answer. I don’t think any one knows just why people have reactions to gold. We are glad to hear of Dr. Obermayer’s gold preparation, ammonium succinimide aurate. It should prove to be of great value. I think one will find that if one uses the subcutaneous method of administering gold in the office or the clinic one will find that it is not as spectacular, but for some of us who have small dermatologic clinics and treat referred patients coming from the outlying districts, I am sure it will be of distinct value.

TERMINATION OF ONE THOUSAND ATTACKS OF MIGRAINE WITH ERGOTAMINE TARTRATE

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NEW YORK

For the past few years in the neurologic service at Bellevue Hospital, under the direction of Dr. Foster Kennedy, we have been studying the etiology and treatment of migraine. Realizing that this affliction is not a disease entity and that there is more than one precipitating factor in the production of this syndrome, we felt it essential to investigate this paradox from many different angles.

In a report in 1934 we1 approached the problem from a pharmacologic point of view. At that time we administered known vasodilator and vasoconstrictor agents, also glandular products such as pitressin, extract of anterior pituitary, theelin and insulin. We also studied the effects of carbon dioxide inhalation, of vagomimetic and of sympathomimetic compounds on the attacks. These various medications were used in order to compare the relative effectiveness of numerous non-sedative measures in relieving the episode, as well as to determine the factors capable of precipitating a headache.

The diversity of our results during these investigations reinforced our belief that the pathophysiologic in the production of migraine is not a single one. We did not prove its mechanism. Our results in appraising the non-sedative medicines used to relieve the attacks were more explicit.

Eleven medications were administered during the migraine headache in order to effect relief. They were caffeine, histamine, epinephrine, ephedrine, methochin, ammoniun, tissue extract, pitressin, amyl nitrate, calcium gluconate intravenously, and ergotamine tartrate. Of these, ergotamine tartrate was the only drug that gave definite and constant results. Its effect was outstanding. The other medications might help on the first injection but fail at another time to benefit the very same person. These other measures might relieve two patients and then fail in seven others. The relief obtained from ergotamine tartrate was dramatic. It completely checked thirty-four headaches in fourteen patients. It failed to relieve only five headaches in four patients. We noticed that, once it relieved an episode, control of future attacks in that individual was assured if the drug was given in adequate dosage.

In discussing the value of a medication in the treatment of as complex a syndrome as migraine, a group of eighteen patients is not a sufficient number from which to draw any worth-while conclusions. Because of this, and because of the consistent and spectacular relief obtained from the drug, we felt that further study of its action in relieving the attack should be undertaken.

Our criteria for diagnosis and inclusion in our migraine research series have been discussed in a previous report.1 These patients have received metabolic studies and blood chemistry and Wassermann tests. X-ray plates of the skull, the sella turcica and the nasal accessory sinuses were taken, and also a gastro-intestinal and a gallbladder series if indicated by tentative diagnosis. The patients were questioned for any pathologic process that might be active in the various bodily systems, since they were examined by a psychiatrist, an allergist, a rhinologist and an ophthalmologist.

CHECKING OF ATTACKS BY SUBCUTANEOUS INJECTION

We have now used ergotamine tartrate over a two year period and can discuss our results after having administered the drug for the relief of 1,132 headaches. There were ninety-seven patients—seventy-eight females and nineteen males—in this later study. Their ages varied from 11 to 51 years. They had suffered from migraine for patients; from six months to forty-eight years; the average duration of the illness was sixteen years; the frequency of the attacks varied from two a week to one or two a year.

All but eight of the ninety-seven patients were benefited by this medicament. It completely checked 1,042 episodes in eighty-nine persons. Of the eight patients whose headaches were not controlled by ergotamine tartrate there were four who believed that the pain was alleviated by the injection. The relief obtained was not complete, however, and “of no more benefit than a headache powder.” They were not included in our larger group because its criterion is abrupt termination of the attacks.

We found that there was no difference in the action of the medicament when given to men and to women. It was administered to nineteen men and all but three of them were benefited by the alkaloid. The proportion, three out of nineteen, is practically the same ratio that occurs with the common use of the drug.

Early in our investigations we realized that ergotamine tartrate could not be used as a cure for migraine. It is most impracticable to dispense it as a preventive of the attacks, even though it is of unquestionable value in aborting them. This ability to check the episodes unfailingly is, however, a worthy tool to use while one is searching for a cause and cure of the malady. It gives the investigator something very definite to offer the patients, without interfering with the effects of his other investigations. It bolsters the patient’s spirits, many of them stating “Well, if you can’t do any more for me than you have done, it will still be very wonderful.”

Ergotamine tartrate has no effect on the frequency of the attacks. Several patients stated, in their usual disheartened manner, that the episodes were coming more frequently since they had been receiving the injections. On examining our charts and studying the intervals of the headaches before and after the use of the drug, we noticed a shorter interval occurring in only three of our patients. Two of these, were women at the menopause, and one was a man aged 48. They had suffered from migraine “all their lives,” and the interval had become shorter and shorter through the years; therefore, this diminishing frequency should not necessarily be considered an effect of ergotamine tartrate. At other

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times, when from our data we felt that the drug was increasing the attacks, with further study this lessened interval was found to be only temporary. Such an irregularity in the occurrence of the episodes is a very characteristic finding in migraine, whether the patients take any medication or not.

A number of these men and women have expressed the fear that the beneficial effects of this medicine would wear off. They said that all the other medications that they had ever taken would relieve the attacks for a few months but after a short time would become ineffective. Their skepticism has so far proved to be unfounded. While using ergotamine tartrate over a two year period we have never seen it fail to check an attack merely because of continued usage. One individual whose attacks have been coming weekly has received 129 injections, another patient sixty-four and a third fifty-eight; they have always had unfailing relief from this medicament.

The same infallibility holds true for all our eighty-nine patients. Once ergotamine tartrate has abolished an attack, it has never failed, in our two years' experience, to check again a migraine headache in that individual if given in adequate dosage.

DOSAGE

The amount of alkaloid required to effect relief, however, is very important in proving or disproving this infallibility theory and is worthy of a little consideration. The minimum effective dose, of course, is directly proportional to the severity of the attack. The severity of the consecutive attacks in migraine, as every one knows, is exceedingly variable. Some attacks will be particularly intense, continuing for two or three days, while others occurring in the same individual will be rather moderate and will last only a few hours. Unless one keeps this in mind, the headaches may be abruptly terminated four out of five times, but the fifth attack may be one of these very severe ones; the dose may be inadequate, the effect disappointing and the patient discouraged. By anticipating this (the patients can usually tell when they are “in for a bad one”), a slightly larger dose may be given and an unsatisfactory experience avoided.

Eight episodes, which would have continued for from three to five days if they had not been checked by the alkaloid in from one to three hours, returned from twelve to twenty-four hours after the injection in eight of our cases. This recurrence of the headaches is the exception and not the rule, however, for the same eight persons have obtained complete and permanent relief from sixty-two other attacks. We believe that this reappearance is again probably the result of inadequate dosage. A second injection will control this returned episode.

While discussing dosage and tolerance, we felt that it would be of value to study our records and to compare the amount of alkaloid required to terminate an attack at the onset of therapy (ergotamine tartrate) with the minimum it will terminate the same attack when given as a dose after the drug had been administered for over a year. To our amazement, we found that not only were none of the patients requiring more of the medication but many of them were requiring smaller doses now than at the onset. I do not wish to leave the impression, however, that we believe that this lessened dosage is due to any effect from ergotamine tartrate; that would not be correct. It is probably caused by several other factors.

In the first place, we have observed that the earlier in the attack the drug is given, the smaller is the dosage required. Once the episode has reached its peak, the patient prostrated, vomiting and unable to raise his head from the pillow, a much larger dose is necessary to check the attack, and it takes much longer for any amount to give relief. The after-effects of both the headache and the ergotamine are much more disagreeable.

If patients will take the medication the moment they feel the prodromes and are sure that they “are in for a real one,” the attack may be completely aborted by a smaller dose in much less time and the untoward effects of the drug will be greatly lessened.

From our experience, after using many experimental procedures in attempting to find a cure for migraine, we have concluded that ergotamine tartrate may be used in conjunction with these other measures without coloring their results. Therefore, we have given this drug during the administration of an expected cure in order to control those attacks which may break through. This explains why many of our patients now require a smaller dose of ergotamine tartrate to check the attacks than they did at the onset of therapy, because these preventive measures have been lessening the severity of the episodes and likewise decreasing the minimum effective dose.

Any disease that will incapacitate an adult, interfering with his work for a day or more from one to four times a month is a definite economic liability. Eighty-four persons in this series suffered from migraine attacks at least once a month or more. The time necessary for ergotamine tartrate to effect complete cessation of the episode, even though it would ordinarily persist for from two to three days when given hypodermically, was from fifteen minutes to five hours. This varied in individual cases with the dosage, with the time of administration and with the severity of the attack. We have calculated from our records that the subjects in our series were freed from approximately 39,000 hours of suffering.

Three individuals whose attacks always occurred in the middle of the night or the early morning, awakening them from their sleep, would get out of bed, take their medicine, return to bed, awaken the next morning and go to work as if nothing had happened. Without this drug they would have been incapacitated from their work for at least an entire day.

One woman who is at the menopausal age and whose attacks have been coming weekly during the entire year and continuing for two or three days has taken it over and over again that she does not know how she would exist if it were not for this medication. She is a school teacher and by necessity self supporting. Without the medicine she believes that she could not carry on.

Concerning the administration and dosage of ergotamine tartrate, there are several points worthy of discussion. In this country the drug is prepared in tablets containing 1 mg. of the alkaloid, and it is also marketed in solution in sterile ampules for intramuscular and intravenous use (0.25 mg. = 0.5 cc. and 0.5 mg. = 1 cc.). Some investigators have applied the drug to the nasal mucous membranes; others have incorporated it into suppositories for rectal absorption.

Our method of administering the drug subcutaneously is to inject a trial dose of 0.25 mg., and the effectiveness of this will be used as an index to future medication. If the drug is well tolerated and if it
terminates the attack within two hours, we consider that dosage a satisfactory one for future episodes. It is advisable to repeat the initial dosage of 0.25 mg, if after two or three hours the headache persists, or if after from eight to twelve hours the attack returns. If repetition has been necessary, we consider our original order inadequate and for future attacks 0.5 mg is given. We have never injected a larger dose than 0.75 mg of ergotamine tartrate subcutaneously to relieve one attack, and this amount has been used only three times in our investigations. It is quite rare that a patient needs more than 0.5 mg, and this is a usual and safe amount.

**Oral Use**

In dispensing the alkaloid orally we have observed that if the required amount is taken at once, rather than in divided doses, a more efficient relief will be obtained. One tablet contains 1 mg of the alkaloid. We have given as many as five of these at one time to check an attack. If as large a dose as this is used, we would strongly advise against administering any more ergotamine tartrate within twelve to twenty-four hours.

If, before the medication is given, nausea and vomiting have set in, it is useless to dispense the tablets. They will probably only increase this condition and will interfere with the use of the medicine hypodermically.

It has been suggested that the ergotamine tartrate by mouth, one tablet three times a day, will prevent the migraine attacks from appearing.4 We do not recommend this method of dispensing the drug. Migraine is a protracted condition and we do not know what serious effects the daily use of the drug over long periods of time may have on our patients.

Although this form of medication may prolong the interval between the periods and although it may abort some of the milder headaches and even diminish the intensity of a few of the more severe ones, it will not completely inhibit or cure the pathologic condition.

In the third place, the migraine attacks occur very irregularly and undependably in most patients. To give as costly a medicament as ergotamine tartrate daily, when if no medication were taken the patient might go for several weeks without an attack, is wasteful. In a patient who has been suffering from weekly or biweekly headaches the attacks may spontaneouly come at monthly or biyearly intervals, and the medication would have been given in vain.

Early in our investigations we tested the value of this method of therapy and found it unsuccessful. One of these patients, after the foregoing method of dispensation failed, took the pills, two or three at a time, an hour or two before it felt an attack appearing. This dosage seemed to stall off an episode for that day, but it usually reappeared on the following one, necessitating further therapy. She continued in this manner for several months and was taking, therefore, two or three pills daily, or approximately 10 to 21 mg. of the alkaloid a week. We have advised against this medication and are administering the drug hypodermically. If the attacks occur weekly she receives only 0.5 to 1 mg. a week, because her headaches are completely terminated by 0.25 to 0.375 mg. when the alkaloid is given subcutaneously.

The results of the alkaloid, no matter how administered, will be much more satisfactory if the drug is used early in the attack. As soon as the patient realizes that an episode is inescapable, the prescribed dosage should be taken. If the injection or the pills are given during the peak, with the patient vomiting and prostrated, the headache will be more difficult to control. The beginning of an attack and the tail end are readily checked by a smaller dose.

It is most important that the patients lie down after the medication. A headache that can be checked within one to two hours may be considerably lengthened unless the patient relaxes after its administration. Our routine clinic order is to rest for from one to two hours or until the headache has completely disappeared.

The results obtained from the use of ergotamine tartrate orally and hypodermically in controlling the migraine attacks are so dissimilar that it is necessary to discuss them separately. A statement which is an accurate description of the effects following hypodermic injection cannot be applied to the response obtained from the tablets. All the previous assertions concern the reactions that occur after the subcutaneous use of the alkaloid.

We have dispensed the tablets to forty-five patients, and only thirty-one of them obtained complete relief; this does not equal the 92 per cent of patients who were benefited by the injection. The time required by the tablets before termination of the attack can be expected varies from one to eight hours, averaging about five hours. The average time required for the injection to check the attack is from one to three hours.

The theory of the individual ineffability of ergotamine tartrate, once it has relieved an attack, is fallacious when applied to the effect of the tablets in relieving the headaches. Their beneficial action is dependent on too many factors, such as the state of the gastro-intestinal tract at the time of dosage, the severity of the attack, and the time of administration of the drug. No matter how many times tablets have aborted a headache, if there is severe nausea, if the attack is too intense, or if their administration has been delayed too long, the oral use of ergotamine tartrate may fail to give relief.

Because the tablets are less dependable does not mean that they should not be dispensed for relief of the episodes. Their advantage over the hypodermic use of the drug is obvious and any medication that benefits 69 per cent of the migraine patients is of definite value in the treatment of this enigma. I have stressed these differences in action between the two forms of the alkaloid because I feel that one should not condemn the drug because of the failure to check the headache following its oral administration.

**Concomitant Symptoms and Their Alleviation**

Although ergotamine tartrate, subcutaneously, caused abrupt termination of 1,042 headaches in eighty-nine patients and, when given orally, it completely checked sixty-three headaches in thirty-one patients, it did produce uncomfortable concomitant symptoms in many individuals.

These untoward effects were nausea, vomiting, weakness of the legs, stiffness of the joints, a sense of constriction in the throat, a heaviness of the chest, and a burning and tingling of the fingers and toes.

These symptoms did not all occur in the same patient at one time. Forty-two patients vomited after ergotamine tartrate. In eighty-three of our patients nausea and vomiting were associated with the headaches, even before any medication was given. There was no direct relationship between the occurrence of the gastric symptoms before and after the medication. Five patients

vomited after the drug, and in these individuals there has not been any gastric complaints with the attack. Ten persons who did not suffer from nausea and vomiting with the headaches felt no gastric distress after the drug.

Twenty persons who suffered from these gastric disturbances before the medication were indifferent to their occurrence after ergotamine tartrate because they associated vomiting with relief of the attacks and rather expected it.

In ten patients, if the medicament was given early enough in the episode the entire attack could be aborted, the headache down and the individual entirely well before the gastric symptoms had a chance to develop.

In these persons, if the attack should continue, for its peak these gastric disturbances would become very intense.

When the nausea and vomiting following ergotamine tartrate therapy are severe enough to disturb the patients, atropine \(\frac{1}{100}\) grain (0.0006 Gm.) injected with the alkaloid, or any time after its use, will alleviate this distress. It was necessary for us to use this combination on only twelve occasions, because we were able by our concurrent therapy—the administration of calcium\(^5\) chondroitin sulfuric acid \(^5\) or an estrogenic preparation (progynon)\(^5\)—to diminish the vomiting occurring both with the migraine attacks and after the administration of the drug. These gastric disturbances were by far the most frequent of the untoward results of the drug. Nineteen of our patients, however, described muscle pains following the injection. In three of them they were very severe and continued for a day after the headache had been abolished. The milder forms of this muscle pain were described by a few other persons as a restlessness and an inability to find a comfortable spot for their arms and legs.

Calcium gluconate 10 cc. intravenously will relieve these muscle pains almost immediately, and daily calcium therapy will diminish or prevent their recurrence. Atropine hypodermically or orally, in the foregoing dosage, has inhibited and relieved them on several occasions.

Thirty-seven of our patients complained of generalized weakness associated with the migraine attack. Fifteen individuals stated that, after the alkaloid had eliminated the headache, their legs felt tired and weak. It is rather difficult to determine whether this asthenia was due to the drug or whether it was a contributing migraine phenomenon that the drug was unable to eliminate. A few of the patients state with certainty that this "all in" feeling is more noticeable to them after the drug than before.

One patient who left the clinic without obeying our routine instructions of lying down for an hour after the medication fell down a flight of clinic steps. She described the accident by saying "My legs just gave way, I buckled under me."

Ergotamine tartrate caused a stiffness of the joints in four individuals; in two it affected the jaw, in one the shoulder and in another the ankles.

Two persons felt a slight heaviness in the chest "as if a weight had been placed there," a feeling that made them want to take a deep breath. Six others said that there was a constricting in the throat, "a funny sensation." This did not seem to be particularly disturbing to any of them and occurred rarely.

Two patients complained of numbness and burning of the fingers, which was increased when the hands were placed in very hot or very cold water. We observed on two occasions a painful swelling and redness of the fingers and toes after we had administered ergotamine tartrate and atropine to one of our ward patients. This woman has since received several injections of ergotamine tartrate alone when this did not occur.

**Significance of Symptoms**

To those who are familiar with the signs and symptoms of ergotism and its complications, some of these symptoms are portentous. I do not know what the patient of the continued use of this drug may be. I have searched for pathologic changes in electrocardiographic studies on those patients who have taken medication for eighteen months or more and have made frequent blood pressure, blood sugar and kidney studies but have never found any organic changes.

Migraine is a chronic ailment, however, and may last from twenty to forty years. What the action of this medicament on the vascular system will be if used for that length of time, no one can say.

It is important, therefore, to consider this affliction as a syndrome and not as a disease entity, and to realize that more than one factor can precipitate an attack in the migrainous individual. Unless one studies patients and treats any pathologic process, including psychic factors, that may be present, one may be injuring the future health of these persons by administering this alkaloid in large doses over long periods of time. If, however, each individual is carefully studied and if any abnormality—ophthalmologic, gastro-intestinal, functional, infectious, glandular or allergic—that may be present is treated, the severity and frequency of the episodes can at least be lessened. In this manner we have in many instances reduced the yearly intake of the alkaloid to an almost negligible quantity.

Spontaneous cessation of the attacks in migraine is a characteristic observation. In almost any therapeutic and statistical study of the syndrome one can report complete cessation of the attacks in a few patients. In this series two women, both at the menopausal age, have now been without episodes for more than eighteen months. Neither of them had received more than two injections and both of them had suffered from migraine all their lives at monthly intervals.

That psychic factors can precipitate attacks in migrainous persons, most of us who have had any experience with the syndrome will not deny. That they are the only factors in the production of the episode is not in accordance with the observations of this clinic. That psychic factors alone can completely check 1,000 full-blown migraine attacks within from fifteen minutes to two hours, I challenge.

Considering this possibility at the beginning of the investigations, we administered almost all our medications subcutaneously. Because of this, we were able to inject sterile water, pitressin, epinephrine, mecholin, and the like without the patient's knowledge of the contents of the syringe. During an attack, after we had attempted to give relief by several of these measures and they had failed, we would administer ergotamine tartrate. Occasionally some other medicament would alleviate the attack, but there was no comparison between the character, the frequency or the constancy of the relief obtained from these preparations and from the alkaloid of ergot. The results of other workers substantiate further the belief that the pharmacologic action of ergotamine tartrate in checking the episode is not merely a suggestive one.
The use of this alkaloid in the treatment of migraine is not a particularly recent therapeutic measure. Lennox and von Storch in their latest discussion of this therapy have totaled the number of cases reported in the literature. They state that the dozen authors who have given the drug to 300 patients agree that the administration of ergotamine tartrate is effective in stopping migraine headache in the great majority of patients.

How the alkaloid checks the attacks no one really knows. From our experience in this clinic we do not believe that the therapeutic action is merely analgesic. One patient, who received ergotamine tartrate during a headache, had been suffering simultaneously from a toothache. Ergotamine tartrate checked the migraine attack but gave no relief to the molar pain.

Another man, who entered the hospital because of a severe continuous pain in the umbre nerve, the result of a gunshot injury, developed, while in the ward, one of his biyearly migraine attacks. He had suffered from migraine all his life. The alkaloid was injected and the headache was abolished. The intense pain in his hand, however, was unaffected.

The theory that the pharmacologic reaction of ergotamine tartrate which relieves the migraine attack occurs at the sensory endings is not consistent with the foregoing. Nor does it explain the large number of headaches that occasionally occur in normal people following its injection. We have given the alkaloid to patients suffering from various types of headache that have not in the least resembled migraine. These headaches are usually unaffected by the alkaloid.

It is very rare for the obstetrician to see the many untoward results that we have noticed following the use of the alkaloid in normal and migrainous patients. The obstetrician casually prescribes doses which from his experience he knows to be perfectly safe and effective, but doses which we would be extremely cautious in using. This increased tolerance to the drug at parturition, this failure to relieve the general medical headache, the abrupt termination of the classic migrainous attack, have led us to the assumption that the activity of the drug does not merely effect a paralysis of sensory nerve endings but is more intimately connected with the complex mechanism of the still unexplainable migraine seizure.


**Summary**

1. Ergotamine tartrate was administered to ninety-seven patients and checked or aborted 1,042 attacks in eighty-nine of these persons.

2. It was calculated that the individuals in our series were relieved from 39,000 hours of suffering.

3. The earlier in the attack the medication is given, the better are the results.

4. When used subcutaneously, the alkaloid has never failed to check again an attack in a person previously relieved if the drug was given in adequate dosage.

5. Untoward effects of the drug may be relieved by simultaneous injection of 750 grain of atropine or calcium gluconate intravenously.

6. I do not consider the drug a cure for migraine. I strongly advise against its dispensation without a consideration of the cause and prevention of the syndrome.

**Conclusion**

Because of the constancy and character of the relief obtained from 1,042 headaches in eighty-nine sufferers of migraine after the administration of ergotamine tartrate, I recommend its use for the termination of these attacks and believe that the drug is a valuable addition to medical therapeutics.

8 West Sixteenth Street.

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**Clinical Notes, Suggestions and New Instruments**

**Duplacing Films of Roentgenograms**

Max Cohn, M.D., Chicago

The making of roentgenograms in a hospital occasionally leads to a controversy between the patient, the physician and the roentgenologist over ownership of the original films.

Positive prints from roentgenograms are unsatisfactory, and except in certain simple cases the fine details of the original are inadequately reproduced.

Until recently it was necessary for the maker of a roentgenogram either to protect himself by keeping the film in his possession or to satisfy the physician and the patient at the risk of criticism, should he be unable to produce the film for medical or legal purposes at some future time.

A new photographic material called "Direct Duplacing Film" is now available. With this film any number of exact duplicates can be produced from original roentgenograms by direct contact printing without the necessity of making an intermediate film with consequent loss of detail. The film has characteristics exactly opposite those of normal photographic film.

If developed by a safelight without having been exposed to light, Direct Duplacing film becomes entirely black, developing to maximum density. If, however, the film is completely exposed to white light and then developed, the film remains clear and transparent. This material forms a positive image directly from a positive, becoming clear and transparent when exposed to transparent areas of the film being copied, and becoming progressively darker and more opaque as the film to which it is exposed becomes darker and more opaque.

Developing, fixing and washing correspond in every way to the ordinary handling of any other film. Provided exposure and processing are correct, the duplicate will for practical purposes equal the original. The duplicating film is a so-called safety film.

In making a duplicate of a roentgenogram it is possible to print a caption on the duplicating film, which may be an identification or may correspond to an official certification that the

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From the X-Ray Department, Mount Sinai Hospital.