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HOW TO USE QUININ AND UREA HYDRO- CHLORID; ESPECIALLY FOR SYSTEMIC EFFECT BY INJECTION IN MALARIA AND PNEUMONIA.

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Quinin and urea hydrochlorid—long known in Germany as *chininum bimuriaticum carbamidatum* and used with confidence by some American physicians, most of whom learned of it a generation ago from Professor Roberts Bartholow, or more recently from his pupils—has within a few years come into prominence as a local anesthetic. Of its use as such, I do not now wish to speak, except to call attention to its great value in acute tonsilitis and in tuberculosis of the larynx. A solution of 1:10 or less is usually strong enough, but even a 20 to 50 per cent. solution may be employed if necessary. It can be applied by spray, sponge, brush, cotton applicator, etc., as may be most feasible in the individual instance. Sometimes the patient may simply take a teaspoonful or two of the solution in his mouth and holding it back toward the painful region of the tonsils or epiglottis, move it gently to and fro by action of the pharyngeal muscles. This is somewhat easier than gargling, and gives more relief. Done 10 minutes before the taking of food, it will sometimes permit nourishment to be given in cases of ulceration of the epiglottis or other painful tuberculous lesion in which all other methods of relief have proved unavailing.

Neither in tuberculosis nor in tonsilitis need the patient be apprehensive of any danger from swallowing the solution, as a dose of 5 grains or so, three times a day, would not ordinarily be hurtful, and in febrile cases might be beneficial. Sometimes, indeed, the specific direction to swallow a part of the solution—or even all of it—is given.

It is, however, more particularly with the systemic effect of the drug and its administration in malaria and in pneumonia that this note deals. I have received many inquiries concerning particular details of the method of administration employed by me in the treatment of acute lobar pneumonia and acute lobular pneumonia by massive doses of quinin and urea hydrochlorid—the favorable influence of which I reported some months ago to the Association of American Physicians (*Am. Jour. Med. Sci.*, Jan., 1912, p. 40)—and this is the easiest method of answering at once all my correspondents.

The drug may, of course, be given by the mouth in solution, powder or capsule, as any other salt of the cinchona alkaloid. It is probably more active, grain for grain, than any other quinin preparation. Possibly the urea is a linking body;

possibly it is merely a question of solubility. I do not know the explanation, but the fact is evident.

The peculiar advantage of the urea compound over the other quinin salts, however, is its availability for hypodermic and intramuscular injections; possibly for intravenous injection also, although I have never found the latter method necessary and thus have no experience to report. A possible danger is injury to the vessel wall.

The superiority of the carbamide for injections is owing to its high solubility. It will dissolve in its own weight of water, especially hot water, and an ordinary syringe-ful may thus contain from 15 to 18 grains (1 to 1.2 gm.) if necessary. The preferable solution is 50 per cent., and the ordinary dose is 1 gm. (15 grains) in 2 c.c. of water.

In *malaria* of the types ordinarily seen in northern latitudes, a single injection of this strength will cause suspension of the paroxysms for from a week to a fortnight ($6\frac{1}{2}$ to $13\frac{1}{2}$ days). One injection daily for a week suffices to bring about complete recovery in the ordinary case. After this, to make sure against chronic infection or sequels, the drug should be continued in doses of 10 grains, in capsule by the mouth, daily, for another week; and then administered once a week, in the same way, for two or three months.

In *pernicious malaria*, larger and more frequent doses are probably needed.

In *pneumonia*, the dose varies with the age and vigor of the patient, the general severity of the case and the time elapsing from initial chill to the beginning of treatment. If the case is seen on the first day, and the patient is a vigorous adult under 50 years of age, the effort should be made to give as much quinin as possible within the first 24 hours. The initial injection may be 25 grains (1.6 gm.), and this, or a smaller dose, may be repeated in three or four hours, according to the effect produced. Aged persons, weak persons, children receive proportionately smaller doses. Should the case be first seen on the third day, the initial dose should be governed somewhat by the height of the temperature and the severity of the general symptoms. If the temperature exceeds 104° F., and the patient markedly labors for breath, the first injection may be 25 grains; otherwise 15 grains should be given and this dose repeated every third hour or fourth hour, according to circumstances, until the temperature falls and remains below 102.2° F.; to be repeated when the temperature again rises. While the object of the treatment is not antipyretic, the temperature line of 102° F. is taken as an approximate index of the severity of the infection, or rather of the toxemia, on the one hand, and on the other hand, of the adequacy of the patient's reaction. It is not desirable to reduce temperature abruptly below 102° by any form of treatment, except, perhaps, the use of specific bacterin.

Sometimes a single injection of 15 to 25 grains (1 to 1.6 gm.) suffices. Usually, however, from six to ten grams or more are given in the course of from 48 to 72 hours. The temperature quickly falls after the first injection; sometimes remaining down, but more frequently again ascending, and thus indicating the necessity for renewed injections. Pulse rate also falls, and with it, at first, blood pressure; but the latter, in cases of favorable prognosis, quickly regains its former level and even tends to go higher.

In my more recent experience I have injected immediately after the quinin, or with it, about one-half grain (0.03 gm.) of cocain hydrochlorid to keep up the vascular pressure; and this dose of cocain is repeated as often as necessary—which may be several times a day, once or twice in an attack, or not at all. The indication is a tendency for the line representing systolic blood pressure measured in millimeters of mercury, and charted upon the same vertical as the line representing pulse frequency (in beats per minute) to fall below the latter. Thus, if the pulse rate is 160 beats per minute, and the systolic blood pressure is 100 mm. Hg., there is indication of grave danger. If pulse rate and systolic blood pressure are each 130, the condition is one of doubtful equilibrium. If blood pressure can be brought up to 130, and pulse frequency reduced to 120 or less, the outlook is favorable.

It will be understood, of course, that these figures are merely illustrations. Although the blood pressure should be only 110, it might be still a favorable sign, provided the pulse rate was at the same time 100 or less. It is *the distance of pressure above or below frequency* that is of significance. This important sign was first brought out in a somewhat casual manner by G. A. Gibson of Edinburgh; and afterwards emphasized and made prominent by H. A. Hare of Philadelphia. I am abundantly able to confirm its value from personal observation. It is not infallible, but it is a good guide in treatment. Fall of pressure with rapidity of pulse indicates vasomotor depression, as well as cardiac weakness.

To raise blood pressure and to stimulate and sustain the heart when necessary, the physician may employ, if he so prefers, epinephrin, pituitrin, camphor, musk, atropin or strychnin with, or instead of, cocain. Digitalis is too slow and in the presence of fever, too uncertain. The adrenal principle is prompt, but its action is fugacious. Its association with cocain or camphor is usually efficacious; quick response coming from one agent, sustained effect from the other.

To resume the statement of the effect of the quinin and urea injection, its most marked effect is upon the respiration, the rate of which falls proportionately lower than temperature or pulse frequency. Even when its rapidity is not markedly diminished, breathing becomes much less labored and distressful.

The most significant fact of all is that cinchonism does not develop under these enormous doses of the most active quinin salt. Should it do so, it would be an indication for withdrawal of the drug—at least until the quinin symptoms had abated.

The *disadvantage* of quinin and urea hydrochlorid injections is, that *handled carelessly, they may excite cellulitis, abscess or slough*. In my early use of the drug (1884) I learned to avoid this by precautions (later stated). Since then I have made and have had made thousands of such injections without accident.

All the instruments to be used are sterilized by boiling. The skin over the part into which the injection is to be made is cleansed with green soap and water; and then an area of some two inches in diameter is painted with tincture of iodine. A high pressure syringe is used and the long needle attached thereto is plunged deeply into the muscle. Care is taken to expel all the contents of the syringe, so that in its withdrawal none of the solution shall be dropped on the surrounding tissue. The puncture is then sealed with iodoform-collodion.

I use by preference a 50 per cent. solution of the drug in hot sterile water; but when the capacity of the syringe available is not sufficient for the quantity of water necessary to make a 50 per cent. solution, one needs simply to dissolve the quantity of quinin and urea hydrochlorid to be used in a syringeful of hot water. I have not seen any local harm from a concentrated solution when due care is observed, in accordance with the directions just given. The site of injection may be arm, back, thigh, buttock, or any convenient place where there is sufficient muscular tissue. Meltzer's site—the spinal muscles of the lumbar region—may be chosen when quick result is a matter of urgency.

In treating pneumonia dependence is not placed on quinin alone. Fresh air (out of doors, if possible); water; saline infusion, if necessary; some alkaline salt or salts in sufficient quantity to keep the urine at least neutral, and preferably alkaline; all the devices of good nursing and good feeding; external applications of heat; inhalation of oxygen, if indicated; administration of any medicine called for by symptoms—these and whatever else may be useful, are to be employed additionally. Their discussion, however, is not here called for.

Whether the treatment of pneumonia here outlined will be superseded by the use of specific bacterin or of mixed bacterins is as yet impossible to predict. In the ordinary case in a person under 50 years of age, seen before the third day, one may be as efficacious as the other. The bacterin method may prove superior in late stages, in old persons and in the most severe cases. When bacterin is unavailable, the use of large doses of quinin as promptly as possible, seems to me after nearly eight years comparative study, and after 28 years experience with many methods, by far the best routine as yet proposed.