EXPERIMENTAL PSYCHOSES AND OTHER MENTAL ABNORMALITIES PRODUCED BY DRUGS*

BY

W. MAYER-GROSS, M.D., F.R.C.P.

Director of Clinical Research, Crichton Royal, Dumfries

The systematic use of drugs for the production of "artificial psychoses" dates from the early work of Kraepelin (1883). A new insight into abnormal mental states is achieved by the subject's observation of his own mental experiences. Kraepelin mentioned this project in 1892 in an introductory paper opening a series of investigations of the effect of drugs on some elementary psychological functions. Thirty years later he wrote a kind of epilogue to this part of his work (Kraepelin, 1925); he stated that the results were disappointing and discouraging, because the method did not succeed in arriving at a generally recognized psychological interpretation of psychic functions. If this had been the only aim, one could to some extent agree with this condemnation: some obsolete ideas of association psychology when applied to experiments with alcohol, coffee, morphine, tea, etc., have proved open to criticism and have not been very fruitful for psychiatry.

On the other hand, experiments with mescaline, hashish, ether, nitrous oxide, cocaine, and similar chemical substances which produce excitation of the central nervous system and symptoms comparable to those in psychoses have led to interesting results which are worthy of reconsideration in the light of present-day problems. This work is not yet complete and so is not ripe for an epilogue. New drugs are still being discovered and tried out.

The father of the method is Moreau de Tours, who in his monograph *Du hachisch et de l'aliénation mentale* wrote in 1845: "By its mode of action on the mental faculties, hashish gives to everyone who submits himself to its strange influence the power of studying, on himself, the moral disturbances of mental illness, or at least the principal intellectual disorders from which all kinds of mental disturbances originate." At this time the *Confessions of an English Opium Eater*, by de Quincey, had appeared and Davy had published his striking observations under the influence of laughing-gas.

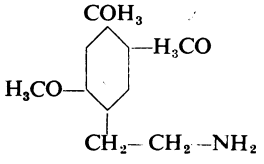
Mescaline

Kraepelin was not only interested in the action of drugs on certain elementary functions; he was equally keen to determine the *specific* change in mental activity which he assumed each chemical substance to produce. With this in view, he initiated experiments with mescaline by Knauer in 1911 (Knauer and Maloney, 1913). Another of Kraepelin's pupils, Wilmanns, organized the Heidelberg experiments and was responsible for Beringer's work in this field, from which some passages are quoted later.

The problem of the specificity of the mental picture following the taking of a certain drug is that of the wider issue of chemical constitution and pharmacological effect. As many of the drugs hitherto employed for psychiatric experiments are time-honoured intoxicants, used in different parts of the world as stimulants for religious and social purposes, there seems to be a large unexplored field in which a systematic search for substances with such central effects would certainly be worth while. The recent chance discovery of lysergic acid diethylamide, the most powerful of all "phantastica" known so far, seems certainly to confirm this challenge to the pharmaceutical chemist.

To add a few more data from the intriguing history of these drugs is a temptation difficult to resist. Many have a considerable anthropological and cultural significance. Cannabis indica addiction, with its wide distribution in the Middle East, including Greece and other parts of Asia and Africa, and its varied modes of intake through the ages and in different countries, could be the subject of a monograph by itself. A few remarks on mescaline, its origin and discovery, may serve as an illustration. The pharmacologist Lewin found it in wide use as an intoxicant to produce ecstatic states for special religious occasions among Red Indian tribes in Mexico and in North America near the Mexican border. He identified the mescal buttons chewed by the Indians as parts of a cactus plant. Inquiry into early reports disclosed that the drug had already been mentioned in the description of this part of Mexico by Sahagun early in the sixteenth century, and that the "prophetic" quality of peyotl, the native name of the prepared cactus, was probably known to Aztec medicine before the conquest of the country by Cortez.

The chemistry of the active principle in peyotl was studied and largely explained by Heffter in 1898. According to Spaeth (1918) mescaline is 3, 4, 5-trimethoxyphenylethylamine, with the formula:



Anthropologists, such as Lumholtz (1894) and Mooney (1896), collected descriptions of the poetic and colourful mythus and elaborate ceremonies practised among the Indians when gathering, preparing, and administering the drug. Thanks to the commercial skill of exporters, the use of the drug spread around the year 1900 from the Mexican frontier to several Indian tribes in the reservations of North America. What was originally a pagan rite—peyotl was considered God-like—was incorporated into the Christian liturgy of Indian groups who had been converted long before but were still ready to revive old tribal customs by chewing the mescal buttons at the time of festival gatherings. They now interpreted their ecstatic and hallucinatory experiences according to Christian ideas. The use of the drug was, and probably still is, a problem for Christian missionaries, who insist that its regular intake leads to increasing laziness and impairment of will power.

Returning to the topic of scientific study, the first self-experiments with the drug were carried out in America by Prentiss and Morgan (1896) and by Weir Mitchell (1896), who gave a description of colourful visual hallucinations. One year later, Havelock Ellis published a note on the phenomena of mescal intoxication which consisted of a graphic description of one self-experiment. The article seems to have attracted little attention, probably because it was obviously regarded as the product of an artist-writer's wild fantasy.

*From a lecture delivered at the Institute of Psychiatry, Maudsley Hospital, London, on February 15, 1951.

Clinical Picture of Mescaline Intoxication

It should be realized that the outward behaviour of the subject acutely intoxicated with mescaline is relatively normal. He may be absorbed in his experiences, and will talk about them freely but rationally. Only if the intoxication has become extreme may he lose control of himself and sink into a sleep-like sopor or delirium.

Hashish, in contrast, produces much more restlessness and movement at an earlier stage; mescaline invites passivity and rest. Hyperkinetic states, sometimes with a choreo-athetotic or other organic appearance, such as catalepsy and muscular rigidity, are frequent in hashish intoxication but rare under mescaline.

For the *mental state*, I quote from one of my own self-descriptions published by Beringer (1927).

"I received two subcutaneous injections between 9 and 10 in the morning. They first produced slight nausea and local pain, soon followed by difficulties in concentration on useful work. A general feeling of pleasant carelessness with slight fatigue took hold of me, but still with a background of sickness. At about 11 a.m. changes in the *colour* of objects were noted and the increased intensity of after-images became disturbing. With closed eyes visions of moving constantly changing patterns appeared and attracted the whole attention: Oriental tapestry, mosaic-like wall-papers, kaleidoscopic coloured geometric patterns, lines in brilliant luminescent colours or in black-and-white, etc. The colours were sometimes dazzling and gaudy, as in some Continental rural art, and shortly afterwards there were tender pastel shades. The colours of real objects appeared more pure, more clean, untarnished by dirt, then a moment later everything seemed vague, remote and veiled, not quite real.

"Meanwhile, *euphoria* heightened into a feeling of superiority and joviality; I was ready to joke about everything, and especially to sneer at some psycho-physical tests and at the people trying to test me.

"While in a dark room, I rested between wakefulness and sleep. Pulling my right ear-lobe, I realized that this was the only part of my body still present. My whole body feeling was concentrated and had its seat in the ear-lobe, which I was holding much enlarged in my hand. Opening my eyes and seeing the room, I was soberly aware of the real situation. There was, however, a marked tendency to *think in visual images:* I pondered over my present level of consciousness, which at once appeared before my eyes as the water level of a harbour with sailing boats, flags, and sunshine. Connexion between this picture and my thinking was self-evident and fully convincing. On another occasion, when thinking of domestic affairs, I had the image of a ceiling or vault entirely made of knitting in grey wool. There were also visual hallucinations unconnected with my conscious thinking, especially friendly animals, little demons and dwarfs, fairy-tale ornaments and mythology from the aquarium such as one sees sometimes on the walls of inns. The faces of people around me were slightly distorted as if drawn by a cartoonist, often with the emphasis on some small humorous but nevertheless rather characteristic feature.

"Jollity and mirth persisted for some time, often mixed with a Swiftian feeling of irony expressed without much reticence or self-control. My remarks were objectively not at all as strikingly witty as I thought them at the time.

"This mood was replaced in the course of the afternoon by an entirely different one: the change began with a bodily feeling of being *cold*. The coolness was not so much of the body surface, although feet and hands were cold too, but seemed to come from inside the limbs and the trunk. A certain restlessness was felt to be the response to increasing waves of cold. The state was not unpleasant and did not sober me up; on the contrary, I continued daydreaming and delighted in changing images illuminating my present condition. One picture, a huge dome of concrete supported by an iron construction, impressed me deeply. I imagined myself inside this dome, and was proud that I understood its beauty so well. It was the perfect representation of my emotional condition, which was far away and completely detached from all the small idyllic things of the little-valley-with-mill type which I like so much in ordinary life. Music of the mouth-organ was offensive; I wanted a symphony orchestra or the organ of a large cathedral. I remained, however, entirely myself, and did not lose my identity. The bodily feeling of cold was like a sting which made the enjoyment of the mental state an even greater treat. On the other hand, there was little progress of thought in this condition; it was a purely *passive* attitude in which I tried to relish and taste to the full this experience, which seemed so important and unique that I took great pains to describe my extraordinary feelings to the observing colleague. . . ."

The impression, from this description, that mescaline necessarily produces enjoyable and unusual experiences, is somewhat misleading. This may be shown by some excerpts from the report of another subject of the same series of experiments, a well-known scientist:

"A most unexpected observation made me laugh, and I exclaimed, 'This is all terribly tasteless.' I see and feel myself in the same position as I was before, lying on my back, the arms crossed over my chest. My right arm is a street with a group of toy tin soldiers. My left arm goes across the street like a bridge and carries a railway. I feel myself like a giant, like Gulliver—but the whole thing is depressing because the toys are terribly common in form and colour; but I feel I myself *am the vision*. . . . In the depth of the intoxication I don't feel well and feel inferior. I tell myself it is an experiment. I know that I soon will get out of this condition. As a continuous state it would be horrible.

"My right shoulder is a hill, and from this highest point the coast flattens out towards my feet. My head forms the right upper corner of the picture. I feel that I am a large scenery, and I see mountains, towns, villages, and the sea behind me, but if I look closer it all is unreal, not really sharp, like cheap prints. The whole thing is unsatisfactory, and I am waiting for something better to come."

Some Important Symptoms

These observations serve to illustrate the characteristic psychopathology of the intoxication, some symptoms of which deserve special discussion.

Predominance of Visual Experiences

The predominance of visual experiences in the picture is striking—not only on account of the persistent visual hallucinations and illusions, but by the impressiveness of seen real objects, their shape and colour: visual images replace thinking and express feelings and moods. Only the tactile senses and the body-image sensations seem to compete with vision at times. When Zador gave mescaline to a patient who had been blind since the age of 2, he became hallucinated in the sphere of the body-image only. Generally speaking, mescaline is the drug of the visionary, and it was probably for this reason that it was so readily accepted for religious use.

Movements of Objects

Within the field of vision the drug interferes with the stillness and movements of objects. The remarkable mechanism by which we normally see things fixed and of persistent shape seems to break down in the intoxication. The process of perceiving and of picturing

our surroundings at an instantaneous glance is disturbed, probably slowed down, and we observe the "scanning" of the picture in progress.

"Looking at a pattern of triangles and dots on the cover of a book, I saw the triangles changing their shape, becoming higher and more pointed, wider and more obtuse; they came out of the paper as though plastic and then withdrew into it. At the same time the whole pattern was in movement. Also the dots were in steady movement away one from another and from the triangles. . . .

"On a printed page of a book I saw the lines of print in quick movement running away from left to right; later they moved in the opposite direction, also towards one another, each letter constantly changing shape and size. The same persistent movement was seen in the changing visual hallucinations, but there were also periods of complete standstill."

Imaginary movement of this kind is obviously related to the creative play of imagination as described by artists of genius, such as Leonardo da Vinci and Goethe, but also by Johannes Mueller, the father of modern sensory physiology. One of Beringer's subjects reported as follows:

"On a whitewashed wall there is movement of grey and white lines apparently at different levels, horizontal and vertical, forming a lattice-work, moving from left to right, behind it the formation of a picture while the movement continues. A larger shady spot becomes a house, like a castle with windows, entrance, drive from the gate, a pond in front, the castle mirrored in the water; behind the castle a mountain range, slow-moving clouds in the sky—the picture is in constant change, new lines becoming more marked and starting an entirely new design. The new design expressed itself clearer and when it was fully developed something different was slowly started. Deliberate intention, independent of the basic material of lines, the will to imagine something entirely different, had no effect."

In this connexion, experiments with the widely used Rorschach ink-blot test are worth noticing: the results revealed little of the personality background, but were mainly influenced by the symptoms of the intoxication (Bleuler and Wertham, 1932). In one case only was the personality more truthfully revealed under mescaline than in a test given beforehand without the drug.

Disorders of Time

Closely linked with the disturbed visual appreciation of movement, but not identical with it, are the frequent disorders of time experienced in mescaline intoxication. They vary a great deal from case to case, but a slowing down of the passage of time, sometimes culminating in a standstill or complete timelessness, is often described. The vortex of kaleidoscopic colours turns without time. Some experiences of heightened insight seem of eternal duration. Time may be discontinuous and fragmented, as in the case of one subject who tried to imagine the stages of the way from the hospital to his home. He made only very slow progress: the different stages of the journey, which ordinarily took 20 minutes, seemed to go on without end; moreover, the stages appeared disconnected, like a series of snapshots. The basic time grid seemed to have broken down.

Synaesthesiae

Among the striking phenomena of the intoxication the interrelations of sensory experiences in the form of synaesthesiae are of special interest. As visual perception prevails, the influence mainly extends from other senses to vision: the knocking of workmen outside the room was accompanied by hallucinatory dots of colour in the air; with each stroke of the clock more red spots appeared in the coloured pattern, etc. But synaesthesiae between other senses are also experienced. The following report of a usually matter-of-fact scientist shows the peculiar result of the synaesthetic perception, but also the inadequacy of ordinary language for such experiences:

"One believes in hearing noises and seeing faces, but everything is one. I hear scratching, the sound of loud trumpets, I am the lattice-work. What I see, I hear; what I smell, I think. I am music, I am the lattice-work. I see an idea of mine going out of me into the lattice-work. This is not a metaphor, but the perception of something coming out of me. . . . I felt, saw, tasted, and smelled the noise of the trumpet, was myself the noise. . . . Everything was clear and absolutely certain. All criticism is nonsense in the face of experience. . . ."

State of Consciousness

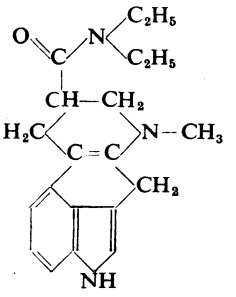
It is difficult to classify the state of consciousness during the intoxication which allows such full self-observation and, at times, seems to foster detachment and self-scrutiny. At other times the same subject seems to have lost all clarity of consciousness, is drowsy and even close to a state of sleep. As for continuity of consciousness, this is at times disrupted and fragmented. Single impressions are dissociated and without connexion, while at other times everything seems to flow in a unified stream of deep significance and importance, and is connected with the whole life of the subject, who identifies himself with the experiences. As for the breadth and capacity of consciousness, these may be narrowed down to one small impression, as in one subject's description that the whole world was contained in a fluff of dark wool on the doctor's white coat.

Relation to Other Mental Reactions

It can be maintained that the symptoms caused by mescaline, as well as those due to intoxication by hashish, cocaine, lysergic acid, and even amphetamine, all belong to the large group of exogenous reactions of which *delirium* is the typical form. The latter may be called one of the basic modes of cerebral reaction (Bleuler, 1944). Differences in symptoms found with various drugs have been attributed to differences in the personality of the intoxicated. This may be true for an early stage or for cases of very mild intoxication. The delirious picture, on the other hand, is probably common to all intoxicants when their effect is most severe. Between these two ends of the scale is a stage in which probably each drug shows certain special features: mescaline produces derealization, followed by visual and tactile illusions in relative clearness of the sensorium; hashish produces special forms of dissociation of thought, with hyperkinesis; cocaine produces mainly auditory hallucinations, with fear, increasing to terror, often with a sexual colouring, etc.

The symptoms of lysergic acid diethylamide appear to be closest to those of mescaline, though its chemical nature differs widely. Its intoxicating properties were discovered by chance by the biochemist A. Hofmann, who had synthesized it from one of the many constituents of ergot which he investigated (Stoll, 1947). If the

chemical constitution of lysergic acid suggested by Jacobs and Craig (1938) is accepted, it has the following formula:



It is much more powerful than most well-known alkaloids, and is effective in about one-tenth of the amount at which adrenaline or thyroxine shows any physiological action.

Symptoms of mescaline intoxication have been compared to those of *schizophrenia*, but it is much more the strangeness experienced by the patient suffering from schizophrenia and the difficulties of describing what is happening in the two conditions which are similar. Many typical schizophrenic symptoms, especially in subacute and chronic states, are never seen in mescaline intoxication. Early psychotic phenomena in acute schizophrenia show certain analogues, especially in the field of hallucinations and other sense abnormalities.

Derealization and *depersonalization*, frequent in schizophrenia, but present also in many other mental illnesses, occur almost regularly after mescaline, if only for a short period. I have recently observed a typical picture of this kind lasting over several hours in a subject after lysergic acid diethylamide. Guttmann and Maclay (1936) suggested small doses of mescaline as an empirical therapy in this intractable condition. Nowadays, when even prefrontal leucotomy has been performed in such patients, it would be justifiable to attempt the production of a severe mescaline intoxication in the hope that the depersonalization may clear together with the other toxic symptoms from the drug.

Results of Experiments

What have we learned from these experiments that could justify their continuation? The subjective experience of an artificial psychosis of this kind is of great value to the psychiatrist, who, without danger, "can live in the strange worlds with which he has to deal in his daily work. He can observe and will be impressed by the oncoming psychopathological symptoms and their recession; he will have a better grasp of much of what his patients report" (Stoll, 1947).

In particular, the problem of *hallucinations* and kindred sensory disturbances has been studied; it was shown that the disordered perceptive system plays an important part in their origin. They are not only uncontrolled imagery released after blocking of higher centres, but may be closely related to quantitative disturbances of the sensory apparatus (Mayer-Gross and Stein, 1926). An attempt was made to extend this principle to the explanation of illusions and hallucinations in psychoses of all kinds; many descriptions of patients reporting bizarre and improbable experiences became better understood in the light of these observations (Mayer-Gross, 1928).

If mescaline was given to a chronic schizophrenic suffering from persistent hallucinations it was found that the patient distinguished the new phenomena and remarked on their appearance, usually laying blame for them on the same persecutors who had molested him before. Patients in a state of delirium, on the other hand, showed an increase of delirious symptoms; they seemed unable to distinguish the mescaline experiences as anything new; they made no comment and reacted in no way differently to them than to other symptoms of the delirium (Zucker, 1930). If a normal subject intoxicated by mescaline was asked to use his visual imagination for deliberately picturing certain objects or past events, it was shown by Zucker and Zador (1930) that the process of imagery was interfered with by the drug.

Zador (1930) has also studied the influence of mescaline on the phantom limb of limbless patients and on cases of blindness due to differently localized lesions. The phantom limb as a recently acquired part of the body image was earlier and much more affected by mescaline than the rest of the body. The visual phenomena produced by the toxic condition were more or less identical whatever the origin of the blindness—injury, glaucoma, optic atrophy, tumours of various locations—but the degree of vividness and persistence of visual sensations was definitely related to the duration of the blindness. For instance, if one eye had lost its function later than the other, visual hallucinations were more marked or appeared exclusively in the eye that had lost its sight later. Altogether, the hallucinatory phenomena of blind subjects were, as one would expect, more frequent in sensory fields other than the visual.

Mechanism and Causation

By what mechanisms, chemical or physical, or both, are the mental symptoms produced? Where is the point of attack of these drugs in the metabolism of the brain cell, and what can be deduced from their effect about the aetiology of psychiatric symptoms and illness? We might expect that these questions could be readily answered by the results of our experiments. Actually, only partial answers can be given.

Cannabinol, the active principle of hashish, was found by Marx *et al.* (1932) to have a considerable diuretic effect, leading to a concentration of the blood. Its influence on carbohydrate metabolism was also demonstrated and, conversely, its psychological effect was much enhanced by the simultaneous intake of sugar. This agrees well with the Eastern habit of taking sweets while smoking or eating hashish.

Quastel and Wheatley (1933) studied the effect of mescaline and other amines of the aromatic type on the oxidation of brain *in vitro*. They found an inhibition of oxidation similar to that of the narcotics, and this would suggest that the effect could be abolished by succinate. J. R. Smithies (1951, personal communication) reports the successful termination of mescaline symptoms by oral administration of sodium succinate. Quastel and Wheatley suspected that inadequate detoxication of similar substances in the liver may lead to their circulation in the blood, causing mental disorder. Hence the importance of hepatic function for the study of the aetiology of psychiatric diseases.

The more recent investigations on mescaline intoxication by Jantz (1941) seem to point in the same direction. He studied the metabolism and blood chemistry of the intoxicated individual from every aspect. His various findings seemed to point to capillary damage caused by the drug. Through the walls of

damaged capillaries protein leaves the blood, entering the tissue, where it is stored. Jantz confirmed this theory by experiments on dogs. The animals showed nitrogen retention when they received mescaline but massive excretion of nitrogen on those days when the drug was withheld. Pathological studies revealed capillary damage in the liver, a picture described by Roessle under the term of "serous hepatitis."

The comparison of these findings with Gjessing's in periodic catatonia is close, but Jantz mentions it with due caution. His findings certainly need confirmation by other workers.

The intermediary role of the liver as a site of pathology in mental disorders has an unfortunate history in ancient and modern medicine. Its latest abdication was in the field of alcoholic psychoses. Delirium tremens and Korsakoff states, after having been hypothetically ascribed to hepatic dysfunction for many years, are now recognized as due to nutritional deficiencies. The mescaline-like effect of 30–50 μg. of lysergic acid diethylamide taken by mouth makes it very doubtful if the liver has any share in the symptoms of the intoxication.

Future Research

Within the last ten years much has been learned about metabolism of the central nervous system that can be applied to experimental psychoses. We can expect the biochemist to give us more information on the action of these drugs *in vivo*, especially if full use is made of parallel experimental studies in animals. Here histopathological and histochemical methods, which have recently widened the field of investigation in the central nervous system, should elucidate the rather special interference with oxidation which one can suspect to be taking place. Finally, the new electro-physiological methods will have their place in this experimental work. So far the standard electroencephalogram taken in mescaline and other intoxications has not revealed any characteristic changes; but with the new method of carefully dosed stimulation—for example, in the visual field—and with electrodes to record the less accessible and more remote electrical discharges some insight into the action of the intoxicants can also be expected.

REFERENCES

Beringer, K. (1927). *Der Meskalinrausch*. Berlin (with numerous references).
Bleuler, M. (1944). *Schweiz. med. Wschr.*, **74**, 923.
—— and Wertham, F. (1932). *Arch. Neurol. Psychiat., Chicago*, **28**, 52.
Ellis, Havelock (1897). *Lancet*, **1**, 1540.
Guttmann, E., and Maclay, W. S. (1936). *J. Neurol. Psychopathol.*, **16**, 193.
Heffter (1898). See Beringer, K. (1927).
Jacobs, W. A., and Craig, L. C. (1938). *J. Amer. chem. Soc.*, **60**, 1701.
Jantz, H. (1941). *Z. ges. Neurol. Psychiat.*, **171**, 28.
Knauer, A., and Maloney, W. J. M. A. (1913). *J. nerv. ment. Dis.*, **40**, 425.
Kraepelin, E. (1883). *Philos. Studien*, **1**, 573.
—— (1925). *Psychol. Arb.*, **8**, 181.
Lumholtz (1894). See Beringer, K. (1927).
Marx, H., *et al.* (1932). *Nervenarzt*, **5**, 346.
Mayer-Gross, W. (1928). In *Handbuch der Geisteskrankheiten*, edited by O. Bumke. Allg. Teil, **1**, 427.
—— and Stein, H. (1926). *Z. ges. Neurol. Psychiat.*, **101**, 354.
Mitchell, S. Weir (1896). *British Medical Journal*, **2**, 1625.
Mooney, J. (1896). *Therap. Gaz., 3rd series*, **12**, 7.
Prentiss, D. W., and Morgan, F. P. (1896). Ibid., 3rd series, **12**, 577.
Quastel, J. H., and Wheatley, A. H. M. (1933). *Biochem. J.*, **27**, 1609.
Spaeth (1918). See Beringer, K. (1927).
Stoll, W. A. (1947). *Schweiz. Arch. Neurol. Psychiat.*, **60**, 279.
Zador, J. (1930). *Mschr. Psychiat. Neurol.*, **77**, 71.
Zucker, K. (1930). *Z. ges. Neurol. Psychiat.*, **127**, 108.
—— and Zador, J. (1930). Ibid., **127**, 15.

SODIUM γ-RESORCYLATE IN RHEUMATIC FEVER

BY

J. REID, M.D., M.R.C.P.

R. D. WATSON, B.Sc.

J. B. COCHRAN, M.B., B.Sc., M.R.C.P.

AND

D. H. SPROULL, M.B., Ch.B., B.Sc.

(From the Clinical Chemotherapeutic Research Unit of the Medical Research Council in the Gardiner Institute of Medicine, University of Glasgow)

Salicylate has an established place in the treatment of rheumatic fever, though the dose required for full therapeutic action may also give rise to undesirable effects. A drug with a greater safety margin might improve treatment of rheumatic fever, and this paper describes an attempt to find such a substance.

Our starting-point was the observation that salicylic acid, which is *ortho*hydroxybenzoic acid, has a therapeutic action in rheumatic fever, yet its isomers—the *meta*- and *para*-hydroxybenzoic acids—are inactive (Stockman, 1920). The physiochemical properties of salicylate and its isomers were examined for some essential difference which might explain why the first is effective and the others are not. A notable difference is that salicylic acid is a much stronger acid; this has recently been attributed to its ability to form an additional or chelate ring, a property not possessed by the isomers (Baker, 1936). The chelate or claw-like ring is known to chemists, but is perhaps not so familiar to clinicians. It is formed by virtue of the hydroxyl group of salicylic acid sharing its hydrogen ion with the ketone of the carboxyl group (Fig. 1).

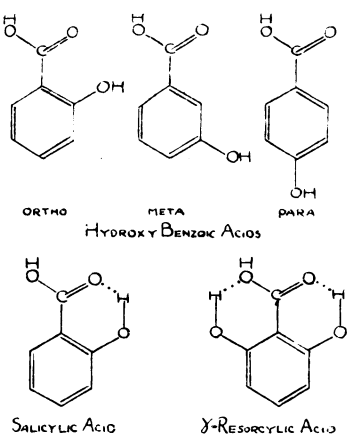


FIG. 1.—Showing the formation of a chelate ring by salicylic acid and of a double chelate ring by γ-resorcylic acid. The isomers of salicylic acid do not chelate because the distance between the hydroxyl and carboxyl groups is too great.

A comparison of the structure of salicylic acid and its isomers shows that the formation of a chelate ring depends on the respective positions of the carboxyl and hydroxyl groups. If the hydroxyl group is in the ortho position, as in salicylic acid, a chelate ring may be formed because of the proximity of the reacting groups to one another. If the hydroxyl groups are in the meta and para positions chelate rings cannot be formed, as the active groups are too far apart (Fig. 1).

If the formation of this special type of ring structure is responsible for the therapeutic action of salicylate, then it might be possible to enhance this action by increasing the chelation effect. This possibility has been explored by investigating the pharmacological properties and therapeutic action of 2:6-dihydroxybenzoic acid, or