188
Mood
and its disorders, 29-30
relationship of to indoles, 38-39
relationship to catechol amines, 31-72
Mordret, M., 91, 93
Morell, A. G., 220, 246
Morris, A., 122, 127
Morris, H. H., 234, 239
Moyer, J. H., 37, 74
Mudd, S. H., 150, 189
Munroe, R. R., 114, 120
Murmane, J. P., 195, 197
Murphree, H. B., 214, 215, 244
Muscholl, E., 139, 145
Mussorgsky, 45
Meyers, J. M., 234, 239

N

Norcotine, effect on function of central nervous system, 119
Naumova, V. V., 65, 74, 237
Nerenberg, C., 147, 149, 186, 209, 242
Neurohormone, desiderata of, 122
Nevin, S., 124, 127
Newton, Isaac, 6, 7, 15
Nezamis, J. E., 154, 187
Nicotinamide
study of use of, 92
use in treatment of schizophrenia, 218-219
Nicotinic acid
use in treatment of depressive and anxiety reactions, 68
use in treatment of schizophrenia, 214-215, 218-219
use to decrease epinephrine levels, 92
use to reverse effects of adrenochrome, 153
Nilsson, J., 214, 241
Niswander, G. D., 192, 195, 198
Norepinephrine
concentrations of in blood, 37
concentrations of in red cells and plasma, 36
excreted in urine, 164
in normal serum, 212
in schizophrenic serum, 212
relationship of anxiety to, 90
relationship to mood, 77
Noval, J. J., 138, 145, 173, 179, 188
Nye, S. W., 153, 185
Nytch, P. D., 119, 188

O

O'Connor, C. M., 126
O'Dell, T. B., 91, 95
Olds, J., 78, 95
Olds, M. E., 78, 95
Osinskaya, V. O., 46, 74, 166, 190
Osmond, H., 34, 40, 73, 74, 92, 94, 100, 108, 110, 128, 145, 158, 169, 170, 173, 174, 187, 189, 205, 213, 218, 228, 231, 243, 245, 251
Ostfeld, A. M., 101, 110, 126, 200, 220, 245
Ovshinsky, S. R., 235, 245
Ozaki, M., 92, 96

P

Paasonen, M. K., 78, 93
Page, I. H., 129, 143
Papez, J. W., 22, 27
Park, C. R., 150, 189
Park, J. H., 150, 189
Pasteur, Louis, 10
Payza, A. N., 46, 74, 129, 145, 147, 149, 156,

159, 162, 166, 167, 168, 186, 187, 189, 196, 198, 208, 209, 210, 219, 221, 222, 242, 245
Pellotine, production of convulsions in animals with, 118
Penfield, W., 122, 127
Penicillamine
case history of reaction to, 68-69
decolorization of adrenochrome with, 137
factors in treatment of Wilson's disease with, 225
use in treatment of schizophrenia, 223-225
use in treatment of Wilson's disease, 223
Pennell, R. B., 205, 240
Pennes, H. H., 128, 142, 145, 200
Peretz, D., 115, 120
Perles, R., 173, 184, 205, 240
Perot, P. L., 153, 189
Perrimond-Trouchet, R., 153, 187, 188
Perrin, G. M., 39, 70, 71, 72, 74
Perrin, M., 195, 198
Petersen, M. C., 189
Peyote
contents of, 111
Mescaline from, 111
use by Indians, 111
Pfeiffer, C. C., 85, 94, 95
Phaechromocytoma, relationship between anxiety, tension and epinephrine secretion in, 34-35
Phenylethylamines
alkaloids derived from, 119
compounds related to, 117
Phosphate, excretion of during study of schizophrenia, 216-218
Phosphorylation, and adrenochrome and schizophrenia, 232-235
Phthalideisoquinolines, effect on function of central nervous system, 119
Pierce, 8
Pilocarpine, effect of on rats, 85
Pincus, G., 158, 186
Piperidines, use for anergic depressions, 76
Piperidyl benzilates
dosage used in study, 126
effect of, 126
use of, 126
Pizarro, Francesca, 82
Pletscher, A., 79, 89, 93, 95, 118, 120
Plummar, A. J., 78, 95
Poloni, A., 123, 127
Poole, T. R., 161, 190
Pope, A. A., 122, 127
Popper, K. R., 3, 7, 11, 16
Porter, C. C., 237, 245
Pregnancy
relationship between schizophrenia and, 222
use of epinephrine to control vomiting of, 42
Preludin, structure of, 117
Price, W. E., 153, 185
Priscoline, as adrenolytic or adrenergic blocking agent, 91
Proctor, R. C., 68, 74
Protoberberines, effect on function of central nervous system, 119
Protopines, effect on function of central nervous system, 119
Psilocybin
as a psychotomimetic, 141
properties of, 200, 201
structure of, 200
Psychedelic reaction, defined, 97
Psychedelics, 106-109
development of term, 108
need to develop, 109
search for state of, 106-107
use of, 108
Psychiatry
and science, 9-15
difficulties of development of, 9-11
effect of Freudian system on, 10-11
Psychopharmacology
and treatment of schizophrenia, 252-253
place in medical science, 252
Psychotomimesis, 104-106
access of researcher to pure compounds, 104-105

pure compounds available, 104-105
Psychotomimetic reaction, defined, 97
Psychotomimetics
antagonists of and schizophrenic therapeutic agents, 214-215
application of result of animal studies to man, 134
bufotenine, 141-142
defined, 199
diethyl tryptamine, 141
dimethyl tryptamine, 141
division of, 123
equation of relation of known, 199
ergot, 129-140, *See also* LSD
groups of compounds, 133-134
groups of substances used for treatment of, 199
harmine, 142
how they work, 199-201
hypothesis of indoles, 128
ibogaine, 143
indoles, 128
mood swing, defined, 106
potentiators, 215
atropine, 215
benzedrine, 215
present in body, 128-129
psilocybin, 141, *See also* Psilocybin
qualifications of drug to be classed as, 105
related to adrenochrome, 128-143
relation of autonomic activity to activity of, 200
schizogenic defined, 106
those similar in structure to epinephrine, 111-119
adrenergic compounds, *See* Adrenergic compounds
mescaline, *See* Mescaline
mescaline analogues, *See* TMA
which interfere with function of acetylcholine, 122-126
Purpura, D. P., 131, 146

Q

Quastel, 112

R

Raab, W., 36, 74, 161, 189
Radmsa, W., 150, 189
Randall, L. O., 149, 188, 189
Ransmeier, R. E., 86, 93
Rapela, C. E., 163, 165, 187
Rat climbing test, with schizophrenic serum, 206
Rausch, 250
Ravel, 45
Rees, L., 234, 245
Regitine, as adrenolytic or adrenergic blocking agent, 91
Renees, 100
Reserpine
action of, 63, 90
cause of sedative effect of, 89
effect on depression in anxious patients, 88
effect on hypertensives who are not anxious, 88
effect upon body, 89
main uses of, 88
mode of action, 89-91
reaction to prolonged use of, 68
relationship of anxiety to, 90
sign of overdosage, 88
source of, 87
types of overdosage effect, 88-89
use in treatment of schizophrenia, 214
Resnick, O., 80, 95
Reti, L., 117, 118, 120
Rice, W. B., 171, 189
Richardson, A. K., 34, 74, 161, 189
Richardson, J. A., 34, 74, 161, 189
Richter, D., 127, 147, 149, 166, 167, 184, 185, 245
Rieder, H. P., 205, 207, 233, 245
Rinkel, M., 26, 110, 119, 135, 139, 143, 144, 157, 158, 170, 184, 186, 189, 213, 217, 231, 242, 245, 247
Ritalin, use for anergic depressions, 76
Ritzel, G., 222, 245
Rodnight, R., 237, 245
Romanoff, L., 158, 186
Rome, H. P., 214, 246
Rosengren, E., 214, 241

Rosenow, E. C., 22, 28
Roskam, J., 155, 185
Ross, S., 78, 95
Rothballer, A. B., 84, 95
Rothlin, E., 98, 110, 215, 246
Rowntree, D. W., 124, 127
Ruiz-Ogara, C., 214, 246

S

Sachs, E., 192, 195, 198
Sackler, A. M., 227, 246
Sackler, M. D., 227, 246
Sackler, R. R., 227, 246
Salna, M. E., 227, 241
Salvador, R., 92, 95
Sanchez, A., 113, 121, 214, 247
Sanders, B. E., 237,245
Sargant, W., 20, 28
Scheid, K. F., 235, 246
Scheinberg, I. H., 220, 246
Schilder, 18
Schizogenic psychotomimetic, defined, 106
Schizophrenia
adrenochrome hypothesis of, 204
adrenochrome levels and, 208-209
adrenochrome model and, 203-239
allergies and, 227-228
and adrenochrome and phosphorylation, 232-235
and antimitosis, 233-234
and changing world, 251-252
and diuresis, 231
and diurnal rhythm, 237-238
and future of mankind, 254-255
and internal pigmentation of brain, 231
and medical research, 203
and oxidation of ascorbic acid, 232
and phosphate excretion, 216-218
and pigmentation of skin, 230-231
and the rat climbing test, 206
and theory of, 203-204
and thyroid function, 231
as functional psychosis, 101-102
auditory hallucinations of, 100-101
autonomic changes, 215-216
biochemical changes, 216-218
biochemical differentiation of fluids from patients and non patients, 204-212
biological assays, 205-208
case history of treated case of, 224-225
changes induced by adrenochrome, 41
characteristics of toxic confusional states, 213
chemical theories of, 22-23
conclusions of schizophrenic plasma hypothesis, 212
confusion as to diagnosis and cause of, 101-102
defined, 20-21
description of, 20-21
destroying adrenochrome in treatment of, 223-225
effect of arecoline on, 85
effect of eserine on catatonia of, 85
effect of Iproniazide on, 82
effect of schizophrenic bile on pigeons, 207-208
effect on body build, 234
endotoxic hypothesis of, 23-24
evidence for schizophrenic plasma theory, 205
exogenous hypotheses of, 22-23
experiments of Berger, 22
explanation of diurnal rhythm of, 65
formation of pigments in patients with, 228-231
future of search for a toxic factor in, 249-255
increase in secretion of urine of, 158-159
interplay of great systems in, 254
logical sequence of diagnosis, 103
L-strain fibroblast toxicity test, 206
methoxy and etiology of, 34
need for early diagnosis and treatment of, 253
neutralizing adrenolutin in treatment of, 220-223
objections to model, 97-104
percent of patients with dark hair, 230
physiological correlates of from adrenochrome hypothesis, 225-239

production of and serotonin, 237
properties of adrenochrome in, 226
psychotomimetic antagonists and schizophrenic therapeutic agents, 214-215
red cells of patient with, 236-237
reduction in production of adrenaline in treatment of, 218-219
relationship between physical type and, 234
relationship between pregnancy and, 222
relationship of to diabetes mellitus, 238-239
relationship to hair color, 228-230
relationship to iron and copper, 235-237
response of patients to DNMI, 59-60
results of adrenochrome tolerance test, 47
results of testing schizophrenic plasma hypothesis, 212
review of studies of, 250-251
search for cause of, 128-129
similarity between experimental psychoses and, 213-218
similarity of experience induced by adrenochrome and, 212
spider web test, 207
spore germination test, 206
steps in diagnosis, 102
study of use of ceruloplasmin for, 221-222
substantiation of adrenochrome hypothesis, 204
Taraxein in blood of, 194
tests of schizophrenic plasma, 206-208
adrenochrome levels and schizophrenia, 208-209
adrenochrome tolerance, 209-210
catatonizing effect on pigeons, 207-208
conversion of adrenochrome to adrenolutin, 210-211
L-strain fibroblast toxicity, 206
rat climbing test, 206
spider web test, 207
spore germination test, 206
theory of contents of serum of patients with, 205
theory regarding hair color and, 229-230
toxicity of normal and schizophrenic plasma, 207
treatment of, 218-225
decreasing production of adrenochrome, 219-220
destroying adrenochrome, 223-225
goal of, 218
neutralizing adrenolutin, 220-223
reduction in production of adrenaline, 218-219
tuberculosis and, 234-235
use of bulbocapnine, 23
use of chlorpromazine for, 214
use of copper binding substance in treatment of, 224
use of epinephrine by, 161-162
use of Frenquel for, 214
use of glutathione in treatment of, 220
use of LSD, 214-215
use of nicotinic acid for, 214-215
use of reserpine for, 214
use of succinic acid for, 214
visual hallucinations in, 99
Schlossman, H. G., 166, 184
Schneider, 200
Schneider, J. A., 143, 146
Schneider, R., 40, 74, 154, 190
Schueler, F. W., 112, 214, 246
Schwarz, B. E., 111, 114, 121, 134, 146, 155, 171, 179, 189, 214, 246
Schwarzenbach, F., 205, 206, 246
Science
and Freudian system, 10-11
and Meyerian system, 11
and psychiatry, 9-15
defined, 5
development of ideas, 6-7
first step, of, 5-6
hypotheses, 7-9, *See also* Hypothesis
Scott, B. D., 144, 224, 242

Sebrell, W. H., Jr., 140, 146
Sechehaye, M., 100, 110, 250
Seevers, M. H., 83, 95
Sem-Jacobsen, C. W., 189
Senf, 235
Serotonin
  action of benzoquinolizines on levels of, 79
  and production of schizophrenia, 237
  antagonism of LSD to, 132-134
  evidence of antagonism of to LSD, 133
  increase of levels of in brain, 78-79
  relationship of anxiety to, 90
  relationship to mood, 77
  release of by reserpine, 89
Sha, J., 162, 187
Shaw, E. N., 132, 146
Shaw, F. H., 34, 74
Shaw, K. N. F., 39, 74, 163, 190
Sheldon, William H., 13, 16, 106, 110, 236, 239
Sherwood, S. L., 13, 124, 127, 171, 172, 190
Shore, P. A., 89, 93, 95
Shorr, E., 151, 185
Shreber, D. P., 100, 110
Siegel, E. P., 195, 197
Siegel, M., 192, 195, 198
Sigg, E. B., 143, 146, 200
Sjovall, T., 205, 237, 246
Sklarofsky, B., 138, 143
Slater, Eliot, 13, 16, 253
Slocombe, A. G., 155, 156, 190
Slotkin, J. S., 107, 110
Smartt, G. G. F., 201, 202
Smith, 53
Smith, C. M., 47, 72, 74, 80, 94, 108, 110, 136, 146
Smith, E. V. C., 237, 245
Smythies, J. R., 34, 40, 73, 74, 115, 119, 120, 128, 145, 169, 173, 187
Sobotka, H., 147, 148, 190
Sohler, A., 138, 145, 173, 179, 188
Solomon, H. C., 189, 213, 245
Sommer, R., 100, 110, 250, 251
Speck, L. B., 115, 121
Spider web test, on schizophrenic extract, 207
Spore germination test, on schizophrenic extracts, 206
Stafford, A., 35, 72
Staub, H., 222, 245
Stavros, D., 192, 195, 198
Stein, S. N., 153, 189
Steven, J. D., 231, 246
Stevenson, I., 112, 113, 121, 214, 247
Stockings, G. Tayleur, 24, 28, 213, 247
Stoll, A., 24, 28
Streifler, M., 205, 233, 247
Succinic acid, use in treatment of schizophrenia, 214
Suffolk, S. F., 35, 72, 236, 239
Sulkowitch, H., 39, 70, 71, 72, 74, 162, 190, 195, 198
Sundin, T., 65, 74, 164, 190
Surikov, M. P., 220, 247
Swan, H. J. C., 37, 74
Sympathetic nervous system, relationship between amine hormones, anxiety, mood and, 63-72
Sympatheticomimetic amine
  epinephrine, *See* Epinephrine
  isopropylnorepinephrine, *See* Isoproplynorepinephrine
  use for anergic depression, 76
Symthies, J., 193, 198, 245
Syndrome, defined, 102
Szara, S., 141, 143, 146
Szatmari, A., 40, 74, 154, 190

T

Takkunen, R., 154, 183
Tanner, J. M., 12, 16
Taraxein
  and uniting of adrenochrome hypotheses, 197
  auditory disturbances following use of, 101
  development of, 194
  extraction of, 192-197
  in blood of schizophrenics, 194
  properties of, 200
  structure of, 200
  toxicity of, 197
Taraxein hypothesis, 192-197

Tatum, J. C., 227, 247
Taubmann, G., 170, 173, 174, 190
Taylor, D. W., 153, 190
Tenney, A. M., 236, 239
Tension, relationship to ratio of epinephrine, 81
Tetrabenazine, structure of, 117
Tetrahydroisoquinolines, in peyote, 117
Thompson, L. S., 68, 74
Thompson, R. H. S., 123, 127, 135, 146
Thudichum, J. W. L., 17, 18, 28
  theory of, 17-18
Thyroid, function of and schizophrenia, 231
Tickner, A., 123, 127, 135, 146
Titus, D. C., 237, 245
Tiwari, N. M., 37, 38, 60, 73
TMA, effect of on humans, 115-116
Tofranil
  use for anergic depression, 76
  use of, 91
Toman, J. E. P., 78, 93
Tomich, E. G., 89, 95
Torda, C., 84, 95
Tozian, L. S., 156, 190
Traherne, Thomas, 108
Trevathan, R. D., 227, 247
Trihydroxy-N-methylindole
  relation to known psychotomimetics, 199
Trimethoxy phenylethylamine, as inducer of anxiety, 33-34
Tuberculosis, and schizophrenia, 234-235
Turner, W. J., 141, 146
Tyler, D. B., 238, 247

U

Undenfriend, S., 79, 92, 96
Urbach, C., 219, 247
Ushakov, G. K., 220, 247
Utevskii, A. M., 166, 190

V

Vallbo, S., 221, 244
Van der Berg, 250
Van Gogh, 176
Van Ophuijsen, J. H. W., 227, 246
Varene, P., 168, 190
Vaughan, M., 238
Verbliunskaia, A. A., 220, 247
Vernadakis, A., 151, 191
Visotsky, H., 101, 110
Voelkel, A., 118, 121
Vogt, M., 78, 94, 132, 139, 144, 145
Von Euler, V. S., 163, 164, 165, 187, 188

W

Wakim, K. G., 34, 73, 111, 121, 134, 146, 155, 171, 189
Walaas, E., 150, 190
Walaas, O., 150, 190, 205, 233, 247
Walaszek, E. J., 205, 212, 244, 247
Waldeck, B., 93
Wallace, 6
Walter, J. W., 215, 244
Ward, R. H., 106, 110
Wasson, R. G., 141, 146
Watts, D. T., 161, 190
Waud, R. A., 118, 121
Weatherby, J. H., 84, 96
Webb, J., 224
Webster, G. R., 123, 127, 135, 146
Weckowicz, T. E., 99, 110, 227, 247, 250, 251
Weil-Malherbe, H., 73, 139, 146
Weil-Malherbe, J., 16, 34
Weinstein, S., 147, 191
Weisbach, H., 79, 96
West, C. D., 238, 240
Westermann, E., 151, 187
Wheatley, 112
White, H. D., 91, 95
Wiedorn, W. S., 222, 247
Wikler, A., 138, 145
Williams, H. L., 214, 215, 244
Wilson, A., 124, 127
Wilson's disease
  factors in response to penicillamine, 225
  use of penicillamine in treatment of, 223
Winter, C. A., 205, 247
Witkop, B., 80, 92, 96, 238, 247
Witt, P. N., 170, 172, 191, 205, 207, 248

Wittman, P., 234, 248
Wojcicki, H., 172, 173, 191, 207, 243
Wolfe, J. M., 80, 95
Wolstenholme, G. E. W., 126
Woodbury, D. M., 151, 191
Woodford, V. R., Jr., 149, 191
Woods, E. F., 34, 74, 161, 189
Woolley, D. W., 92, 96, 132, 146
Wundt, 251

X

Xanthines, in beverages, 86

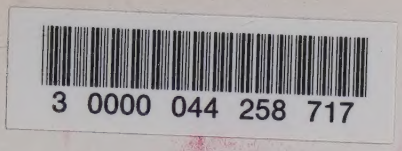
Y

Yohimbine, as adrenolytic or adrenergic blocking agent, 91

Z

Zaehner, R. C., 106, 110
Zaleschuk, J., 168, 189, 196, 198, 221, 222, 245
Zechmeister, L., 120
Zeller, E. A., 77, 96
Zetler, G., 87, 93, 138, 144
Zinkin, J., 26
Zubin, 30
Zurgilgen, B. A., 235, 240

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