THE CASE OF MR. KOVISH*

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Introduction

Nowadays when clinicians feel happier guided by methodologists and statisticians, only the brash or the sophisticated care to report single cases in detail. Yet medicine has in the past profited greatly by careful observations of this sort, and so good is this precedent that we have decided to defy fashion and report the affair of Mr. Kovish, one of those curious happenings which, we think, deserves a permanent record.

Some months ago we received a rather diffident letter from a Mr. Kovish of Chicago, suggesting that we might be interested in a recent experience of his. He had been an asthmatic for many years who took adrenalin regularly by inhalation and was well acquainted with its effect. Some time before writing to us he had bought some adrenalin of a wine colour and after taking it had suffered about four weeks of wholly unaccustomed mental distress. His account of this was so vivid that we recognized immediately that he was an accurate observer with an inquiring and reflective mind, who had endured what was for him a uniquely unpleasant experience. Further, he was knowledgeable enough to realize that such an experience carefully recorded might be very useful to those who research into the relationship between schizophrenic illnesses and those model psychoses which can be produced by chemical and other means.

The Nature of the Data

While we had the advantage of a co-operative and intelligent subject who was able to give a clear and detached account of his experience, limitations are imposed by someone who has not been under medical care, who has volunteered help and who lives a long way off. As soon as we heard from Mr. Kovish we wrote asking him to send us a full and exact account of what had happened to him. He supplied us with this is a series of letters and a carefully prepared schedule. His first letter was written about two months after the episode which we shall describe occurred. Then by good luck in early November, 1956, business took us to New York and on the day of the presidential election, Mr. Kovish flew in to join us. He spent nine hours with us. We had two meals with him, recorded nearly an hour of questioning on a dictaphone and at the end of the meeting we each recorded our impression. We sent him a transcript of our recording and asked for his comments. We received letters from his wife and a friend who plays a large part in the story.

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Early in 1957, we were able to make separate visits to Mr. Kovish's home town, and each of us spent most of two days with him, seeing him in his home and at his place of business. We questioned his wife, his brother, his friend, and saw him with his children and with colleagues. So we have been able to compare the account that he had given of himself in his letters and in New York with what we saw on the spot. We feel that we have checked his statement thoroughly and so far as clinical evidence in psychiatry can be accurate, this is. We concluded that he is an unusually successful young businessman, much above average in intelligence and alertness, who by his mid-thirties has worked himself up from poverty to substantial affluence. We did not consider that he was engaged in a publicity-seeking prank or suffering from a delusional illness. Our method prevented us from undertaking many procedures usually thought necessary in psychiatric examination. But, on balance we believe that by denying ourselves formal investigations and tests of various sorts we have gained more than we lost.

In addition to information collected from Mr. Kovish, we have been able through the kindness of the Connaught Laboratories, Toronto and the Parke, Davis Company of Canada, to examine over 500 bottles of the 1 per cent. adrenalin solution used by asthmatics—every bottle had been returned to them because it was discoloured.

We have further made a small number of personal experiments to see whether we could throw any light on Mr. Kovish's story. These experiments, while not conclusive, are we think suggestive.

Our data then are mainly descriptive and biographical. They have been collected and checked with care. We hope that we succeeded in doing this without wearying our subject who was most generous with his time and hospitality.

Letter from Mr. Kovish Dated July, 1956

"My interest in your article is a personal one as it deals with an experience which I endured and which may be of some interest to you. I have had asthma and have used an adrenalin spray for the past 15 years (1:100 in strength). For the past seven years I have usually only had to use the spray at night before going to bed. I have noticed no unfavourable effects from its use except that about 10 years ago I used some discoloured adrenalin and had headaches and became dizzy. I have always felt myself to be a normal individual—unneurotic and with a zest for living. It was therefore quite a shock to me to find one day that I had suddenly become an individual who: (1) saw the world as through a distorted glass—I sought to interpret the visual distortions as being due to strange mental processes, (2) became quite anxious and depressive, (3) had compulsive thoughts, and (4) began to doubt myself and my sanity. I became quite panicky for I had never experienced anything even remotely like these feelings. They were alien to me and I had nothing to compare them to. I could only conclude that something had gone wrong with me psychologically. However, because I am very organically oriented, I felt for a few fleeting moments that since I had never had any of these strange feelings before (in fact, they were diametrically opposite to the feelings which I had always had), there might be a physiological basis. The only drug that I had taken was adrenalin and I recalled that this had all started one night about two months ago when I had been travelling and needed adrenalin. I stopped at a drug store and the druggist said that all he had was one bottle of adrenalin but that it was quite discoloured; he seemed hesitant to sell it to me but I bought it anyway. I was able to fix the day all my unrest started as the day I used the discoloured adrenalin. However,

I dismissed this from my mind as being pure coincidence and felt that I was just rationalizing and that I was actually having a mental 'breakdown'. This threw me into a panic and I spiralled downward and was getting progressively worse. (In the meantime I kept taking the 'bad' adrenalin for about a month at various intervals until I had finished the bottle.) I was thoroughly frightened and ashamed at what was happening to me as I attached a stigma to mental imbalance. I think I should point out that my off thoughts, discomforts, etc. were all internal and that my associates did not comment on any difference in my behaviour; however, internally I was in a state of terrific strain and almost collapsed at times.

"About three weeks ago I felt so bad that I discussed this with a botanist friend of mine, who knows me quite well. She would not agree that psychologically I could have so drastically changed, and asked me if I could think of any physiological cause to lay this to. When I casually mentioned the adrenalin, my friend immediately reminded me of Gerard's article in last August's *Science* on 'Biological Roots of Psychiatry' in which he discussed breakdown products of adrenalin as causing temporary psychoses. In re-reading Gerard's article I found a description that seemed to fit my feelings exactly. I wrote Dr. —— for further information on this subject and he referred me to your article.

"I became better—due mostly to the insight into the cause of my disturbance. I felt that the adrenalin effects would wear off, hoping that none of them were irreversible. However, while my mental outlook progressed to normalcy, I still felt physiologically different: (1) I had always been a sound sleeper. Now I developed insomnia, easy arousal, and strange hypnagogic effects before sleep came. (2) I seemed to have a dull, anxious feeling inside me. (3) There was heightened nervous attention to my surroundings. (4) One of the strangest occurrences was that despite my lack of sleep and my not taking adrenalin, I had no asthma and felt almost as if I had just taken adrenalin.

"I began to think that I had been using the adrenalin as a handy handle to lay my troubles to—because it would seem that after several weeks the adrenalin should have been removed from my system. Was I actually becoming a neurotic? This again caused me to feel panicky. Forcing myself to look at this scientifically, I wondered if the adrenochrome might have triggered off a metabolic change, affecting my own adrenal functioning and causing continuing disturbance. I looked up your article and found it extremely interesting as it describes in so many ways my own feelings during the episode.

"Had I known that I was going to have an artificially-induced psychosis, I am sure the severity of the consequences would not have been felt because, not knowing the origin, I ascribed it to psychic difficulties and this led me deeper into my feelings of unrest, I went into a tailspin, and perhaps this had something to do with the length of the effect. I also should mention that I was in a personally stressful situation which might have been a contributing factor."

Table Prepared by Mr. Kovish, September, 1956

Time	Symptoms	Comments
Sunday, 20 May (11 p.m.)	Before adrenalin felt fine, very normal. After, vividness of surroundings.	Took adrenalin (Epinephrine 1:100 inhalation Parke, Davis) of wine (grape) colour with definite amber tint. Took it several times through the evening. I recall inhaling through the nose as well as through the mouth.

Time	Symptoms	Comments
Monday, 21 May	Unusually awake. Difficulty in judgment in driving. Some bizarre thoughts. Distorted vision, no people on the road.	Took it again in the morning at approximately four o'clock.
Tuesday, 22 May	Tendency toward fixed thinking. Feelings of excitement for no apparent reason. Surroundings especially people (men much more so than women) looked peculiar, including pictures in newspapers.	Took adrenalin probably twice; in the evening and in the morning with a possibility of taking it in the middle of the night.
Wednesday, 23 May	Some anxiety. Visual sensitivity which appeared somehow as distortions. I believe there were some fixed strange thoughts.	Adrenalin again two or three times.
Thursday, 24 May	Great personal shock. Accident to friend. Mounting anxieties and unrealness.	Anxiety has never been a noticeable part of my personality. I can never recollect anxiety ever in the form that it was developing.
Friday, 25 May through Sunday, 27 May	Anxieties and internal excitement. Visual sensitivity and distortions, strangeness. Compulsive thoughts recognized as not being based on reality therefore considered delusionary.	Adrenalin approximately three times a day. The taking of adrenalin (Epinephrine) was a matter of habit. I would take it before sleep in order to assure the wheezing did not disturb me. If I woke up in the middle of the night I would take it again as a matter of habit, and sometimes in the morning I would do the same. Intake therefore is approximately the same as the first night.
Sunday, 27 May through Thursday, 31 May	Anxiety. Depression. Compulsive thoughts. No relation to reality. Some panic realizing I was not able to shake the bizarre thoughts. Thoughts seemed to be connected with the visual appearance of people.	I spoke about it to a friend (due to the nature of the thoughts, see detailed report). It was dismissed as of no importance and possibly connected to the anxiety-producing situation that I was involved in. Adrenalin (Epinephrine) intake approximately the same as before.
Thursday, 31 May to Tuesday, 5 June	Increasing tension. Increasing noticeability of strangeness of visual reactions. Increasing panic. Increasing compulsive thinking. I reproached myself for all the things I had confidence and belief in, my work, etc.	The panic element was increasing greatly. As it was evident that I could not wilfully get rid of the strange feelings that I was experiencing. I was definite that there was something wrong with me mentally which frightened me. The more frightened I got, the worse it became.
Tuesday, 5 June (Flew to Florida)	Fear. Threatening and foreboding feelings. Groups of people accelerated my attention to surroundings that I never had had. Everything appearing to be as never seen before. Extreme anxiety. Was bothered by it while flying. Flying had never bothered me through any storms, or other anxiety-producing situation and had never bothered me previously.	Adrenalin intake the same. *Note:* Somewhere, I cannot recall the time, I purchased another bottle of adrenalin and used part of it. Still seemed to be taking adrenalin as a habit although I did not seem to need it as I had before.

Time	Symptoms	Comments
Wednesday, 6 June and Thursday, 7 June	Continued anxiety and agitation.	I noticed that in the movies the figures on the screen seemed to increase my discomfort.
Friday, 8 June	Extreme anxiety, almost unbearable. Agitation due to continuing feelings that I could not stop the situation and return to normal.	Still taking adrenalin.
Returned from Florida		
From Friday, 8 June to Wednesday, 27 June	Recollection unclear of detailed dates. Anxiety. Tension. Visual strangeness. Depression. Compulsive internal thoughts.	Still taking adrenalin.
Wednesday, 27 June	This was an extremely bad day for me. Anxieties. Worries. Difficulty in driving at night. Extremely bad, almost unbearable. Panic.	Adrenalin taken the same. I believe that it is around this time that I must have been using different adrenalin. As I recollect, the clean adrenalin still had some colouring left from the inside of my bottle. Whether it was the same colour as originally, I do not know, inasmuch as small parts of tobacco sometimes get into my nebulizer. However I think I alternated between the two. (The other bottle was Epinephrine Solution 1:100, Burroughs Wellcome & Co.)
From Wednesday, 27 June to Wednesday, 4 July	Compulsive thoughts. Visual stimuli the same. Anxiety and depression.	Found it hard to concentrate on other thinking which I normally would have occupied myself with. My whole mental activity was at a qualitatively different nature than it had been prior to the initial taking of the adrenalin.
Tuesday, 10 July Trip to Newhaven	Anxiety was bad. Compulsive thinking.	However, I was looking forward to discussing my situation and felt that if it was personal anxiety that I would find out. I found that I did not need to use the adrenalin; something which I had felt for some time. I decided not to use it. Probably used it only four times on the trip.
From Tuesday, 10 July to Friday, 13 July	The anxiety was not as bad. Depression not as bad.	I spent my time fully discussing every aspect with a very close friend.
Friday, 13 July	Improved, but still in the background.	I had a discussion where adrenalin was first mentioned as a possible cause. *I stopped taking adrenalin.*
Saturday, 14 July	Greatly improved.	The thought that it could be adrenalin seemed to aid me greatly.
Sunday, 15 July	Much better. Only occasional thoughts.	
Returned from Worcester.		
Monday, 16 July	Again great improvement.	Read Gerard's article.
From Monday, 16 July to Saturday, 4 August	Varying, but sometimes feeling worse and some days feeling almost normal.	Would feel worse when I lost insight and thought perhaps it was not the adrenalin.

Time	Symptoms	Comments
Saturday, 4 August	In the afternoon picked up book. Fair in my feeling of strangeness.	Read article by Hoffer and Osmond. Tremendous qualitative difference in feeling. Felt a sustained recovery (I felt that this article was specific in that I could test my feelings against others, where Gerard's was so general). Once the feeling of sureness, every day seemed better than the last. What helped most was when I found that the drug *should* wear off and not be retained. This thought helped me see an end to the ordeal.
Friday, 24 August	Went fishing. Felt good. Broke a bone in my foot and ruptured a blood vessel. Still felt good but felt depressed when thinking about my past experience. A general feeling of unease. (This was occurring less and less.)	
Month of September	Through the month of September only thought about the strangeness of the episode and therefore still looked for visual distortions rarely, but would notice none. Returned to normal physiological and psychological feelings.	
Monday, 17 September	Short of breath with the change of weather to cold. (Something that seems to happen every year.) Have again taken adrenalin every night and sometimes in the morning. Feel entirely normal except an occasional worry as to whether the whole episode showed some imbalance in myself, and at present, am very productive, physiologically normal, psychologically alert and have been able to do a great deal of planning and feel myself as I used to be. The tendency to dispersonalization seems to be entirely reversed as I feel as I used to.	

General Comments

1. All through the time from start to present (actually the situation has been on for 1½ years, sometimes much, much worse without any feeling of the kind noted or anxiety) I have been in a personally anxiety-producing state. However, now that I am back to normal, it does not bother me, and it did not before I took the Epinephrine (discoloured).

2. My physiological feelings can be described (when I stopped taking the Epinephrine) as insomnia—not being sleepy, not falling asleep at times for a whole night, then trembling especially of the lower lip when I laid down, as if I was too "charged up", uncertain visual patterns and shapes (few times) right before I dropped off to sleep (never experienced before or since), feeling aroused and much nervous energy. No asthma or wheezing at night under any circumstances (except once when I was at the home of a friend who had dogs), completely without the symptoms (asthmatic), even after heavy exercises.

It can be summed up by saying I felt like one is supposed to feel when they have had a lot of adrenalin.

3. I experienced several anxiety-producing situations; one in a talk and a drive to another city (21 August). I looked with dread on both (normally I would have been looking forward to it). I felt that driving for several hours and alone with my thoughts would re-activate my anxiety and fear and compulsive thinking. It did not (that gave me self-confidence). Another time when I went to a doctor for a urine analysis for an insurance policy, I was called and told to come back in two days as there was something wrong. While anxious for a

while, it was a normal anxiety and did not cause me any recurrence (14 August, 1956).

Personal data: Born 7 September, 1922; married; two children.

His friend writes, "In answer to your questions, I did look at the discoloured adrenalin but I don't actually remember what it looked like. I feel the colour I name is almost a guess. I do vaguely remember it to be a sort of colour of rose wine, a light yellowish rose. He did mention its being discoloured but took it nevertheless. At first I didn't feel his upsetness was more than I would have expected under the circumstances, but this may have been because he didn't tell me how bad he felt so as not to worry me. He said that when he was with me he felt good and like himself. I made him feel normal again, and it was when we were apart that he had the strange thoughts, fears etc. His feelings as he described to me were very strange for him, not at all like him. He told me details of his extreme feelings of anxiety, strange visual perceptions etc. He was looking for all sorts of psychological causes for these feelings rather than looking more objectively for physiological explanations as I would have expected him to do. I kept trying to find a cause for his extreme anxiety which he felt was out of line, even though he had expected to be upset by my going, he hadn't expected it to throw him that much. I asked him if he could think of anything unusual, any drug that he had taken, etc., which might account for this and he suddenly remembered the discoloured adrenalin but was loathe to lay the cause to it. I remembered Gerard's article, 'The Biological Roots of Psychiatry', in *Science* of August, 1955, in which he spoke of adrenalin metabolic products as being possible causes of mental disturbance. He went back to Chicago feeling immensely relieved that the adrenalin might be the cause of his troubles. He had always been so sure of himself, so proud of his way of thinking and so unneurotic, so having these thoughts came as a terrific shock to him. Yet he kept saying he didn't want to lay all the blame on the adrenalin but I was sure that was it. He never showed any strange symptoms, had any thoughts or feelings before the adrenalin as he did in the period after taking it.

"I felt the episode was very unlike him and from his report he is entirely better now. When I last met him he was (at the end of January, 1957) completely his old self, but that's not surprising. He always acted and felt okay when with me. He used occasionally to fear the possible recurrence of anxiety thoughts but didn't get them. What I think is most amazing is he doesn't ever need to take adrenalin any more. No more asthma."

This lady's report, like that of his wife and brother and his own account, bears out our impression that this was an exceptionally disturbing event and one that was unique for Mr. Kovish.

Part of Dictaphone Transcription of Meeting with Mr. Kovish in New York on 6 November, 1956

Osmond—I wonder perhaps now if you would tell us a little about the unusual disturbances in perception you had, particularly those dealing with seeing groups of people. I think those were extremely interesting and we would like to hear a little more about them.

Kovish—I remember groups of people bothering me. I felt that there was something distorted or different appearing about them. This was not localized to any one person. There was a strangeness about seeing groups of people which had a somewhat frightening effect on me. I noticed distortion in many things, some animate and some inanimate. As far as the animate subjects went, it did not seem to me that women looked strange but it seemed to me that the

faces of the men particularly had a different sort of appearance than I had ever seemed to have noticed before. I can't really explain it, except to me, it seemed sort of distorted. In order to try to find an explanation to myself for this, I recalled a conversation of just a little while previous to this happening with some psychologist friends of mine about a review I had read in which it had been stated that one of the tests for latent homosexuality according to one of the writers was the fact that the recognition of an object of the same sex means latent homosexuality. I am heterosexual; it did not affect my sex life. I did not feel that I was a latent homosexual or a homosexual or anything. However, this thing became very obsessive to me. I thought that the possibility of what if I was and it seemed to me that it was the only reasonable explanation that I had heard as scientifically minded people had written something about this—that if people appeared distorted to me, especially men, that maybe I was. However, the peculiar part of this, and it bothered me, at no time did I believe I was, at no time did I feel that I was or were there any reactions of that nature to suggest that I did and the fact that I couldn't shake off something which to me was so ridiculous to my mind, so untenable, frightened me considerably.

Hoffer—One question Mr. Kovish regarding your vision. How long have you been wearing glasses, and during this period were you especially sensitive regarding your eyes or the eyes of other people and did you notice any type of visual disturbance that you have not had before or since?

Kovish—I thought quite a bit of it at the time. I have been wearing glasses since I was seventeen years old and did not associate any visual problem with it, except that I wore my glasses, sun glasses, more than I had, I seemed to be sensitive to light and I felt the direct relationship between my visual distortions, when I say visual distortions, it is hard to describe. I saw people more or less like I have seen before except that they impressed me differently, and this was very frightening to me and what happened was that I panicked, I mean, I could find no logical reason for this strange thing that was happening to me and I spiralled downwards to the depth of despair at having lost my mind and I felt that that was a very disgraceful and shameful thing to do.

Osmond—May I add at this point. You say that it seemed as if you had seen these people before. I wonder if you could pick that point up and the other point in which you say inanimate objects also seemed to have changed. Could you give us some examples as exact as possible.

Kovish—When I say I saw these people before, I meant that they were people who were very familiar, who I had seen all the time and never thought a thing about. I had seen them all my life, some of them. There were no distortions previous. All of a sudden, they appeared strange to me. There wasn't a strangeness, such as two heads and four arms; it seemed to be some strangeness that was inherent in what I was seeing and yet nothing that was recognizable as to being that different to me in their appearance and this is what bothered me. All of a sudden if I saw horns growing out of their heads, I don't think I would have been nearly as worried. I would have known that I had gone stark raving mad but the fact was that there was something that I couldn't quite fathom happening to my visual perception. This was greatly noticed by me at the time when I was worst off where I went to a movie. Movies to me have been sort of an escape and instead, it seemed the figures on the screen, well put me in a state of anxiety and despair and certainly, there was nothing relaxing. One that I have just recently come out of, that is I can go to movies and think, how can I ever feel that way; it still has a triggering aspect of making me think of how I felt

then even though I feel or see nothing different. As far as inanimate objects, it was a certain change which can hardly be described. It was an internal change. I mean, this girl and I were riding in a car and I told her that—and she repeated this to me later, I can remember her saying it but it was good that she witnessed it, because I didn't know of any way I'd expressed it before—I said that it seems like the trees are foreboding, it seems like the road is threatening to me. I mean I described to her what seemed to be a strange feeling and yet there isn't any real change in my vision except what I look at seems to disturb me internally and that is about the best way I can describe how inanimate objects affect me.

Osmond—When you were driving the automobile or being driven in it, did you notice any difficulties in perception then in particular regarding time and distance?

Kovish—Yes. Again, it wasn't anything that I could rationalize. I noticed, for example, one evening after I first took the adrenalin, coming back at night, I had driven the road many times. It was about four o'clock in the morning. I usually fall asleep quite often on the road, barely avoiding getting killed. Well, this night after having driven several hundreds of miles during the day and having had no sleep at all over the weekend to amount to anything, in driving the road looked different to me. It was a very familiar road. I was alert to an extreme that I had not been alert previously and I recalled going off the road which I had done in the past only under the influence of being sleepy but not on the influence of being awake. I have done much driving, sometimes on test runs and considered myself a very skilful driver. This seemed to me extremely strange.

Osmond—When you say that you saw familiar people looking strange, how about strange people, the figures you saw in the film.

Kovish—I think I should say that I was able to reconcile myself to the familiar people very easily, by saying—now look, you have seen these people before. They are not really changed. They haven't changed. It's got to be you and I wouldn't think about them being strange; so it was only the passing time when I first see them. Everybody else passing on the street, everybody would institute these thoughts in my head that there was something different about them. I felt in some instances—I remember this was the strangest thing—I was getting a haircut and I remember I have seen the barber before but I never recall having a haircut by him but it seemed to me that he seemed quite different being as close to me as he was, quite strange and I felt, for instance, I don't know as I would say threatened but I didn't feel comfortable. This is as close as I can get. I really can't. I really don't want to answer that because I don't recollect anything except feelings of foreboding which I felt were generalized and not specific to any one person. However, I am sure that there was some feeling of that, it couldn't have been that strong for an individual person. I think it was more—, for example, I would stand in a crowd, like at an airport, like Washington airport; I used to enjoy standing in airports and watching all the strange people going by. I mean everybody looked different; it was a pleasure observing people going by. However, the very hurry of the people going by disturbed me greatly and initiated these compulsive thoughts in my mind—why am I looking at them and so on. Actually standing in an airport was—became a hideous torture to me rather than any pleasurable thing as it had always been in the past.

Osmond—How about relationships with those close to you—your own wife and children and your close relations, like your brother and people of that sort. Were these either enhanced or altered or did they remain just the same?

Kovish—I would say, that it is my point of view, knowing that there was something wrong, I tried to be understanding in my relationships with other people but I was extremely irritable, felt low, couldn't participate in the normal social functions of my family that I always had, such as playing with the children properly and discussing things with my wife and things of that sort. I would like to go back to this physical, the inanimate objects again. I just happened to recollect that I did feel extremely—in flying, in other things which I normally take for granted, that I do quite a bit of, or even driving—I did feel a sense of foreboding and threatening. I don't think I can put it in any more general form, except that I became almost terror stricken at times for no apparent reason.

Osmond—When you were driving, were you certain where the other vehicles were?

Kovish—I feel, I feel that there was some impairment in that, but it was of such a nature that it was only relative to previous feelings that I had nothing really to measure it by. I did feel that, for example, lights of a car would come, all of a sudden, it was just as if I had gotten a shock reaction. I felt that it was going to hit me or something of that sort. That is the only thing that I can recollect.

Hoffer—Were you aware of any movement in your visual field either around the edges or in the centre, any type of slight quivery movement.

Kovish—I don't believe so.

Osmond—I wonder if you would perhaps put on this record the bit you told us about the family and the history. It needn't be too long.

Kovish—I have given considerable thought as to my family history and was unable to find anybody who had either required any kind of doctor's care for mental illness or any kind of upsets or breakdowns of any sort that seemed to me——. The only thing that I found was that my brother at approximately I would say the age of fourteen, I don't know exactly, he is twenty-eight, I think had some strange sensations which were diagnosed as epilepsy. I wasn't living at home at the time. I had never seen them. I guess they were rather rare. I understand they don't recur but it has never been discussed. He doesn't like to discuss it. I actually lived and worked with him for over ten years and have never noticed this in him. He is also asthmatic and I have found, as far as I can see, I think he must have had some sort of minor epileptic episode at one time in his life. I know nothing more about it. Mentally, he cannot be classified as either neurotic or psychotic or having any tendencies that I can see and I have known him very closely.

History and Description of Mr. Kovish

He is a personable man in his middle thirties, about 5 feet 8 inches. His body build is lean and muscular, though by no means lacking in a fat component (Sheldon would describe him as being a mesomorphic with ectomorphic features, though by no means endopenic). He moves gracefully and is neat and well turned out, though not dandified. His co-ordination is excellent. He drives a car with skill and aplomb. His hair is dark and plenty of it, his features aquiline, his skin clear and without blemishes, his eyes brown. His beard growth though strong is not excessive.

His manner is friendly and open. He can state his opinion and hold his own in discussion on a variety of subjects without being either subservient or overbearing. He has a lively sense of humour, and although of a curious and enquiring nature, is tactful, so that he is not in the least impertinent.

He was born in New York of poor Jewish parents. His father worked as a garbage collector and secondhand clothes dealer. His mother, who is still alive, managed to keep the family going in spite of many difficulties. He did well at school but left early to earn. At 14 he began as a helper in a small construction firm. He soon acquired extra skills by attending night school, correspondence courses, etc. and achieved a high degree of mastery in his work. He became recognized as an expert in developments in structural engineering so advanced that they are only just finding a place in formal engineering education. Patents which he made on some inventions have allowed him a great amount of independence. His work in recent years is largely of a consulting nature.

He was always keen on Trades Union work and this interest has not been reduced by his new status of a semi-managerial sort. He is a radical, anti-racketeer and anti-communist. He is very critical of both political parties and votes for neither, but he is not indifferent to politics. He is sharply aware of the shortcomings of the society in which he lives and does what he can to encourage those with whom he comes in contact to think. He has not however become either a bore or a fanatic on this account. To further his knowledge he has an honorary position in a social science department of a local university where he puts his knowledge of the construction industry at the disposal of the scientists.

Apart from asthma his health has been excellent and although this sometimes troubled him gravely, it has never prevented him from leading a full life. He has taken adrenalin by inhalation regularly for at least a decade and has never had any disturbance from it previous to the one we report here apart from a light headache when he took some that had turned black. Changes in weather he considered affected his asthma much more than fluctuations in his emotional life.

His family have been healthy. He knows of no one who suffered from serious mental illness. His younger brother has asthma and hay fever and may have had minor epilepsy in childhood.

Mr. Kovish does not consider himself nervous nor does his wife, his brother or a friend. Rather the reverse—they say he is a man with good reserves of humour and optimism even when things seem difficult. Consequently they were very much surprised and disturbed when he seemed so unlike himself in mid-1956. They had none of them seen him like this before. His brother says he will sometimes withdraw from a party or conversation, but this is only when he is preoccupied with new ideas in his work. Mr. Kovish prides himself on his ability to cope with social, professional, business and domestic problems. It was very distressing for him to be unsure whether he could do this any more.

He holds that he is sexually well adjusted. In his subculture, sex mores were free with little guilt and no recrimination. He has never been much preoccupied with sex as a problem because it was not considered to be one. He married twelve years ago, has two children. In the last three years he has been in love with a married lady. For various reasons they both recognize that nothing can be done about this. His wife and he have not quarrelled over this, they had discussed the matter freely so that it has been less a source of tension than of puzzlement as to what was the right thing to do. When Mr. Kovish took the wine-coloured adrenalin solution this situation had been in existence for at least eighteen months, and far from becoming more difficult he considers that he was getting accustomed to it. Shortly after he first took the wine-coloured adrenalin his friend broke her arm and also left town, although this was long expected and prior to it had not been looked on as a source of worry. He ascribed his upset to this.

Out-of-Date Adrenalin for Inhalation

Mr. Kovish remarked on the unusual colour of the adrenalin solution which he bought on the evening of 20 May. It seemed odd to us if asthmatics frequently take a wine-coloured solution that more cases of this sort have not been reported. We were assured by the Connaught Laboratories and the Parke, Davis Company of Canada that they have not heard of any. While this might be due to failure to see any connection between discoloured adrenalin and the development of psychotic-like conditions, another possibility is that commercial adrenalin very rarely goes this colour. Thanks to the courtesy of these two manufacturers, we have now examined over 500 bottles of discoloured 1 per cent. adrenalin solution used for inhalation. This solution was examined by eye and then samples of the discoloured material were examined spectroscopically.

Mr. R. Hall, R.P.N., S.P.N.A., examined the solutions and used this procedure. Any solution that was pink, red or yellow was preserved. Brown solutions, of which there were many, were discarded except for a sample which was then examined spectroscopically by one of us. These solutions which range from cloudy brownish to some having a thick black precipitate, gave no evidence of adrenolutin or adrenochrome. There were no pink or yellow solutions.

It seems that adrenalin solutions used for inhalation turn wine-coloured very rarely though it might be a wise precaution to advise asthmatic people very strongly against using any discoloured adrenalin, but particularly that with a pinkish, reddish or bright yellow hue.

Our Experiments

We are reporting two incomplete series of experiments because they illustrate some of the difficulties inherent in research of this sort. These experiments are inconclusive but we think they are interesting and suggestive. Their design is, of course, unsatisfactory, a common feature of early work. With Mr. Kovish's experience, they may be worth following up.

A.H.'s Experiments

These were begun as an exploration after we had heard of the effect of inhaled discoloured adrenalin on Mr. Kovish. Later we started a double blind design but discontinued it after we found that our adrenolutin had deteriorated. Using resin absorption columns, we have estimated that only 25 per cent. of our adrenolutin was the pure substance. The rest of it had become a variety of melanin-like compounds. We have included details of two out of five of these experiments, all of which showed in our view significant, though small changes. Minor changes of this sort are hard to describe accurately.

First Experiment—Inhaled Adrenolutin

Adrenolutin Experiment—A. Hoffer

20 September, 1956

2.10 p.m. Inhaled ½ mg. of adrenolutin in phosphate buffer at pH 7·25.
2.18 p.m. An additional ½ mg. in buffer.
2.15 p.m. Slight suggestion of tension in the temples similar to onset of headache. No change in pulse rate.
2.25 p.m. No noticeable change.
2.26 p.m. Slight moistening of palms of my hands and heavy sensation in temples.

2.27 p.m. Slight feeling of unsteadiness while working, still a suggestion of headache, speech feels a bit thick, and no change in pulse.
2.58 p.m. Slight feeling of unsteadiness since last report. Spent time with Dr. —— discussing some somato-typing. Found this dull. He appeared very distant from me. Feel less secure with myself. Palms are still sweaty. Headache definitely present but a bit higher on temples. Some difficulty in focusing vision.
3.20 p.m. Headache is gone; feel more secure. Spent some time with Dr. ——. Feel not in control of the situation.
3.55 p.m. Feel quite normal now.
4.00 p.m. 1 mg. adrenolutin taken—same preparation as above. It is now appreciably darker than it was.
4.24 p.m. Feel tired, disinterested and sweaty.
4.25 p.m. Sweating palms.
4.29 p.m. Still sweaty and feel warm. At this time, the room was warm and Miss —— opened the window without noticing that I felt warm.
4.45 p.m. Feel O.K.

Fourth Adrenolutin Experiment (Inhaled)

5 October, 1956

I inhaled 20 sprays, approximately 1 ml. at 11.00 a.m. of the usual adrenolutin preparation in saline and phosphate. About two minutes afterwards, I noticed the same sensation of tension in my forehead, a slight sweating and a continual feeling of tension around the forehead and eyes for about twenty minutes.

About 11.30, I was interrupted by a visit from some senior members of our department who strongly supported the research programme and advised me that we would not be short of funds. This produced in me a strong feeling of euphoria which continued throughout the day.

At noon, I noticed no effects from the drug and concluded that I had had placebo. I had a normal lunch but was over-talkative at the luncheon table. We had just received an extension ladder which I had ordered and as I had not yet put on my storm windows, I decided to try out the ladder. As the coffee was not quite ready, I went out and put up a couple of windows in between the main course and my dessert. I noticed while putting up the windows some unsteadiness which I usually do not have and at one time while I was on top of the ladder with a window, I had the feeling that the bottom of the ladder was going away from the house. This was only momentary. I managed to put up a couple of windows and then finished my dessert. Looking back on this behaviour, it appears that my judgment was a bit off. I had had adrenolutin and this illustrates the importance of not making a prediction while under the possible influence of drug.

H.O.'s Account of His Experiments

One way of following up the lead that Mr. Kovish had given us was to inhale decomposed adrenalin as he had done and see what happened. Our original intention was to try a commercial sample of the sort that Mr. Kovish had used but this proved so resistant to oxidation, remaining gin-clear though boiled for several hours in a test tube, that instead a home-made solution was used.

Method of Preparation

Fifty mg. of adrenalin supplied by Dr. Hoffer was weighed and placed in a 15 ml. test tube. Five ml. of normal saline was added. Only a little of the adrenalin dissolved, most lay in the bottom of the tube. The supernatant fluid slowly went a pinkish colour and to speed this up it was placed in hot water. When the adrenalin failed to dissolve when put in hot water, two to three drops of dilute hydrochloric acid were added. The residual adrenalin then disappeared and the solution became a very pale pink. This solution was then placed in hot, not boiling water for perhaps one to one and a half hours and became a clear salmon pink or "vin-rosé" colour. Another tube started at the same time but heated longer before the acid was added became a pale sherry colour. This was done on the evening of 16 October, 1956 and the two tubes spent the night in the deep freeze of the refrigerator. Next morning (17 October, 1956) the sherry coloured tube (yellow) had frozen solid and on unfreezing it seemed darker than before with some brownish pigment showing. The vin rose-coloured tube was not frozen solid but lying in the pinkish liquid were some long, lanceolate crystals which were transparent and white. These disappeared on warming. The two tubes remained on ice outside the deep freeze but did not freeze again. Their colour remained constant to the eye and stayed so for several weeks when kept in the refrigerator.

The First Experiment

To make this account more understandable, a few domestic details may help. My daughter was ill with 'flu on the evening of the experiment and was sleeping in our bedroom with my wife. I had not told my wife of the projected experiment because a minor one a few days previously had been negative and I expected this one to be so too. I was confident that nothing much would happen. I had a notebook on hand and prepared to make continuous notes. I did not have a recorder. I used a deVilbiss 33 sprayer which throws a fine cloud of small particles which can be inhaled easily. It takes about three minutes of vigorous pumping to get 1 c.c. into the mouth. I put a little more than 1 c.c. into the sprayer which would mean about 10 mg. or so of adrenalin and its derivatives. My concern was that I might be made uncomfortable by the residual adrenalin. However, I know that I am sensitive to it and respond quickly. So placing the sprayer in my mouth, I made a few squirts and inhaled deeply and watched carefully for sweating, palpitation, dryness of the mouth, or any change in pulse. None came. My resting pulse is 64 to 70 and during the experiment it remained steadily at about 66.

The first inhalation was at midnight 18 October, 1956 and the notes read as follows:

At 00.05: "I noticed things seemed very clear. A piggy bank of Helen's (my daughter) held my eye quite a time. *No* palpitations, sweating, tremors or dry mouth." By 00.15 hours I had had three good bouts of puffing. I felt there was some increased significance of objects and a raised general awareness. I looked in the mirror and noted that my pupils were not enlarged, my hand was steady. 00.22—Fifth puffing. "No very certain feeling except a slightly warm feeling in the face and a poised feeling, not unpleasant, of everything being sharp and significant."* 00.30—"Slight feeling of nausea, not very much, running nose. An undoubted sharpening of perception. Looking at my watch

* After reading the first draft of this article Mr. Kovish wrote to us "I could not have explained my first night reaction in any better terms, except to add the term colorful."

about three feet away, it seemed an immeasurable distance. Everything I look at holds the eye. The sinking feeling in the stomach definitely there. Mouth moist, slightly anaestheticy feeling in the roof of the mouth. Discomfort in the pit of the stomach. Pulse 64. Some bowel discomfort and farting." 00.35—"Marked bowel discomfort—sinking feeling in the pit of the stomach, not exactly nauseous, unpleasant. This may come from having swallowed the stuff." 00.45—"Defaecating, difficulty in writing because of sinking feeling. Stool well formed. Feel bad." 00.50—"Weak, solar plexus kicked feeling. Very uncomfortable, cannot write feel so ghastly." 01.00—"Very weak and uncomfortable. Kicked in the stomach feeling—objects hold me. Weak, very uncomfortable, alone, lonely, beyond feeling, cut off. Know this is very interesting, don't feel so. Very fatigued but wakeful, alert, uncomfortable and disinterested. Beastly. No headache. Can think clearly but no feeling. Can write but feel too weak to move." 01.10—"Another bowel movement. Suddenly began to feel much better. Hope it continues." 01.20—"Cleaned my teeth which I felt incapable of doing before and came back to bed. Still get discomfort but not so bad as before. Comes in waves. Not nauseating but very unpleasant. Only visual signs increased significance of objects." (No notes for the next three hours. My writing fades out on the pad at this point. I lay on my bed awake but did not like the bed clothes touching me. Objects had a curious significance; leaves on a tree outside might have been a snake. The size of the room seemed uncertain. I had great difficulty in initiating action. But once I managed to do this I could act. For instance, I let our dog out of my room. I was concerned that I might get worse and die—in a very detached way. I was perfectly well orientated and knew where I was. I knew that I wanted to write but I couldn't summon up the energy to do so. I seriously considered trying to summon a colleague or my wife, but felt that she would be worried and that the colleague, in his concern for me, might give me some morphine and that this might well kill me. I decided I was safer as I was.)

04.30—(notes continued). "Vomited. Incapable of writing in the interval. Awake but lessening discomfort. Curare-like effect, some slight visual disturbance, but most acute aspects have gone now.

(*i*) Either this stuff has a mule kick, or

(*ii*) I very suddenly developed flu at 00.00. I felt very well then and in no way expected anything of the sort."

10.45—Awoke about 07.45 feeling very weak but noticed the perceptual changes had gone. No nausea or vomiting or bowel discomfort but considerable lethargy. However, got up and felt much better. Have been at work. Don't look as if I'd been ill. No fever or dry mouth. Breath clean.

15.10—Did my rounds, attended conferences, made decisions as before. I do not even feel very tired.

20 October, 1956—I did a further experiment using the same vin rose-coloured substance which had been kept unchanged in the refrigerator. It remained in this condition for several weeks after, because I'd hoped we'd be able to analyse it but at the time we were not able to do so. The question was whether it was the fraction that had been atomized and inhaled which had been effective or the fraction which had been swallowed. I put 1 c.c. into a wine glass and noticed "odd etheric smell which is difficult to account for", taste "slightly burning". (Note: Although I had put a little more than 1 c.c. into the spray on 18 October, 1956, next morning there was still about half of this left so that at that time I must have got between 5 and 7 mg. of adrenalin by-products. This time I swallowed 10 mg. of adrenalin by-products.)

23.35—I wrote "the 1 c.c. must have 10 mg. of adrenalin by-products in it. I am somewhat apprehensive after my previous experience but this seems a necessary course of action. However I am hopeful that it will have no effect by this route. 'Little H.' (my daughter) making a beastly row, having woken howling. The cries are irritating and I am edgier than last time. Pulse 64."

23.45—"H. still bellowing. I feel irritable but this is probably not abnormal. Warm feeling in my substernal region unpleasantly reminiscent of the last episode." 23.50—"No heightening of perception yet. Some slight gastric dis comfort—heaviness, apprehension."

21 October, 1956. 00.05—"Quite marked discomfort, heaving feeling in the epigastrium—no perceptual changes. Though do feel very alert. I hope this damned thing is not starting all over again." 00.10—"Gut rumbling, belching, not very much, and farting (once). Pulse 67. No perceptual changes that I can notice at present. Am reading Slotkin's book with enjoyment though some concern about another night up and hope I am mistaken. What I'd not considered was that this stuff might become more potent on standing in the refrigerator."

00.25—"My impression is that the discomfort is less than last time. I have not yet had a bowel movement." 00.30—"Went to toilet but didn't have a bowel movement." 00.45—"Some discomfort, no lethargy, apathy or lack of energy. Reading Slotkin's book with keen enjoyment and marking relevant paragraphs. Keep wondering if this is just suggestibility, but don't think so. I am not commonly suggestible. It just seems a very minor variation on Thursday's massive theme." 00.55—"Unless something unexpected happens this is now passing over, a little belching and no more. Merely the ghost of that other night when at one time I thought I might die." 01.10—"Still some gut uncertainty but not very much. No weakness etc., I am going to sleep. Either the stuff's potency has fallen or it is less effective by the stomach than by the inhaled route." 09.00—"Awoke feeling well, if slightly tired—not irritable." I did a day's work without feeling any difficulty and had no residual troubles.

Discussion

1. *Mr. Kovish's Experience*

Those who work with psychotomimetic agents and who come to believe that they may serve as models of naturally occurring psychoses, find that much is made of the difference between the laboratory experiments and the illnesses being studied (usually schizophrenia). This criticism, so far as it goes, is valid. One might expect the critics would hasten to fill this gap in our knowledge by suitably designed experiments of their own. They have not done so, even though they repeatedly emphasize how slender a resemblance the highly artificial psychosocial setting of the laboratory can bear to real life; while the most refined double blind experiments usually leave the subject well aware that something is happening.

Why then do critics carp without advising, because they must know well enough the sort of experiment necessary to prove or disprove this point? It is simple and entails giving repeated doses of a particular psychotomimetic agent to an unsuspecting and unprepared subject without the knowledge of his family, friends or those with whom he works, while closely observing him for a more or less prolonged period. However scientifically desirable this might be, it is ethically impossible and would never occur unless nature took a hand.

Thanks to Mr. Kovish's permission and nature's co-operation, we have the nearest thing to the sort of experiment which it would be improper to essay.

What then happened to Mr. Kovish? A short time after oral inhalation of small quantities of a wine-coloured solution of 1:100 adrenalin hydrochloride he noticed some changes in the brightness of the room where he was. One of the persons has reported a rather similar experience after taking adrenochrome (15). While accounts of unusual light are not infrequent with schizophrenic people—for instance Madame Sechehaye's Renée (33) refers to it in this manner: ". . . I ran home to our garden and began to play 'to make things seem as they usually were', that is, to return to reality. It was the first appearance of those elements which were always present in later sensations of unreality: illimitable vastness, brilliant light and the gloss and smoothness of material things. I have no explanation of what happened or why."

Later in that same night while driving, although he felt alert and wakeful, he twice went off the road. We have reported a rather similar experience after adrenochrome. At first Mr. Kovish did not connect this with the discoloured adrenalin which he continued to inhale, as was his wont. He became aware of changes in perception of a subtle sort, especially when driving and when he saw groups of people. Because of previous discussion with a psychologist friend he wondered whether this might mean that he was a latent homosexual. He became unshakably pre-occupied with this disturbing thought. At the end of about a week of increasing discomfort and anxiety, he wondered whether the discoloured adrenalin could have anything to do with his predicament, but he dismissed this idea as a rationalization. His symptoms continued and his disturbances in perception and thinking were accompanied by anxiety and depression. These were noticed by his wife and brother who ascribed them to pre-existing domestic difficulties. He ruminated increasingly on the strange appearance of people. Here again this is not unlike Madame Sechehaye's Renee, "One day we were jumping rope at recess. Two little girls were turning a long rope while two others jumped in from either side to meet and cross over. When it came my turn I saw my partner jump towards me where we were to meet and cross over. I was seized with panic; I did not recognize her. Though I saw her as she was, still it was not she. She seemed to be smaller but the nearer we approached to each other the taller she grew, the more she swelled in size." There are many references in this excellent book to perceptual changes of this sort. Because of this rumination, his usual pre-occupation with his work, which is of a creative sort, was reduced. However, when he did get down to work he believes that its quality was if anything enhanced and he has evidence of this in some of the ideas and projects which came to him during that time. It is of course, hard to prove this but Parfitt (29) and Fitzherbert (11) both suggest that in some phases of schizophrenia, at the beginning of the illness in particular, intellectual performance may be increased. At the end of about four or five weeks in which he took the discoloured adrenalin, he diluted it with clear solution from another bottle.

When his friend suggested that the discoloured adrenalin might be responsible for his condition he stopped all adrenalin on Friday, 13 July. But it was not until 4 August, after reading the literature that he became convinced and his apprehension lifted. After this he improved rapidly. Some of the symptoms which he describes can be found in such famous accounts of schizophrenic illness as those of Boisen (5), Beers (4), Hennel (12), Ogdon (26), Judge Schreber (31) and Madame Sechehaye's Renee, already referred to, particularly in the early phases of their illnesses. They have also been described in experiments

with psychotomimetics such as mescaline, LSD-25, adrenochrome, adrenolutin, ololiuqui, ayaheusca, and hashish.

Again, it is particularly in the early phases of experience with these substances that one gets these "mild" but persistent disturbances. Mildness after all is a matter of one's viewpoint and Mr. Kovish himself has emphasized how much easier he would have felt had he seen people with two heads or with horns coming out of their foreheads. Then he'd have known for certain there was something wrong. As it was he was left in extreme uncertainty.

After our careful investigation of Mr. Kovish's story, we believe that he is telling the truth. We know that he is what he claims to be. But what can we learn from him? How could such a small quantity of decaying adrenalin produce such grave and sustained effects? The 5 c.c. of 1:100 adrenalin for inhalation can at the most contain only 50 mg. of degradation products lying between adrenalin and melanine. Is that enough? Our experiments with adrenochrome and adrenolutin suggested that by vein or by mouth doses of at least 20 mg. would be needed to produce these effects. and probably twice as much. How then could 50 mg. by inhalation produce such remarkable changes in him?

There are at least three explanations possible:

(*i*) Mr.Kovish might be unusually susceptible to adrenalin and its by-products. He has however taken it regularly for over ten years, sometimes in large quantities and has never had an experience of this sort. He seems, like many asthmatics, to be more tolerant of adrenalin than most people.

(*ii*) There may be a very powerful psychotomimetic agent or combination of agents in wine-coloured adrenalin. While our work with adrenochrome and adrenolutin gives some support to this, the colour described by Mr. Kovish is far too light for the whole 50 mg. to have been converted into adrenochrome or adrenolutin. Indeed it suggests that perhaps only a few hundred gamma and at the most a milligram of adrenalin had been changed to these brilliantly coloured compounds. Here is a hint that at least one other adrenalin derivative may be present whose existence we have suspected but not yet proved. We know that LSD-25 is effective in doses of 100 gamma or less, may it not be that an adrenalin derivative exists which is as powerful as the ergot compound?

(*iii*) Perhaps inhalation is more effective than other routes of admission. Hashish, opium and henbane (30) are particularly potent when inhaled. Hofmann's (35) original LSD-25 experience arose from accidental inhalation and so did Sherwood's (34) discovery of the psychotomimetic nature of his B.G.I. Cronheim (7) has shown that adrenalin itself is more effective given this way than by other routes.

Oddly enough at first the full implications of the lung route were lost on us because of an error, which readers of the Macy Foundations Transactions of the Second Conference of Neuropharmacology (2) will find, that we committed in company with far more learned men than ourselves. This was to assume that asthmatics commonly take adrenalin through their noses. To test this one of us snuffed up 50 mg. of adrenolutin with no effect except a handkerchief heavily stained with a melanine-like pigment. It is true that some South American Indians do inhale cohoba snuff, said to contain bufotenine, and an immensely powerful snuff derived from a nutmeg-like tree, through their noses but they use a specially designed apparatus for this which ensures that the particles of snuff are driven at high pressure into the lungs. Most asthmatics however, inhale their adrenalin by mouth using some sort of atomizer.

2. *Our Experiments*

A.H.'s experiments suggest that an exploration and comparison not only of adrenolutin but of every other psychotomimetic or psychedelic using the lung and other routes, is now overdue. It must be remembered that the adrenolutin that A.H. used was, owing to difficulties of manufacture, by no means pure. At most about half of the amount which he inhaled reached his lungs and if all of that was quickly absorbed, only about a fifth of that half went directly to the brain. Since we know that this quantity, about one-tenth of a milligram, taken by mouth or by vein, would be wholly ineffective, we are left with the strong hint that when adrenolutin can go directly to the brain by the lung route, it is enormously powerful. We have not yet been able to repeat this work on a large scale because of our continuing difficulties in synthesizing adrenolutin, but we believe that these have lately been solved.

H.O.'s experiments were intended to be part of a series starting with the pale pink substance which he describes, and moving slowly to darker and darker derivatives of adrenalin. Owing to the dramatic nature of the first experiment this orderly progress has been halted. The pale pink liquid cannot have contained very much adrenalin because it is unlikely that someone usually sensitive to this substance could have inhaled at least 3 mg. of it (for we may assume that about half of the 7 mg. was swallowed) in so short a space of time without noticing any pressor effects. Yet not very much adrenochrome was present for the salmon pink solution was far too pale to harbour much. It seems likely that there is some soluble, colourless, rose-tinted stable substance without pressor effects lying between adrenalin and adrenochrome. This substance may itself have psychotomimetic properties or may develop them in the course of its journey from the mouth to those brain centres which it seems to affect.

Adrenalin shares with serotonin, lysergic acid diethylamide and adrenochrome the ability to interfere with synaptic transmission of stimuli, Marrazzi (24). When administered into the ventricles of animals it produces changes in consciousness, Leimdorfer (21), and when given intramuscularly to humans, produces tension and anxiety (13) as well as an increase in blood pressure. Because it is toxic and strongly pressor, one cannot determine directly whether or not adrenalin is psychotomimetic. However, the molecular structure of adrenalin may be changed in such a way as to remove its pressor effect. In this event one might have a compound with interesting psychological properties.

The pressor activity of adrenalin may be removed by fusing the side chain with the benzene ring to form an indole; i.e. adrenochrome or adrenolutin or some similar substance or by adding another chemical radical to the free phenolic hydroxyls; e.g. methyl groups. Both adrenochrome and adrenolutin induce experimental changes in behaviour in cats (32), and in humans (14, 15). Adrenochrome changes the behaviour of the Siamese Fighting Fish (1).

When the phenolic hydroxyls are bound by methoxy groups, pressor activity is lost but whether or not these compounds are psychologically active is unknown. Mescaline, which of all the known hallucinogens resembles adrenalin most closely, has no pressor effect. 3·4-dimethyl-phenyl-ethyl-amine, more similar in structure to adrenaline than mescaline, produces experimental catatonia in cats, De Jong (8). It is reasonable to assume that an adrenalin compound with both phenolic hydroxyls bound might have interesting psychological properties.

Tryptamine, like adrenalin, is toxic and a potent pressor substance. In animals it induces experimental catatonia, De Jong (8), in dosages equivalent

in a man to 2 grams. However, about 50 mg. of dimethyl or diethyl tryptamine (Szara, 36) administered intramuscularly produces an experience very similar to that induced by LSD or mescaline, with no change in blood pressure.

It is thus possible that the detoxification of adrenalin *in vivo* under the influence of adrenochrome may result in the formation of a product having strong hallucinogenic properties.

But how does the lung route come to be so much more effective than the gastric or the intravenous? The former encounters the double barriers of stomach lining and liver before it reaches the general circulation and so the brain. But substances taken by vein do not go to the liver but travel only about 18 inches to the heart, and then to the lungs, so that about one-fifth of the amount injected should reach the brain. It is noteworthy that neither LSD-25 nor mescaline seem much more efficient when given by vein than given by the stomach, which suggests that the liver may not have very much immediate effect on either of them. LSD-25 inhaled does not seem to be very much more effective than when swallowed. What could happen in those eighteen inches or so to reduce the effectiveness of adrenolutin so greatly? We know that adrenalin (3) readily attaches itself to red cells and possibly the same things happen with adrenochrome and adrenolutin. This could account for the prolonged action of adrenolutin (15) when given either by vein or by mouth. Perhaps Mr. Kovish's unpleasant experience continued for some weeks after he had stopped taking adrenalin in any form because some of it was released from red cells when they were destroyed. This may be of some importance in a model for schizophrenia. If a naturally occurring psychotomimetic agent was stored in the red cells and possibly elsewhere in the reticulo-endothelial system, we have a mechanism which would become loaded with M-substance, and unless its production stopped almost entirely so that a prolonged period of detoxication occurred, the patient would remain ill.

Lovett Doust (23) has already shown that there is some peculiarity in the oxygen carrying capacity of the red cells in schizophrenia. While Boszormenyl-Nagy and Gerty (6) in Illinois have demonstrated that red cell metabolism is disturbed, he considers that something is wrong with the phosphorylating process.

It is also possible that the alveolar tissue of the lung, with its immense surface area covered with mucin and other potent substances, may in the presence of high concentrations of oxygen produce some unknown changes in some adrenalin derivatives. Whatever the explanation, there is clearly a rich field for research calling for immediate attention.

3. *Toxic States and Schizophrenic-Like Conditions*

Mr. Kovish's experience brings up the old question of the difference between "toxic" states and "true" schizophrenic like conditions. Where are we to pigeon-hole Mr. Kovish? In a sense this was a toxic state resulting from the regular admission of wine-coloured adrenalin. Yet in no sense does it resemble a toxic state of confusion. There was no confusion, no disorientation and no evidence whatever of clouding of consciousness, through the whole appalling five to six weeks. He said of this period, "Life did not have its full significance —I did not know whether I was awake or asleep." This is very close to Jung's (19) description of schizophrenia as a waking dream, or that excellent and evocative metaphor of Menninger's (25) "cold delirium". Attempts to differentiate between schizophrenic and toxic confusional conditions on an either/or basis suggest the possibility of a precision which for all its exact pretensions

is unsound and unscientific. What we are dealing with is a continuum with clouding and confusion at one end and disturbances of thinking and mood at the other, with changes in perception which can sometimes be common to both and may be absent from either. In such a continuum overlap is likely. Mr. Kovish's experience lies at the end without confusion and clouding, and so resembles that "cold delirium" or "waking dream" called schizophrenia. This simple notion, long ago noted by Louis Lewin (22) can save endless futile controversy as to whether some response is schizophrenic-like or not. The illness schizophrenia is in our view an end product of an interaction between a basic disturbance in brain function and the biopsychological endowment of the particular sufferer seen in a unique sociocultural setting. Such an illness could not be produced artificially for ethical reasons. Indeed as Johnson (18) has pointed out, to attempt to do so would be a form of criminal poisoning. Only in rare accidents of this sort can we expect to unravel some of the knotted strands.

Apart from such weighty matters, this story may help internists to pick up some similar cases and we trust that asthmatics will view their adrenalin with increased respect and caution.

So far those wishing to use the newer psychotomimetics have been prevented by the great difficulty in synthesizing them. Now, however, the sceptic or the enthusiast will not be incommoded by this and doubt can be speedily allayed. A bottle of 1:100 adrenalin solution, a few drops of hydrogen peroxide, a kitchen saucepan to speed up the change from adrenalin to adrenochrome, etc., a deVilbiss or other atomizer and a reasonable amount of caution is all that is necessary to prove or disprove our contention. We would emphasize that caution is essential, a proper recording apparatus desirable, that the effects may be subtle and prolonged and that if one's wife has a sick child, it is wise to have a colleague in to keep an eye on one. We hope in the near future to be publishing a method of preparing adrenochrome and adrenolutin which will make them more readily available than presently.

4. *The Significance of the Whole*

The involuntary prolonged experiment which Mr. Kovish made with some adrenalin catabolites and our own much less ambitious ones provide one with plenty to think about.

Changes in perception have been ascribed rather arbitrarily to prior changes in thought or mood. This seems to have sprung from Kraepelin's (20) dictum that perception was not disturbed in dementia praecox. True to his master, the great Wundt, Kraepelin made a distinction between perception and apperception. Wm. James (17) strongly disagreed with this separation which he held was misleading and artificial and his views seem to have only begun to percolate into psychiatry recently. So that psychiatrists have been comparatively unconcerned about disorders of perception in schizophrenia. Lately, refined testing techniques have shown perceptual anomalies in less acutely ill schizophrenic people but the most ill patients are still more or less inaccessible to the meticulous and lengthy testing necessary. The phenomenologist (37) and existentialist (9) psychiatrists in Europe and the widespread work with psychotomimetic agents of the last few years are now drawing more attention to perceptual disorders and the dismay and anxiety which they can easily provoke.

Mr. Kovish had unusual perceptions shortly after inhaling his wine-coloured adrenalin and later that evening they may have been the cause of his driving off the road. He continued to be plagued by them until some time after

he stopped all adrenalin. They were difficult to describe and he thinks it was the uncertainty which they engendered which disturbed him so much.

Language has been developed as a means of communicating socially recognized experience; experience which has no social recognition will not be represented by symbols allowing verbal communication, and in consequence it has no social reality. Language, as Whorf (39) has shown, restricts us to certain ways of describing our world which are usually effective in limiting what we perceive. This limitation is not however absolute, so that when we perceive something for which our language makes no provision we usually attempt to describe it in terms of something with which we and others are familiar. However, it may be that this does not communicate the experience because it is culturally inacceptable, so that the person whose perception differs from what is usual will, unless he is a deviant, become anxious and pre-occupied. Mr. Kovish could find no adequate way of rationalizing and so verbalizing these inexplicable happenings. The only explanation with which he was acquainted was a psychoanalytic one, so with some reservations he felt bound to consider it. A natural readiness to consider any explanation for inexplicable occurrences makes one sceptical of some of the formulations which psychoanalysts have elaborated to account for the genesis and symptomatology of psychotic illnesses. Have they forgotten the common human failing of demanding some explanations for weird happenings of any sort? Everyone likes to be able to communicate experience to others, and the schizophrenic person, aware that what he perceives no longer tallies exactly with language, is glad to use any means which will allow his experience to be clothed in the decent swathings of language.

The phenomenologist and existentialist schools of psychiatry under Binswanger's aegis are trying to bridge this gap by a deeper understanding of schizophrenic experience. Neither of us is particularly imaginative or sensitive, but a series of experiments with a variety of psychotomimetic agents during the last six years has made us less inclined to retreat into scepticism or to trot out some ready "explanation" when confronted with a story such as that of Mr. Kovish. We have learnt to listen respectfully.

Mr. Kovish did not begin to despair until at least a month had passed, in spite of disturbances in perception, morbid fears, sleep difficulties and low spirits. Weinberg (38), in a series of acute cases of schizophrenia, suggests that it takes from one to five months before the sick person comes to hospital. Presumably when onset is even more insidious, the patient may take much longer to come to hospital, and develop ways of rationalizing his experiences which make contact, treatment and re-ablement far more difficult. These rationalizations may also of course be extremely destructive to his relationships with other people and so further hamper his return to the community.

We have already noticed and made some suggestions regarding the lag between stopping all adrenalin and complete recovery. Mr. Kovish lays emphasis on having what he feels is an adequate explanation for his misfortune. He was incredulous "that this could happen to me—I'd always looked on those who gave way to nerves as being weaklings". After it had happened, even after he had made a complete recovery, as he was showing signs of doing, he would, he thinks, have always been wondering "whether this or that could bring it on again". Those who have themselves endured some of the bewilderment and uncertainty which an experience of this sort engenders will recognize what Mr. Kovish means. Luckily the passage of time dulls the vividness of it and self confidence increases. Yet how many recovered mentally ill people are

haunted by the ghosts of their illnesses, which constitute in themselves a major source of worry and insecurity.

Work with inhaled adrenolutin and other so far unspecified adrenalin derivatives has promise. The special value of the lung route, if we are correct, lies in its effect being much greater and more dramatic than the intravenous, but less likely to result in accumulation in the body, probably in the red blood cells from which it is slowly released over a period of time, producing insidious psychological changes, particularly when the subject experiences emotional disturbance. The lung route may be the nearest we can approach to the intraventricular instillation, and so offers the opportunity for a variety of experiments with psychotomimetics, both old and new. It may also provide clues as to how they work, some doubtless will show no more activity by lung than in other ways—some are much more powerful.

The adrenalin derivatives inhaled by H.O. did not give the familiar effects of adrenochrome or adrenolutin, neither did they resemble those of adrenalin itself. There was some similarity to his catatonic-like experience with ololiuqui (27) though the bowel discomfort and the extreme weakness was not present with the chief narcotic of the ancient Aztecs.

One could elaborate these speculations, but this is simply an account of the fortunate mishap which overtook Mr. Kovish and some experiments which it engendered. We hope that others will be encouraged to seek answers to some of the many questions which it raises. It may be possible to implant an indwelling catheter in the trachea of an experimental animal, with a covered diaphragm of the sort that Feldberg and Sherwood (10) have used in their cats, and so introduce to the lungs a variety of adrenalin derivatives in aerosol form and observe the behavioural changes. Toxic substances reaching the brain via the blood stream may produce a more exact model than those instilled into the ventricle. We may find that some fractions of adrenalin catabolites will produce very different changes from others. It would be unwise to forget that while our immediate attention has been on adrenalin, aberrant derivatives of noradrenalin and other precursors may be equally involved.

Finally Mr. Kovish reports the virtual disappearance of the asthma which afflicted him for so many years. A year after his ordeal he no longer takes any adrenalin and has no need of it. Psychosomatic problems of this sort are peripheral to our immediate interests so that we have not dealt with these aspects of the matter fully. One does not require much imagination to see some fascinating questions to ask. Has Mr. Kovish, inadvertently, achieved some permanent and beneficial change in his adrenalin metabolism? If this has happened (and we have only the merest hint of it), then perhaps the same principles could be used in a less drastic way to help other sufferers from asthma. We can only ask a question and hope that those who are especially concerned by these matters will be tweaked into trying to answer it.

These are a few prospects which lie ahead. They suggest that we now have tools allowing us to delve deeper into schizophrenia. As we do so we can hardly avoid a greater respect, understanding and sympathy for our patients as they struggle in loneliness against a world disintegrating around them.

SUMMARY

The authors describe the experiences of an asthmatic man who inadvertently inhaled at least 50 milligrams of "wine-coloured" adrenalin over a period of about four weeks. He had disturbances in perception, thinking and mood which convinced him that he was "going out of his mind". After he had stopped taking the adrenalin he felt better but not fully recovered. About six weeks after he had begun using this sample of adrenalin he chanced to read an article describing the effects of adrenochrome in a volunteer, which he considered very similar

to his own experience. This information coincided with a marked improvement in his condition.

After giving accounts of experimental admission of adrenolutin and mixed adrenalin metabolites by inhalation, the authors discuss the implications of these findings. They suggest that it may well be that the red cells act as a depot for some of these derivatives of adrenalin, and this might account for the different effect of the same substance when swallowed, given by vein, or inhaled. Commercial adrenalin for inhalation rarely goes pink, far more often it is brown or black. Asthmatics are well advised to beware of wine-coloured adrenalin.

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