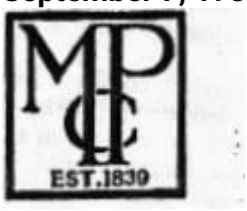
BY JOSEPH HENRI MAISIN, M.D., Director, Institut du Cancer
Louvain University;
MEDARD DE JAEGHER, M.D.; YU-HAN TANG, M.D. and JEAN RUBAY

Reprinted from
THE MEDICAL PRESS AND CIRCULAR
September 7, 1938, Vol. CXCVII, No. 5183



The Use of Peroxide Diformaldehyde and Organic Un-saturated Compounds in the Treatment of Anergy and Hyperergy.

Origin of this Research

THE use of the substances discussed in this article in the treatment of anergic and hyperergic states is an outcome of extended experimental work with them in other directions.

One of us (1) has made a long study of the action of peroxides on experimental cancers, in an attempt to re-establish, with the aid of these peroxides, those oxidation processes which, as is now generally known, are defective in the malignant cell. He succeeded in obtaining definite prophylactic results against benzpyrene cancer in white mice.

Having subsequently tested the action of the peroxide of diformaldehyde in a large number of desperate cases of human cancer, he was struck, from the very beginning of the work, by the remarkable influence of these products on the general health of the patient; euphoria, increase of appetite and weight, diminution of pain.

In addition, he noted coincidentally, in certain patients, a very definite influence on various infective processes as well as on such hyperergic conditions as asthma, eczema, etc., which happened to accompany the malignancy in certain of our treated individuals.

These results were of such a nature that he was prompted to inquire into the action of these products on ordinary cases of anergy or hyperergy, uncomplicated by any malignancy. The early results having been good, he then carried out, with his collaborators, a series of experimental and clinical researches. The products employed were the peroxide of

diformaldehyde and certain unsaturated compounds, of which the method of preparation is given below.

Nature and Method of Preparation of the Products Used

The substances in question are of very simple chemical composition and are easy to prepare. The first group of products comprises the organic peroxides, of which several have been used with a measure of success. We will describe here one only, the peroxide of diformaldehyde, since it has been particularly studied and is very efficacious.

The formula, of this peroxide is:

H\ /H
H—C—O—O—C—H
HO/ \OH

It is readily saturated solution anhydrous ethyl saturated solution hydrous ethyl ether.

The second group of compounds comprises certain highly unsaturated chemical substances, of which we do not know the exact formula, but which may be prepared by the action of phosphoric acid on malonic acid, or by the action of sulphuric acid on ether, or also by the action of sulphuric acid on a solution of acetaldehyde in ether. The first reaction should theoretically give as a final product, malonic anhydride, having a formula of OC = C = CO. We have reason to believe that the general formula of those active products would correspond with the structure

R=C=C=R.

An Experimental Study of Anaphylaxis In the Guinea Pig

One of us has undertaken the study of the action of these two groups of substances on anaphylaxis in guinea pigs. Guinea pigs were sensitized by the injection of five centigrams of crystallized egg albumen. When the animals were sensitized, i.e., three to four weeks after the injection, he proceeded to test the possibility of desensitizing these animals by the use of the two groups of substances in question.

These researches have shown, as did those with experimental cancer, that only very dilute solutions were really efficacious. It is necessary to use the peroxide of diformaldehyde, or the unsaturated compounds in a dilution of the order of 1 X 10(-9) at least. Actually, our best results have been obtained with dilutions from 1 X 10(-9) to 1 X 10(-18). These very high dilutions (1 X 10(-18)) still contain several thousand molecules per c.c.

We desensitized our animals by injecting subcutaneously 1 c.c. of the chosen dilution every eight days. Altogether, three or four injections were made. Several hours after the last injection we gave the treated animals, as well as the controls, the shock injection intraperitoneally, viz., 40 to 50 centigrams of crystallized egg albumen.

All the control animals died; 30 to 60 percent, of the desensitized ones survived.

We have also attempted, with success, to control an anaphylactic crisis, which was already under way.

In the desensitization of guinea pigs to egg albumen, both types of product were successful, if the shock injection is made a few hours after the last injection of the products. But if the shock injection is given several weeks or months after the last desensitizing injection, then we see difference between the two types of products; the unsaturated compounds remain effective months after the last injection. We are still studying this phenomenon, in order to determine the reason of this marked difference, which may lead to a chemical definition of allergy, allergy and hyperergy.

Clinical Researches

In human beings we have observed carefully all the variations in blood pressure, as well as variations in the blood contents and the coagulation rate, in our patients to whom injections have been given. The results have been very definite and very interesting. With a dilution of 1 X 10 (-9) of one or other of these products, one finds in 90 percent, of the cases who have never before received an injection, a haemoclastic crisis, i.e., a temporary leukopenia plus lymphocytosis, plus lowered blood pressure and changes in blood coagulability. Thus a fall in the blood pressure is noticed, which takes place from 5 to 15 minutes after the injection. The blood pressure is taken with the most painstaking precautions, with a view to avoiding every source of error. It should be noted that these results have been obtained in patients resting in bed, the blood pressure being taken first tiling in the morning, i.e., fasting.

As in the phenomenon of shock, certain febrile manifestations may follow in persons who were a febrile at the moment of injection. Increases of temperature are particularly noticeable in patients who have a latent focus of infection, which is disclosed by tile injection. These elevations in temperature may follow from two to several days after the injection.

On the other hand, patients who have a temperature at the moment of the injection frequently show a reduction to a normal temperature during the following day. Finally, we have observed delayed temperature reactions appearing as late as three weeks after the injection.

Clinical Applications

The various phenomena, which we have just described, suggest that several morbid states may be favorably influenced by this entirely inoffensive therapy. Briefly, one may say that it is applicable in any case where shock therapy is indicated; in anergic and hyperergic states, with or without infection. We would like in this paper to confine ourselves to certain indications in which this therapy has been successfully tested by us.

Infectious states: acute or chronic colds; furunculosis, where generally one single injection suffices; osteomyelitis, acute or chronic; various febrile skin conditions.

Hyperergic states: asthma and eczema, either acute or chronic.

Notes on Treatment

In most of the ordinary infections, such as furunculosis, coryza, and in certain mild eczema, a single injection is sufficient to obtain the desired result. In cases which have become chronic, or where one has to obtain a considerable desensitization, it is necessary to repeat the injection at intervals of 7 or 14 days. Three or four injections are so given, and then the patient is left for two months or more. If the Treatment is successful no further injections are given; if not, they may be repeated at the same intervals as before.

Extremely high dilutions are always used. Only one c.c. is injected at a time, preferably in the arm muscle (brachial triceps). The injection is painful, and is followed in a few seconds by violent muscular contractions at the site of injection. The pain is transitory. We recommend that the injection be given with the patient lying down.

At present it is impossible for us to recommend one product more than the other, i.e., peroxide, or the unsaturated compounds. In the majority of cases in practice but particularly in hyperergic conditions (asthma, eczema) we use the latter, as they are much easier to prepare and keep better, and also on account of the late result in experimental anaphylaxy in guinea pigs. This we strongly recommend (it is known as “Allergosil “).

Case Notes of Several Cases of Eczema and Asthma

Eczema

i. L.E. A child of 5 1/2 years. —For two weeks had had skin eruption. The child is the son of one of our patients treated by us for neoplasm of the breast. Constitution excellent. Nutrition good. The hands and limbs had been covered with a tar ointment prescribed by his doctor. Small pinhead sized patches, pruriginous; on the wrists, back of hands, knees and several papules on the shoulders. The rest of the body clear. One injection of one c.c. of the unsaturated bodies was given. One week later more irritation. A further injection was given. One week later the child returned. All the eruption had disappeared (some slight desquamation).

ii. Mr. B.F. Age 37. Bricklayer. —Weeping eczema on both hands for four years. Has had various treatments, autohaemotherapy and sodium thiosulphate. The eczema disappears at certain times, but always returns regularly. Small groups of vesicles, situated chiefly on the fingertips, and oil the back of the hands and spaces between the fingers. The eruption sets up an intense itching, and forces the patient to scratch. There is also considerable oozing. The patient suffers much, and each time has been obliged to give up work. During an acute attack three injections of the unsaturated compounds were given at seven-day intervals. Local treatment. One month after Treatment, great improvement. Only a few isolated vesicles remained on the back of the hands. Desquamation over tile healed patches. The patient was seen three months afterwards. He had not had an outbreak since our Treatment, and he was well pleased.

Asthma

i. M. Sp. Age 24. Medical student. —Had asthma since the age of three years. Until ten years of age bad often to stay away from school on this account. Between 12 and 17 years old slightly better, but always liable to attack. Since he came to the University in 1931 he has had at least two attacks each week. In July 1936, an injection of peroxide of diformaldehyde was given. Twenty-four hours after, a violent attack of asthma with temperature 102° F. to 103.6° F. Eczema between the fingers. Six weeks after the injection, no good or bad effect. In September 1937, an injection of the unsaturated compounds was given. He was much better during the days following tile injection. FTC remained fairly well until the end of 1937, having one attack every four weeks. In May 1937, he was not so well. He was given another injection of the unsaturated bodies in alkaline solution. Twenty-four hours after this injection he had an acute attack of asthma, temperature 102° F. for three days. At the same time the patient again had eczema between the fingers. During the following weeks he got better and better and only had a slight attack each week. His eczema disappeared steadily. At the moment he is very well, is free from attacks, and is practically rid of his asthma.

ii. Mr. V.G. Age 55. —He has suffered from asthma for some time. The patient had received three or four injections of adrenaline each week, and is practically never free from attack. We gave him an injection of the unsaturated compounds. This injection was followed by another some hours afterwards. The same day the patient had received an injection of adrenaline. He did not have an attack the following week. At present he is well and has commenced to work again.

iii. Mrs. C.J.L. Age 34. — Bronchial asthma from 11 years of age. The attacks, infrequent at first, have become more and more frequent during the last few years, and she was having an attack every two or three days. The patient was given an injection of the unsaturated compounds in March 1936. She returned in November 1936, and reported that her asthma was much improved. The attacks were less severe and occur less frequently than one month. The patient was injected with tile same compound and since then there has been a progressive improvement. There has been no attack of asthma since November 1937.

iv. Mr. A.C. Age 36. —Has had asthma since 1921. Eczema on the hands since 1925. Since1931, the attacks of asthma have become more frequent and the patient has received as much as 4 mgs. of adrenaline in 24 hours. Since 1932, he has had morphine and he has taken as much as 75 cgr. in four to five days. He has tried several other treatments without effect — Heckel serum, autogenous vaccines, etc. We saw the patient in December 1937, with a typical attack and a permanent shortness of breath and considerable wasting. On December 24, 1937, we gave him an injection of tile unsaturated bodies in alkaline solution. The next day he had a critical attack, which lasted for eight days, and increased in intensity at the beginning of 1938. On January 20 a further injection of the unsaturated compounds in alkaline solution was given, followed by three days of reaction; dis-intoxication of the morphine. By January 27, the attacks were not quite so frequent, and did not last so long. Another similar injection was given. On January 28, there was an outbreak of eczema out the hands. On February 3, a further injection was given. On February 8, he could sleep without morphine. He was pleased and only had a slight attack each day. From February 22, 1938, until March 14, 1938, he had no more attacks. His health was excellent and his weight increased by 9 kilos. Between March 14 and March 29, 1938, he had some attacks, and was re-injected with the same compound. From March 29 until April 4, 1938, no further attack. Since then the patient has had attacks, but always less intense than before treatment was commenced. No morphine. General health good. This is an extremely refractory case, winch required long treatment. Up to the present we have only succeeded in improving the general state, cutting out morphine and in obtaining a transitory diminution in the attacks of asthma. We are following with interest the course of this case. From June 1938, to the end of August the patient has remained practically without attacks. This is a remarkable result.

Discussion

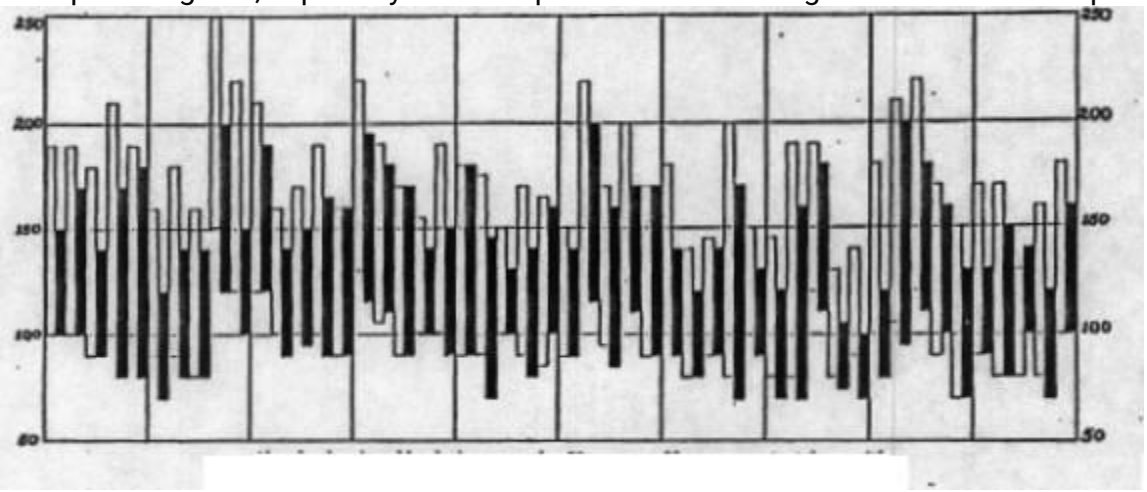
The results obtained are clear, and can be repeated easily by anyone wishing to do so. They are obtained with doses of extremely high dilution, which serves to prove that the active substance can act when exhibited in extremely small traces, as do catalysts, or enzymes. The injections have a lasting action, and do not often have to be repeated, which is an advantage from the patient’s point of view. The Treatment is absolutely harmless. We have given several thousand injections without the least untoward incident, except that some may have a passing malaise, due to a fall in the blood pressure. It is still too early to be able to say with certainty exactly how these substances act, but we know already with certainty that peroxide of diformaldehyde has a deep and prolonged action on the catalase of the blood.

There is no doubt that we are dealing with new phenomena, which deserve, to be carefully investigated, and whose application in therapeutics appears to us to be of interest.

This work is not finished, but is leading us to believe that these two substances are not alike in their action. Finally, a curious fact which we have proved and one which we would stress, is the lengthy effect produced in a large number of cases, as well as the prophylactic action which we have proved the peroxide of diformaldehyde to have on benzpyrene cancer produced in white mice.

Conclusions

I. Peroxide of diformaldehyde and certain unsaturated compounds have a definite physiological action on the organism when only minute traces are injected.
II. Their therapeutic use is indicated since they are very effective in the treatment of various infections and of hyperergic states.
III. The results obtained are better than those obtained with any other shock-producing therapeutic agents, especially from the point of view of the general health of the patient



Investigation carried out at the Cancer Institute at Louvain. Director J. Maisin.
Graph showing blood pressures in 50 cases. Measurements taken with a Vaquez Laubrey apparatus. The figures give the pressure in millimeters of mercury. Blood pressure immediately before the injection of a solution of the unsaturated compounds—dilution 1 x 10(-9).—Blood pressure taken 15 minutes after the injection.

REFERENCES

1935 Koch and J. Maisin: C.R. Soc. Biol. T. 120, p. 106,

J. Maisin and F. Robert: C.R. Soc. Biol. T. 123, p. 156, 1936.

J. Maisin and V. Pourbaix: Ileme Congrês Internal de Cancerologie. Bruxelles. Sept. 1936.

J. Maisin. V. Pourbaix and P. Caeymaex: C.R. Soc. Biol., March 1938.