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Morphine addiction with special reference to treatment

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MORPHINE ADDICTION WITH SPECIAL REFERENCE TO TREATMENT

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From time immemorial, certain unstable types of mankind have sought relief from or aid to their inabilities in order to meet the requirements of their environment. This has usually been accomplished by resort to drugs that may or may not have been habit forming. The extent and scope of this practise is common knowledge. In recent years, by means of a concerted international movement to control traffic in opiates, drug addiction has been materially reduced. However, when we realize that in many countries about 40% of male morphine addicts are members of our own profession, not including allied professions such as nurses and dispensers, we can realize how far we are from a solution of this problem. Because of this, I am especially interested in reviewing the literature to ascertain the possible etiology of addiction and the past and present theories as to treatment of the morphine addict.

During recent years, a great change in feeling on the part of the physician in regard to morphinism has occurred.[5] Where formerly it was generally regarded as a "vice" or "habit", it is now increasingly being recognized as a functional disease. If even a large minority of so-called "addicts" discontinued the use of the drug unaided, through their own efforts, one might rightly hold the majority responsible for not doing likewise; but less than one-fifth of one percent accomplish this task. Undoubtedly the logical explanation of this fact lies in the peculiar properties of the drug which affects the body and mind of the user in such a manner that attempts at discontinuance lead to extreme mental and physical suffering. The depression and mental anguish are intense and horrible in themselves, but moreover they leave the user in no condition to bear physical pain. This functional disease involves the nervous system primarily, but the glandular system and metabolism are affected as well. To

understand morphinism, it is essential to understand the pharmacodynamics of morphine.

Morphine seems partially to paralyse the motor nerves, apparently making it necessary for the brain to send out greater and stronger motor impulses, as the addict becomes more deeply involved in his addiction.[31] On the other hand, the need for the inhibitory impulse becomes progressively less. At least C. B. Pearson was of this opinion after observing the effect when the drug was too quickly withdrawn. Where the drug is rapidly removed, the mental machinery is as violently disturbed as the physical mechanism. Even when the drug is removed slowly and cautiously, there is a lack of emotional control and a lack of mental inhibition. As to inhibition as regards speech, an elderly lady said, towards the latter part of the reduction, "I was a good Methodist when I came here, but I don't know what the devil I will be before I leave". Even when the reduction is managed slowly and carefully, that is, in from thirty-five to seventy days, according to the severity of the case, nature does not have quite time enough to adjust herself completely to the change.

It is best to consider the effect of morphine on the nervous system under two heads namely, on the parasympathetic or extended vagus nervous system and on the central cerebro spinal nervous system.[49] On the parasympathetic system it acts as a decided stimulant in the addict. It stimulates the nucleus of eppinger-hess in the nucleus of the third or occulomotor nerve situated in the mid-brain which by way of the ciliary ganglion goes to the circular contracting muscle fibers of the pupils causing a marked miosis.

It stimulates the dorsal nucleus or motor nucleus of the vagus proper situated in the medulla oblongata, causing a contraction of the fibers of the larynx with huskiness of the voice. It stimulates the fibers of the esophagus, at times causing a globus hysterions. It stimulates the motor fibers of the stomach and intestines, which often causes bobyrigmus and would cause a rapid emptying of the stomach but for the marked stimulation of the pyloric sphincter

which takes place at the same time. It also causes a stimulation of the sphincter of oddi, preventing normal emptying of the gall bladder, although the muscle fibers of the gall bladder itself are stimulated. The motor fibers of the small intestines are stimulated through the ileum to the coecum from the above-stated nucleus. It also stimulates the large intestine, but due to stimulation of the internal sphincter causes spastic constipation. On the cardiovascular system it acts through the inhibitory fibers of the vagus causing a slowing of the heart -- but gives a strong full pulse. This covers R. L. Young's description of morphine's action on the parasympathetic system.

Morphine's action on the central cerebro spinal system is quite different in addicts than it is in non-addicts. It stimulates the sensory side of the cord, causing the patient to be very much more susceptible to pain. In the non-addict, it depresses the sensory side of the cord. It stimulates the motor side of the cord, causing an increase of reflexes with attendant quick, jerky movements in speech, gestures, gail, etc. It stimulates the cerebral cortex as a whole causing hypercerebration, flight of ideas, rapid speech, faulty judgement and the lack of or poor insight. This causes the patient to fool himself, so to speak, and live in a world of unreality.

In 1883 Marme[24] conducted a series of experiments with dogs, and concluded, from the result obtained, that morphine was converted in the body into oxydimorphine, a substance having a dimetrically opposite physiologic action to that of morphine. He concluded that this substance produced the abstinence symptoms which make their appearance on withdrawal of the drug; required increasing amounts of morphine to neutralize its effects; and in turn neutralize the morphine, thus accounting for the increase in tolerance. This theory however seems to be untenable in view of the fact that Donath, Stark, and Marquis, respectively, operating under similar conditions, could not identify oxydimorphin in either the blood or urine in dogs in which tolerance to morphine had been established.[5]

A theory which appears more plausible and which has acquired a certain degree of acceptance was advanced by Faust in 1900.[5] From his investigations he was led to the conclusion that the system in the case of dogs acquires the power to destroy increasingly large amounts of morphine. The question of the destruction of morphine in the system as far as its being the sole cause for the establishment of tolerance appears to be definitely settled by Rubsamen in 1908. After experimenting with rats he advanced the theory that, in addition to the increased power of the organizm to destroy morphine, the cells of the tissues, during the period of increased tolerance become less sensitive to the action of the drug.

Another theory brought forth by Wholey in 1912,[5] who states that he believes increased tolerance, in part at least, is due to the fact that the nerve cells become exhausted from continued reaction and the accumulation of waste products, and for these reasons require an increased dosage to bring about an adequate effect.

Light and Torrance,[22] experimenting with a large number of addicts, found that the intra muscular injection of morphine sulphate in dosages of three, four and six times the usual amount given, and the intravenous injections of dosages six, seven and nine times the amounts usually given resulted in insignificant changes in the pulse and respiration rates, electracardiograms, chemical studies of the blood, and the behavior of the addict. The physiological changes brought about by these additional amounts taken as a whole may be regarded as practically negative. All the intravenous experiments were accompanied by a distinct flushing of the face, neck and upper part of the chest auteriorly. All the addicts complained of feeling more or less warm, as well as "loaded". However, careful studies of the blood pressure and pulse rate did not reveal any essential difference accompanying the sensations described by the addict. The additional amounts have no effect on the central ner vous system since it failed

to bring about any obvious changes in the respiration, and the absence to sleep on the part of the addict proved the ineffectiveness of the normal pharmacological action of morphine on the nervous system. After the drug was given intravenously, most of it had left the circulation at the conclusion of the injection -- on an average, less than 1 mg. in 25 c.c. of blood was found. The additional amount of morphine must be either rapidly excreted or removed from the blood by tissues other than those of the central nervous system and destroyed, or chemically bound and made inert, and slowly returned to the blood for excretion. Light and Torrance conclude, that in consideration of their own experiments they believe that these large amounts of morphine introduced into the circulation are promptly removed by the muscles, so that only small quantities are available for action on the central nervous system. Having once been removed by the muscles, the morphine must have been destroyed or returned slowly to the circulation in small quantities. Theoretically then, with the development of a mechanism in the muscles for the removal of morphine from the circulation, one can conceive of it becoming so effective as to leave an insufficient quantity for action on the central nervous system and the addict consequently prompted to increase his regular dosage. From their experiment they have found that the quantity of morphine required to prevent the appearance of withdrawal symptoms is considerably less than is normally used by them.

Faust[5] arrives at a similar conclusion as to the cause of tolerance. He believes it is due to the increased capacity of the addict to destroy morphine. The destruction would have to be at a rate practically equal to the rate of absorption. Morphine has been found in the tissues of addicted dogs by Faust in quantities sufficient to be distinctly toxic to unaccustomed animals. Furthermore, the vagal slowing of the heart, the intestinal motility and the miosis continue unmitigated, indicating the continued presence of morphine in the system.

Another interesting phase of tolerance development in the addict is what

is known as "crossed tolerance". By this is meant the development in addicts of tolerance toward other hypnotics -- beside morphine. Tatum, Seevers, and Collins[42] in their experiments found, that large doses of sodium barbital (0.5 grams) could be given to a morphinist twelve hours after his last injection, and another 0.5 grams one hour later, without any change in blood pressure, respiration, or any subjective symptoms. Many diversified opinions appear in the literature in an attempt to explain the cause of withdrawal symptoms. Bluemel[50] in 1919 offered the opinion that morphine disturbs the normal secretory and excretory functions of the body, and by its prolonged use thus induces an autotoxemia. But it is by no means clear why this toxemia should suddenly fulminate when the morphine is withdrawn, and the lack of explanation on this point materially weakens this theory.

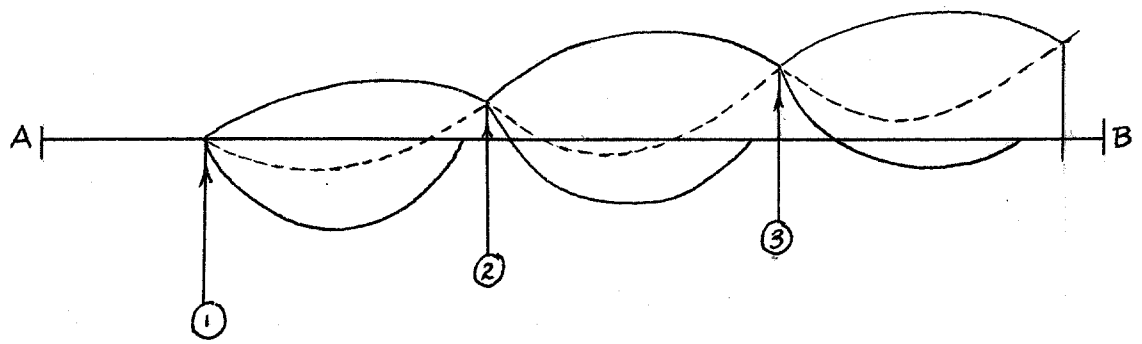
Kraus,[20] from his work on withdrawal symptoms of chronic morphinism, states, that the reason that any vegetative symptoms appear is that, in the course of acquiring an increased tolerance to the drug, the threshold of irritability of the vegetative nervous system is gradually raised. Were this not so, two things would happen: there would be continued occurrance of symptoms while the drug was used in toleraged doses, and there would be no symptoms upon withdrawal. He has shown in his paper, that morphine causes functional depression. The symptoms of withdrawal are the opposite of morphine administration in chronic morphinism, i.e., functional acceleration. The explanation of this sudden reversal of symptoms lies in the fact that morphine taken as a habit forming drug upsets the normal equilibrium between the sympathetic and the autonomic systems, establishing a new one. When the new equilibrium is destroyed by taking away the drug, symptoms naturally result. The hypoacidity of the habit reverses itself. Hyperacidity takes its place, and this forms the basis for giving alkalies in treatment. The cramps in the extremities during withdrawal are among the most distressing symptoms. Kraus explains this as being due to a vasoconstriction.

Nitrites and warm baths are therefore of great benefit for this.

Light and Torrance[23] in their experience with addicts and all cures, including "cold turkey" (abrupt withdrawal without the substitution of any drug), is that at the end of the week to ten days all acute withdrawal symptoms have disappeared. The addict was then able to satisfy his craving as well as to derive a "kick" with dosages as low as from 1/8 to 1/4 grains. It would appear from this that within a week or ten days the muscles lose their ability to remove the drug from the circulation.

Many theories regarding the various phases of morphinism have been forwarded. In this review I will mention those which have the most logical conclusions. Teruuchi and Kai[43] after extensive experimentation with rabbits drew these conclusions: That morphinism is due to the acquired power of the living organism to destroy morphine, and to excrete it besides the augmented power to reserve it in a large amount by the muscles, so that even though a large amount of it should be introduced into the body all at once, it can be prevented from immediately attacking the central nervous system.

Tatum, Seevers, and Collins[42] in 1929 presented a very clear picture of the emotional changes taking place during the period of morphine injections. They made a graph which I have reproduced here. The base line A-B may be taken to represent the normal level of irritability of the organism as a whole. At the same time an increase in irritability occurs, as represented by the line rising above the base line A-B. The dotted line represents the integration of the depression and stimulation curves. At 2, manifestations of increased excitability are still evident. At 2, another injection, or long series of injections through a period of weeks or months, occurs. At this moment the depression begins, not at the original base level but at a point above this, so that the depression beginning at a higher level of irritability has more to overcome than originally was necessary, hence does not go down to the same absolute depth as before. On the



EMOTIONAL CHANGES TAKING PLACE FOLLOWING INJECTION OF MORPHINE

other hand, the stimulant phase starts in at a level above the base line and acts additively reaching a level higher than before. A continuation of this process sooner or later leads to a condition in which the depressant phase of a subsequent injection of a proper size brings the irritability level down to a level approximating normality. Should this subsequent injection be withheld, the irritability continues uncontrolled giving rise to withdrawal or abstinence symptoms. The same diagram also illustrates how a human addict is able to tolerate a dosage that would be fatal to a normal man. These men summarize their report with four statements:

1. Morphine simultaneously stimulates certain parts of the central nervous system and depresses others.

2. Irritability increases with repeated administration of morphine because of the increment of stimulant effects.

3. Abstinence symptoms are plainly due to the fact that stimulation of the nervous system, or increased irritability, outlasts the depression, and not to a specific need for this particular drug.

4. The increased nervous irritability observed after the depressant effects have largely worn off are quieted by a large dose of morphine. This increased dosage further augments the nervous excitability, hence a vicious cycle is developed. Finally the increased nervous excitability becomes so extreme in man that no amount of morphine will suffice to produce sedation. This condition is the stage of intolerance.

Kraus,[20] in his report, concludes ;

1. The action of morphine is bifold. The first stage consists of depression of inhibitory activities, stimulation of acceleratory activities. The second stage consists in stimulation of inhibitory activities, depression of acceleratory activities.

2. The most noticable effects of the action of morphine are those of the

second stage. This is due to the transitory nature of the first stage.

3. The effect of the action upon function is depression.

4. The effect of the action upon visceral activity in some cases is increased muscular activity, as in the eye, gastro-intestinal tract and bladder.

5. The site of the action is believed to be central, and upon the central sympathetic inhibitory control of the autonomic centers.

6. The action of morphine upon pain sensations is a depression of a stimulatory action, according with its other actions.

Van Dorgen in 1915 found that there is a specific tissue immunity in which the different organs and centers acquire immunity with a varied readiness and to an unequal degree.[5]

An explanation of an entirely different character has resulted from the researches of another group of laboratory workers. These investigators attempted to show an analogy between the immunity produced by bacterial vaccines and that of opium or its alkaloids. Gioffredi[5] in 1897 experimented along this line and concluded that an antitoxic substance was found in the blood of tolerant animals and that this neutralized the effects of the morphine. Results pointing to a similar conclusion were obtained by Hirschlaff, Von Marikovszky, and Berri and Belgrano. Bluemel, after extensive experimentation states, that it seems probable that the immunity developed is due to the presence of an antibody or antitoxin in the blood. Physicians have come to believe, he states, that a definite antibody to morphine is formed in the blood, and that unneutralized antibody is the cause of the withdrawal symptoms. Ostromislensky[27] holds a similar theory. He believes that when morphine preparations are injected daily in man for a sufficient length of time there appears in the blood a new kind of protein -- an autoprotein which acquires the properties of an antigen. Although formed in the body, this protein acts on the organism in the same manner as a foreign protein, causing the formation of a specific antibody. The quantity of

the specific autoantigen circulating in the system of morphine addicts gradually increases. Therefore, as a rule, a morphine addict requires a gradual increase of his daily dose of the drug. The basic premises and conclusions he arrives at may be formulated as follows:

1. The symptom-complex appearing in withdrawal of the drug should be considered as the symptom-complex of the anaphylactic shock.

2. An individual who takes morphine daily in about three weeks usually becomes an addict, supposedly at the time when the corresponding specific antibody is formed in his system.

3. The addict's imperative need of morphine can be explained through the ability of morphine to prevent the possibility of chemical reaction between the antigen and its antibody. To avoid the anaphylactic shock, and prevent the withdrawal symptoms, one must replace the morphine by a chemical substitute preventing the combination between the antigen and antibody.

4. A morphine addict who has stopped taking morphine continues for a long time to be a carrier of the specific antibody. Hence he may be said to remain in a state of potential addiction for an indefinite length of time. Subsequently, on the very first injection of a quite insignificant dose of morphine, if the antibody still exists, there appears again in the system of the addict a specific autoantigen which provokes the inevitable relapse.

5. At any given period of time during the disease, a definite quantity of the antigen is circulating in the system of the morphine addict. Therefore, at any given period of the disease an addict always requires a definite and precise quantity of morphine which suffices to neutralize all of the auto-antigen present in the system. Although this theory answers most of the questions in morphine addiction, Dr. Ostromislensky's experimental proof is lacking.

In 1924, Valenti[5] found that the serum from dogs immunized to morphine -- during abstinence symptoms, when injected into normal animals -- readily produced

pseudo-withdrawal symptoms. This was demonstrated not to be due to the toxic properties of the serum as such, since no evil effects were obtained when the serum from unmorphinized dogs were employed. While the identity of this toxic substance has not been established to date, it is not in keeping with our present theories of immunity to pronounce it an antitoxin. In no disease in which antitoxin formation has been demonstrated have there been observed untoward symptoms that could be attributed to the action of the antitoxin. DuMez, and Kolb[19] are in agreement against the possibility of an antitoxin being present. They state, that the assumption that substances so well defined chemically as the alkaloids can give rise to the formation of antibodies is contrary to the generally accepted principles of the theory of immunity. In the experiments these two men completed, the minimum fatal doses of morphine sulphate and heroin hydrochloride, when injected subcutaneously in aqueous solution, were established, and the protective effect of the serum against the dose was then tested. The serum used was obtained from morphine and heroin human addicts. The results failed to show that the sera offered the slightest protective action, it therefore being concluded that the blood of human beings addicted to these drugs does not contain antigens, antibodies, or other transferable immunizing substances.

Wuth[47] points to the resemblance between the symptoms of morphinism and of hypofunction of the thyroid; also of the resemblance between the violent disturbances from sudden abstention and the symptoms from hyperthyroidism. Gottlieb[11] showed that thyroid fed rats had a diminished tolerance to morphine, while thyroidectomized rats showed an increased tolerance. The evidence of the physical findings in chronic morphinism points to a depressor effect upon thyroid activity. The thyroid is the familiar accelerator of metabolism and the vegetative nervous system. Thus there is depression of an accelerator function. Morphine has no effect upon the gland tissue, its effect probably being on the vegetative nerves going to the thyroid.

Williams and Steele[57] are more of the opinion that the adrenals are influenced in morphinism. The adrenal involvement conception is confirmed in a measure at least by the effects produced by substances that stimulate the adrenal system, namely, adrenal cortex preparations, strychnine, non-specific proteins, morphine -- bearing in mind always that these substances affect as well the whole endocrine system and all body structures. There are other things that suggest adrenal involvement as a dominant feature in morphine addiction. There is a hypocalcemia, frequently a heightened pH, usually a lowered red blood count resembling a beginning Addison's, and the severe hypotension seen in hypoadrenal conditions in contrast with the mild hypotension of pituitary dysfunction. Also, the drug withdrawal symptoms are improved by the same agents just mentioned that stimulate adrenalaction. And, of some significance at least, is the fact that adrenal failure cases are peculiarly susceptable to psychic effects as are also drug addiction patients.

Lewis[21] in 1921 published a report which stated that after double adrenalectomy, white rats become 400 to 500 times more sensitive to morphine than normal rats. After much detailed work, Rogoff and DeNecker state, that there is no evidence that any significant change in tolerance occurs after adrenalectomy. Howard, after administration of insulin in treatment of morphinism in a large number of cases concludes, that the gradual increase in blood sugar with the withdrawal symptoms suggests to him that the secretion of addrenalin has some influence on the fluctuation of the blood sugar curves.

Another viewpoint as to the causation of withdrawal symptoms is given by Gelma.[10] He states that it is his opinion that the phenomena is due to intense emotion, and secondary to disturbed equilibrium of the vagosympathetic. Apprehesion and depression are the chief emotional symptoms, an obsessing fear of the results of deprivation of the drug. The emotions induce changes in the endocrine secretions with subsequent hyperexcitability of the vagus. This hyper-

excitability entails perspiration, increase of gastric acidity, diarrhea, low temperature and asthenia. The psychic theory suffices by itself to explain all phenomena of demorphinisation without calling in a theory of intoxication, by which the phenomena are ascribed to chemical changes in the nervous tissue. Accordingly the treatment in his opinion should be psychic. Persuasion, auto-suggestion, appeals to ethical or religious feelings are of little use. The essential thing is to keep anxiety and terror from getting possession of the patient, to make him believe that he is not being restricted in his habit. Therefore, Gelma states, the patient should be allowed to keep his syringe and a solution, the titer of which, of course, is prescribed by the physician.

After making an extensive check on a large group of addicts during their abrupt withdrawal symptoms, Light and Torrance found that the circulation, respiration and blood concentration more or less normal except for a moderate hyperglycemia and a mild leukocytosis. Because of this the question arises as to whether withdrawal symptoms are on a functional or organic basis. The incessant begging and the annoying behavior of the addict during this period often leaves the observer with the firm conviction that these men are not organically sick, the whole picture being an emotional one. Just as frequently one observes men in this period suffering with violent muscular twitches, voimting, perspiration, and yawning and showing such a sickly appearance that we become convinced that there must be an organic basis for their apparent suffering.

In favor of an emotional basis as a cause for the withdrawal symptoms, Light and Torrance[28] cite their negative observations. Despite the fact that the addicts claim to be so weak as to be scarcely able to move, their responseto a staircase climbing test was carried out with the same efficiency as when drugs were administered, with the exception of the respiratory response; following the readministration of the drug, the response was, if anything, poorer. Such differences as exist in basal blood pressure, heart rate and respiratory rate are

too small to indicate any significant change. Addicts will admit that when they are unable to obtain drugs, and when withdrawal symptoms with extreme weakneww have become serious, the assurance of an available supply at a considerable distance will cause them to travel this distance with remarkable speed and efficiency. The concentration of the blood and loss of weight would indicate some organic disturbance, on the surface, but these investigators believe that these two positive manifestations can be explained on the basis that the addicts will not take food or water and perspire to such an extent that they cannot help showing this loss of weight and the degree of concentration of blood found in these cases.

Yawning, restlessness, vomiting, diarrhea, perspiration and extreme weakness are found in many emotional states. This type of behavior has frequently been observed by one of us in a group of football players just prior to the playing of a so-called "important game". The players will state that they are so weak that they can scarcely move.

Further evidence that the picture has as its basis an emotional state, is the response often seen of addicts during withdrawal symptoms obtaining complete relief after the hypodermic injection of sterile water. Despite his obvious suffering, he immediately quiets down and often goes to sleep.

The presence of diplopia, marked increase in the number of leukocytes, and occasional albuminuria, constitutes sufficient evidence for one to look on withdrawal symptoms as having a true organic basis. Leukocytosis has been described in emotional states, but the degree reached -- from 20,000 to 27,000 as seen during withdrawal -- would make one proceed with caution in attributing such a count to pure emotionalism. Also, muscular twitches are, at times, of such magnitude as to preclude any possibility of pure nervousness. To those who are inclined to accept an emotional basis as the cause of withdrawal symptoms, a satisfactory explanation would be that the craving for the drug brings about emotional

states sufficiently powerful to cause organic changes and that readministration of the drug brings mental relief long before the resulting organic changes can rectify themselves. On the other hand, if some true organic disturbance is the basis of the suffering, the readministration of morphine brings about relief from the peripheral sensations just as morphine relieves the patient from the pain of cancer but not from the cancer itself.

Ashworth[2] is of the opinion that most drug patients, if not outright, are at least borderline psychopathics. He does not believe that the drug habit per se is inherited or transmitted, but the history of a large percentage of his drug patients reveal psychopaths among their progenitors.

Yoder,[48] in the study of thirty-five women, consecutive and unselected cases of morphinism without psychosis, admitted to the Kalamazoo State Hospital, Kalamazoo, Michigan, during the past nine years, 23% of these patients had a family history of psychiatric interest. Another point of interest was that of these thirty-five women, there was a history of forty-five major surgical operations for some somatic disease. This is indicative of the general tendancy toward hypochondrical personalities in morphine addiction.

Young[49] states, that of all inebriates, there is none sicker (nervously usually), than the morphine addict. As in the whiskey addict, you have different degrees of the malady. You may effect a cure in one of twenty years duration and not be able to in one of only a couple of months duration. This may strike the physician as being peculiar, but it isn't so much the drug as the individual, especially the personality make-up, which influences the prognosis. The drug is isomerically the same -- morphine is morphine, but this is not true of humans. We are each biologically different. Some of us are so different we are potentially abnormal and only a few doses of the drug will throw such an individual out of kilter. Mainly because of its mental impression -- and the morphine craving will follow. The person with a good thyroid and adrenal

glands, or well functioning testes would not succumb, everything else being equal -- such as early training and environment.

Pearson[31] believes that the impression that only the neurotic are in danger of becoming addicted is a dangerous teaching. He feels that the direct cause of morphinism is morphine. Those who are not neurotic should not be led to think that they can take the drug or leave it alone as they please. He found many of his drug patients were of the phlegmatic temperament. This all leads up to the question, is morphinism a toxemia or a neurosis. The word morphiomaniac would indicate that there are some who look upon morphinism as a psychosis. There are many psychotic symptoms that are both characteristic and persistent. The psychic changes are only part of the pathology of this disease however. It is a psychosis, a neurosis, a toxemia, and probably a number of other things besides. Because of this, treating cases of morphinism becomes a very complicated problem.

For years different methods have been tried to supplant the unsatisfactory gradual withdrawal method. When a patient presents himself for treatment he has marshalled all the physical and moral courage he possibly can, and it generally lasts as long as the first time he feels a cut in dosage, be it real or imaginary. This constitutes one of the difficult problems of gradual withdrawal.[14]

The rapid withdrawal treatment was first introduced by Erlenmeyer in 1883. Gardner[8] uses a modified form of the rapid withdrawal treatment. After thoroughly checking the patient over both physically and as to mental attitude, he starts on his withdrawal. He is isolated from friends and family with absolute restriction of visitors of any kind, and is not allowed to send or receive telephone messages, notes, or mail. His clothing including his night clothing and bathrobe, are surrendered by him and thoroughly searched, as is his person. After a preliminary observation period of 24 to 48 hours, withdrawal proper is begun. The patient is placed upon a dosage of about one half

the amount of morphine by hypodermic that he has been taking. The dose is divided and at definite scheduled time -- the late evening injection being strongest, in order to secure a good night's rest. The early morning dose is next in potency. As absinence symptoms set in and increase in intensity, sedatives are administered in the form of bromides, sulphonal, trional and luminal, including sodium luminal by hypodermic. Analgesics other than opium and its derivatives, and occasionally combined analgesic sedative preparations such as allonal or cibalgine are also given. Gardner believes in free catharsis, but not drastic purgation. In case of cardioc embarrassment, the usual supportive treatment is used and if collapse is feared morphine is given by hypo at once.

Bluemel[50] mentions that the present treatment of chronic morphinism involves three principles, namely, cathorsis, the rapid or gradual withdrawal of the drug, and the administration of belladonna or alkaloids derived from the belladonna group -- the alkaloid most generally used being scopolamin. The use of the first two is obvious. The use of the alkaloids seems to be to effect a stupor or intoxication and thus reduce the suffering caused by the withdrawal symptoms. Various other explanations are offered for the use of belladonna and the alkaloids, one being that the active principles of the belladonna group are physiologic antidotes capable of "unpoisoning" the patient. The explanation of "unpoisoning", Bluemel feels, is a little fanciful.

An anonymous physician,[1] for three years a morphine addict, believes the only way to cure the habit is to discontinue the drug at once. This makes the patient bedridden which is an advantage. He states that insomnia lasts months -- but the terrible restlessness lasts only a few days. The patient, in his opinion, should not be left alone for at least six months. A relapse is easily possible within a year. The patient is cured only when full ability and zest in his work has returned.

Pearson[32] holds that the favorite treatment of locking the addict up and

taking away his supply is wrong, even in those cases where it does succeed in permanently breaking up the addiction. It is wrong therapeutically, he argues, because it is needlessly dangerous, because it is unnecessarily brutal, and lastly because it is founded upon the assumption that the addict is a criminal. His experience leads him to believe that there is such a thing as breaking an addict's spirit and courage to that extent that even if the addict becomes cured after passing through what the doctor believes is good enough therapeutics for him, that he will never make as good a citizen as he would have been had he been treated by some more kindly and humane method. Also, in case of relapse, these patients that have been mistreated, he found, he was unable to secure cures again because their courage had been completely broken.

Hosslin[15] regrets that the law makes it impossible to treat morphine addicts against their will. Strict isolation with unpaid nurses (nuns), gradual withdrawal of morphine within from three to ten days and combating of abstention disturbances with large doses of phenobarbital gave fair results. Recurrences, in his experience, are frequent.

Gunther, Harold, and Behneman[12] reported in 1928 the use of sodium phenobarbital in treating morphine addiction. The method of administration was essentially that used by the Los Angeles General Hospital. One tenth gram (1½ grains) of the powder was dissolved in sterile distilled water. The drug was given subcutaneously. Its action became apparent in from ten to twenty minutes, and relief of pain occurred in twenty to thirty minutes. They cite a case of a male, age 45, who had been taking between 5-7 grains of morphine sulphate daily. Morphine was wholly withdrawn, and the patient was strictly isolated. Next day he was in considerable distress and sodium phenobarbital gr. 1½ was administered twice daily by hypo, subcutaneously for two days. On the third day this was increased to four times a day because of restlessness. After six days the barbital was reduced to three injections daily -- and no withdrawal symptoms

were observed. This report means little, since a large amount of clinical proof is needed to recommend any treatment.

Williams, and Steele,[57] have observed over 250 addiction cases examined and treated under hospital conditions, and have reached some definite conclusions, and feel warranted in publishing these results. After much work and experience it is their belief that rapid morphine withdrawal in the chronic addict may be satisfactorily accomplished by the use of the non specific protein of alfalfa, alfalfa proteal, then by any method as yet available. They did not get corresponding results with other foreign proteins, either in subjective symptoms or objective symptoms. This tends to corroborate their belief that each non specific protein has individual qualities and systemic effects quite apart from the generally accepted ones credited to all such proteins. Alfalfa proteal is a two percent alfalfa protein -- which insures antigenic stimulation without producing disagreeable protein reactions. The disagreeable protein reactions such as chills, depression, thermal reactions, and general feeling of dilapidation are eliminated. In their experience the foreign proteins tend to stimulate the whole endocrine and hemopoietic systems. If the patient is in fairly good physical condition he is kept under observation for at least 48 hours before starting treatment. This gives time to regulate his elimination, get him accustomed to his surroundings, and keep him comfortable on one-half or less of his regular narcotic dosage. The cardinal sin is that of letting the patient know "what he is getting". Yet you must keep the patient's confidence. And as a mainstay you must have experienced nurses -- trained, and familiar with addiction cases. The average registered nurse, inexperienced in this field, is actually detrimental.

In treating with foreign protein, the protein is usually given in the A.M. with the usual morning dose of morphine. One c.c. of the solution is given subcutaneously every four hours for the first 24 hours, the same amount at six hour

intervals for the following 48 hours, then one c.c. daily thereafter for a week or ten days. In an ideally responsive case, no morphine is given after the alfalfa protein treatment is started. There is usually no great discomfort from withdrawal symptoms. If there is pain or distress, hot baths will often give relief. Sleeplessness is the most dreaded thing in the addict world -- so a stiff dose or two of sodium amytal by mouth or hypodermically each night will always be helpful. Any addict requires at least twice the average dose of anything in these investigators' estimation. Hot milk is also of some use in inducing sleep and of tremendous help in large quantities as a food and calcium restorative. At the end of the 72 to 90 hours the active withdrawal process will have been completed. Naturally it is an uphill course for a week or ten days thereafter, even in most favorable cases. Tonics and restorative measures of every kind are indicated. Coffee in large quantities is most helpful. The addict's intestinal tract is always abnormal. The pH of the colon and lower ileum is usually abnormally high. Correcting this helps, and for this purpose they use lactic acid in a seal-in coating that is acted upon by moisture and releases in about five hours. This combination with sweet cascara glucoside makes an ideal acidulating laxative tablet. As a routine measure they give strychnine sulphate in 1/30 grain doses hypodermically four times a day -- in intervals between that of the protein. Besides satisfying the addict's "craving for the needle" -- the strychnine stimulates the adrenals and helps to hold up the patient and tide him over distressing periods. The "needle wise" patient can tell a sterile hypo or almost any other substance that isn't an opiate, but strychnine is the exception. Most patients require some morphine during the first two or three days of withdrawal treatment. The rule, subject to indications, of course, is to give ½ grain doses t.i.d. the second day, and 1/8 grain dozes t.i.d. the third day. Thereafter no morphine is given. Indeed, if an opiate seems imperative after the third day, the patient is probably inherently

incurable or suffering from some organic disease that contraindicates further treatment, in their opinion.

Jenkins[17] reported a treatment in 1930, which is a combination of the treatment outlined by Pettey and Neuberger. Capsules containing the following constituents were made:

℞ Hydrargyri chloridi mite

Rhamni purshianae extractia a	gr. X (0.65 gm.)
Ipecacuanhae	gr. 1 (0.065 gm.)
Strychninae nitratis	gr. ¼ (0.0162 gm.)
Strophinae sulphatis	gr. 1/150 (0.0013 gm.)

M. et sig. -- make 4 capsules.

Now, ½ grain of morphine dissolved in physiological saline was first given the patient. These capsules were next administered -- one at a time -- at 4, 6, 8, and 10 P.M. The next morning at 6 A.M., two ounces of castor oil are given plus strychnine gr. 1/30 hypodermically. Both drugs were again given in the dosage at 8 and 10 A.M. The patients took it for granted that the strychnine was morphine, and were not informed of their error. No morphine was allowed from this point on. Occasionally sterile hypos of NaCl were given.

The use of chloriform, which was Neuberger's contribution, was next instituted. Fluids were forced to prevent oliguria and urine was daily examined for ketones, the appearance of which would demand the immediate suppression of the chloriform. A damp folded towel was applied with its center over the chin of the patient and either end brought up obliquely along the angle of the mouth and the side of the nose to cover the eyes. An ordinary gauze covered cone was placed over the mouth and nose and the chloriform administered a few whiffs at a time. This is repeated as often as the patient demands it. The amount of chloriform administered the first day was from 15-20 grams. The second day this was increased to from 30 to 60 grams. No more than 120 grams were given in 24

hours, and this amount was steadily diminished until the chloriform was withdrawn altogether, which was between the ninth and fourteenth day of treatment. The patients are surprisingly comfortable, according to Jenkins, the abdomenal pains were absent or slight, nausea and vomiting not marked, and the chloroform controlled the restlessness. The administration of a sterile hypo of saline followed immediately by a little larger amount of chloroform usually gives the patient a sleep of several hours duration. In more obstinate cases of insomnia, hyoscine, and in patients who did not tolerate hyoscine, dial (ciba), the former administered subcutaneously, and the latter intramuscularly, give good results. This treatment has the special advantage of being possible to carry out in the home. The cardiorenal system must be checked carefully before starting the treatment.

In 1926 Alexander Lambert, and Tilney[52] introduced a treatment which used a solution of lipoids, together with non specific proteins, and water soluble vitamines. The substance was discovered by Horovitz, a biochemist, and named "narcosan". The theory of the action of narcosan in the body was that narcotics, such as morphine, called forth in the body certain protective substances to neutralize them. If the narcotics be suddenly withdrawn, and not given, these neutralizing substances are themselves toxic to the body. The lipoids in narcosan neutralize these toxic substances theoretically, in place of the narcotic. After seventy-two hours, because the withdrawal symptoms are over, these neutralizing reactions have ceased, the lipoids are then continued to replace the depleted lipoids in the body. The non specific proteins of the narcosan are added to stimulate the blood forming tissues.

According to Lambert and Tilney, the convalescence of the patients under a daily injection of narcosan is encouraging. The narcosan patients have a voracious appetite, are always hungry, especially for sugar, and can digest all they eat on the fifth and sixth days of treatment without any digestive disturb-

ances, and without recurrence of their withdrawal symptoms. They acknowledge that they no longer "think of dope". This report was made after treating 366 patients with narcosan. In spite of the encouraging words these men have for this treatment, within a little more than two years later, the Mayor's Committee of New York on Drug Addiction reported that after thorough trial in their penal institutions of narcosan -- there was a greater occurrance and intensity of all symptoms in those treated with narcosan. Also, they found, that there was no advantage shown in recuperation after the withdrawal period. From then on the treatment has been condemned.

Reddish,[53] in 1931, reports his results after experimenting with an entirely new type of treatment. A series of ten morphine addicts was selected for this study. The cases ranged in age from 35 to 56 years of age. The amount of morphine these addicts had become addicted to averaged 6-8 grains daily. The method employed in this treatment was essentially as follows: A plaster about eight square centimeters in size is applied on some region of the patient's body, preferably the lower part of the chest in front. Twelve to fourteen hours later, or until a blister with sufficient liquid has been formed, the blister fluid is drawn off by means of a syringe and injected immediately under the skin near by the site of the blister. This procedure is repeated once or twice a day, according to the yield of the blister. If the yield is approximately 5 c.c. or less -- two injections were made daily. If approximately 7 c.c. or more -- one injection is made a day. The rational of this procedure is explained by Modinos, who is Director of the European Hospital in Alexandria, and the outstanding exponent of this form of therapy. He states, that the fluid found in blisters contains endothelial cells, albuminoid substances, hydrocarbons, lipoids, oxydases and lipases. The most significant finding is the high leukocyte count which ranges from 20,000 to 80,000. Antibodies in the readily pass into the vescicle serum. It is the presence of these, he states, which gives it the therapeutic properties

for this treatment. On the first day of treatment the patient usually received one grain of morphine regardless of his habitual requirements. On the second and third days this was reduced to one-fourth grain. It was rarely necessary, he found, to administer morphine after the third day. The number of blisters employed ranged from four to six. The time required for complete withdrawal ranged from three to five days. After complete withdrawal the patient expressed no further desire for the drug even when it was offered to him. This treatment does not offer enough experimental evidence to recommend it to the medical profession.

Two treatments merely mentioned by Bluemel[50] -- are the Sceleth and Petty treatments. The Sceleth treatment involves initial catharsis with the subsequent administration of a solution the chief ingredience of which are scopolamine and ethymorphine hydrochloride. The Petty treatment involves catharsis, rapid reduction of morphine, and the administration of scopolamine.

Ashworth[2] adds the suggestion that the use of eserine and pilocarpine as adjuvant drugs for the relief of the nervousness and aching of the limbs which follow in the wake of morphine withdrawal -- is of great benefit in any treatment.

This leads us down to a treatment which has quite an extensive following in sanitariums throughout the country today. The treatment referred to, is the Towne-Lambert treatment.[50] This treatment combines catharsis with the rapid reduction of morphine and the hourly administration of a mixture of belladonna, hyoscyamus, and xanthoxylum. The proportions are as follows:-

Tincturae belladonnae	15%	62
Fluid extracti hyoscyami		
Fluid extracti xanthoxyli	aa	31

Catharsis is effected with 5 grains of blue mass and five compound cathartic pills. When the bowels have moved freely, the patient is given two thirds or three fourths of his daily dose of morphine, and his initial dose of the bella-

donna mixture, which is given thereafter every hour through the day and night in increasing doses. Ten hours after the morphine has been given, the pills and blue mass are repeated. When free catharsis has been effected the patient is given one half of his former dose of morphine. In another ten hours the cathartics are again repeated, and after further purging, the patient is given his morphine with the dose once more cut in half. This is the patient's last dose of morphine. Soon afterwards there appears from the cathartic a characteristic green stool, and with its appearance the belladonna mixture is discontinued and the patient is given castor oil to cleanse the intestinal tract. The treatment here sketched is modified to suit varying conditions. It is supposed in some manner, to relieve the craving for narcotic drugs, alcohol, and tobacco. Bluemel highly favors this treatment. He states, "I am sure suggestion cannot eliminate toxins from the morphinist's blood stream -- possibly they can be neutralized to some extent by the belladonna mixture". Elimination would also appear to be of special value for the reason that the withdrawal symptoms of sweating, vomiting, and diarrhea represent an attempt at elimination by nature. To greatly augment the elimination idea, Towne added the intravenous infusions of physiological sodium chloride solution. This solution is eliminated by the kidneys and intestine. Gardner[7], in discussing the Towne-Lambert treatment, which was first introduced in the Towne-Lambert Hospital of New York, states; with this treatment, altho the patients suffer little pain from the withdrawal symptoms, if the patient remained in the ward for a period longer than ten days or two weeks -- they begin to have a certain restlessness and nervousness. Sometimes an actual craving for the drug reappears. Gardner tried this treatment in the City Hospital of Louisville with questionable success. They next tried hyoscine alone -- as was recommended by Forsheimer. This treatment allows a quick withdrawal without any immediate after effects of pain. The objection to this method was that sometimes the patient becomes delirious from the use of the hyoscine.

Bluemel, after careful experimentation, advises the use of the combined

Towne-Lambert and Infusion treatment. He treats his cases as follows: The patient is put to bed and his morphine stopped entirely. He is placed on a semi-solid or liquid diet, and is given cathartics as prescribed in the Towne-Lambert. The patient receives from two to four intravenous infusions a day according to his condition. The standard infusion consists of 1,000 c.c. of 0.9 per cent sodium chloride in sterile freshly distilled water. During the first few days of treatment the patient is given enough chloral, usually about 30 grains, at bed-time to insure a night's sleep. Hypnotics are an important element in the treatment, for the sleep they induce not only blots out large periods of discomfort, but also fortifies the patient mentally and physically for the ordeal through which he is passing. The semi-solid diet is continued as long as the patient feels any nausea, and he is kept in bed during the cathartic period until all acute discomfort from the withdrawal has disappeared. If at any time the patient complains unduly of his withdrawal symptoms, he is given a saline infusion. There seems to be no contraindications to the saline infusion, according to Bluemel. Patients have suffered no ill effects from receiving thee or four infusions daily for a period of a week or more. The decreased viscosity of the blood following the infusion lessens capillary resistance, and thus reduces the normal heart load. This reduces the tendency to cardiac weakness so often seen with the withdrawal symptoms. With this treatment Bluemel found that patients recovered more quickly from the subsequent periods of nervousness.

Another treatment which has gained recognition in the last few years is the insulin treatment. Modern[25] reported in 1932 that the use of insulin and glucose during the withdrawal symptoms was extremely helpful. Other such men as Sakel, Anton, Jacobi, and Braum were of the same opinion. Modern's report is the eighteenth case in the literature up to 1932 of the use of insulin in treating morphine addiction. He reports of a patient he had, 54 years of age, who

previously had undergone four withdrawal cures for morphinism and alcoholism -- with relapses in less than four weeks time. After he had been admitted to the Hospital of the Good Samaritan, Los Angeles, morphine was at once withdrawn and "shots" of insulin were substituted. Ten units were given thirty minutes before each meal. The patient was placed on a high caloric diet, and two hundred c.c. of orange juice were given two hours after each meal to obviate late reactions. He received ten grains of sodium bromide every two hours through out the day, and three grains of luminal before retiring, to be repeated in two hours in case of sleeplessness. The insulin dosage was raised to fifteen units on the second day, before breakfast and lunch, and to twenty units before dinner. This latter dosage was adhered to for the remainder of the patient's stay -- and for two weeks after discharge. The time interval between insulin and meal was increased simultaneously from one half to one hour, which caused a moderate hypoglycemia just before bed time. Modern states, that at no time was there any twitching, nausea, abdomenal cramps, diarrhea, itching, or sneezing. Motor restlessness was very slight, the loss of sleep negligible and perspiration occurred only in conjunction with hypoglycemic reactions. The appetite was poor the first few days -- improved rapidly, and he gained four pounds during withdrawal. Hypoglycemic reactions became frequent after the third day. The patient was discharged the sixth day -- and there has been no relapse in the ensuing seven months, either into morphinism or alcoholism despite heavy financial and mental strain during that period. The hypoglycemic reaction "relaxed" him and extinguished all craving, so that now, the patient remarks, if craving appears, he is able to ward it off by taking from five to twenty units of insulin and permitting himself to go into a hypoglycemia.

Howard,[14] in 1933, reports that he believes patients who have been taking more than three grains of morphine a day over a period of six months or longer should have the dose of morphine gradually reduced by half before substituting

insulin. He adds that probably no treatment will be 100% successful because of the constitutional and psychological factors that enter into the symptomatology.

Braum[4] found the use of scopolamine and barbital preparations were desirable adjuvants to the insulin treatment. Complete withdrawal with 20-100 units per day of insulin to replace the morphine was advised. He explains that altho insulin might serve to replace the stimulating action of morphine on the parasympathetic nervous system, the metabolic changes effected by its use were in reality the most essential.

Ostromislensky[27] considers the withdrawal symptoms as symptoms of anaphylactic shock. On this basis he has prepared a drug which can be administered in all cases of anaphylactic shock. This drug is called "Rossium" -- and has the formula $C_{20}H_{18}O_2N_4$ - or diphenylmethylpyrazolonyl.

As to the method of treatment, Rossium is given 0.5 gm. per 10 pounds of body weight daily over a period of 6-7 days. For instance a 120 pound man gets 72 capsules (0.5 gm.) spaced over six days time. Two capsules are given at a time. Forty-eight hours after administration of Rossium the habitual dose of morphine is discontinued. All withdrawal symptoms disappear in 72-96 hours after discontinuation of the drug. During the first night of abstinence, insomnia is controlled with hypnotics to which the patient is not habituated. Some of these include, barbiturates, amytol, phenobarbital, Dial ciba (diallyl malonylurea), and chloral hydrate. Some patients find hyosine hydrobromide given hypodermically grains 1/400 to 1/800, a good sedative. Others, when everything else fails, find that adrenalin chloride concentration 1:1000 minums 2-2½ hypodermically a good hypnotic and sedative.

Ostromislensky states, that relapses occur 15-25 days after complete abstinence, which is analogous to "post anaphylactic states". The symptoms are asthenia, restlessness, polyuria, cardiac neurosis, and insomnia.

Alexander Lambert, after careful administration of Rossium to his patients states, "I have clinically tried Rossium to alleviate the withdrawal symptoms of morphinism. This it does exceedingly well, but this is not eradication of the morphine habit, which is quite another story".

The Council of the Journal of the American Medical Association on Pharmacy and Chemistry were unable to accept Rossium for N.N.R. Although Rossium has been known for three years, no convincing therapeutic evidence in support of its claims have been submitted. Also the studies of its toxicity are wholely inadequate. Its supposition as to the presents of antibodies in the body of the addict is absolutely contrary to the present theories of immunity. Pellini, and Greenfield express the same opinion.

After direct observation of the Rossium treatment for a period of three months, I feel thoroughly satisfied that Rossium is unsuccessful, even as a palliative measure in the treatment of morphine addiction. In eight cases observed -- not one was free from the classical withdrawal symptoms -- upon use of this form of therapy.

During the latter period of the treatment, as stated before, the patient is in great danger of relapse. Well-meaning friends have been known to smuggle in morphine to the unhappy patient. To detect this is of prime importance to the attending physician. Juarros[18] has found that the sedimentation test and the Hecht reaction are the simplest and most convenient means for ascertaining whether the patient is obtaining morphine. The sedimentation of erythrocytes is accelerated in proportion to the amount of morphine in the body. Hecht insists on the reliability of the response when intradermal injection of 0.005 gm. of morphine induces a wheal, like those of urticaria. It appears in a few seconds and disappears in an hour or two. Of course, if the patient gives a positive test -- the whole treatment has been defeated.

The prognosis in chronic morphinism is at best not very favorable.

Robinson[35] is of the opinion that "once a drug addict, always a drug addict" is not far wrong. He states, that once a weak personality -- and morphine is evidence of a weak personality -- finds an aid such as an opiate, he will always turn to its use in time of stress. While cures give temporary relief to all and permanent relief to some, this investigator finds that 80% of their cases are repeaters. Treadway[44] reports that their complete cures varied from 15 to 20% up to as high as 70%. The abrupt withdrawal treatment gave, in his experience, the highest per cent of cures. He advises institution treatment, never home treatment.

Gardner likewise, is of the opinion that relapses occur in a large per cent of cases. He recommends proper care after discharge from the hospital as the greatest help in preventing a relapse. Unfortunately the doctor comparatively seldom has the opportunity to carry out this much needed part of the treatment. Above all, should the patient become irritable, depressed or fatigued, he should at once report to his physician. At these times relapses are especially threatened. Rebirth of a personal honor and desire to be a useful human being is of primary importance. Finally, the patient must be led to develop real faith and confidence in himself.

- The End -

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