

On the internal administration of nitrate of silver, and on the occurrence of a blue line upon the gums as the earliest sign of argyria / by William Pepper.

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ON THE
INTERNAL ADMINISTRATION OF NITRATE OF
SILVER, AND ON THE OCCURRENCE OF A
BLUE LINE UPON THE GUMS AS THE
EARLIEST SIGN OF ARGYRIA.

By

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[Read March 7, 1877.]

IT is of course not within the province of the present article to discuss the very numerous and varied conditions in which the internal administration of nitrate of silver is strongly indicated. Suffice it to say that there are few remedial agents whose therapeutic value and range of application are equally extensive. This is not surprising when it is remembered that nitrate of silver possesses a peculiarly valuable local action in addition to its power of directly affecting the nervous system by absorption. The topical action of nitrate of silver, given internally, even in small doses, may be said to extend throughout the entire gastro-intestinal tract, with, perhaps, the exception of the rectum. In addition to this, it appears to me to be established by clinical evidence that a certain amount of influence is produced on the continuation of the duodenal mucous membrane into the common hepatic duct, and possibly into the pancreatic duct. This local action is in part that of an astringent, but

in addition it presents a peculiar, alterative character. Its power of influencing nutrition enables the nitrate of silver to modify the morbid action of ulcers of the stomach or intestinal canal, and to cause the reduction of chronic inflammatory thickenings of the mucous membrane, and of hypertrophies of its glandular apparatus. Associated with this is its power of allaying morbid irritability of the nerves of the mucous membrane, and of influencing the secretions.

The exact form which nitrate of silver assumes after entering the stomach is not known, and probably is not the same in all cases. It is evident, however, that it cannot long retain its integrity. Probably it is sometimes converted into a chloride, though more frequently it would seem to unite with the albuminous peptones, forming a compound which does not coagulate albumen, and which is readily dissolved in albuminous liquids. In this form it may easily be understood how, even when given in minute doses, if frequently repeated and continued for a considerable time, it may produce a powerful action throughout the entire extent of the mucous tract before mentioned.

Among the special morbid conditions for which it has been recommended, on account of its local action, I would especially mention the following, based upon my own personal experience: in the stomach—gastric ulcer, chronic catarrhal gastritis, especially with frequent vomiting or with pain dependent upon morbid irritability of the nerves of the mucous membrane; in the intestinal canal—cases of follicular (catarrhal) enteritis, both in the adult and in the child, subacute and chronic dysentery, chronic typhlitis, and tuberculous diarrhœa. I have also lately obtained remarkable

results from the administration of nitrate of silver in cases of gastro-hepatic catarrh, with or without jaundice from occlusion of the ducts by tumefaction of the mucous membrane. Recent observation has, moreover, led me to believe that the administration of this drug in typhoid fever, as originally recommended by Boudin in 1836, is a very valuable element of treatment in this important affection. In addition to all of these must be mentioned the great value of injections of nitrate of silver in many forms of rectal disease.

With regard to its absorption and effects upon the general system, the evidence is no less satisfactory. The fact of its absorption does not indeed admit of doubt. Apart from the positive therapeutic effects observed, there is the actual proof of the detection of silver in various internal organs, and of its deposit in the skin after its long-continued administration. Given thus internally, the chief action of the salt would seem to be upon the nervous centres, whose nutrition it possesses the power of modifying to a considerable degree, though the precise mode in which this is accomplished is still uncertain. The diseases for which nitrate of silver is used in view of its constitutional effects are chiefly affections of the nervous system, such as epilepsy, chronic meningitis, and sclerosis of the spinal cord.

In regard to a remedy of such value and wide application, it is important to consider what difficulties attend its administration, and how they may best be overcome. The first difficulty which suggests itself is connected with the local irritant action which nitrate of silver occasionally produces. This, however, can always be avoided by giving the remedy in pill form,

and by graduating the dose carefully in accordance with the sensibility of the stomach. Thus, my own rule is to begin the administration of this drug in doses of from one-sixth to one-fourth of a grain three times a day, to give it in pilular form, and soon after a little light food has been taken. If necessary, its irritant action may be still further guarded against by combining with it a small quantity of opium.

It is usually stated that when the local action on the alimentary canal is desired, the drug should be given one or two hours before meals, on an empty stomach; while when the constitutional effect is desired, the pill should be given after meals, during the process of digestion. In most cases where nitrate of silver is given for its local action, it is necessary to employ a diet carefully restricted, both as to quantity and character; and it has seemed to me that the good effects of the remedy are not interfered with by its being administered half an hour to an hour after a very light meal, especially of a fluid character, such as skimmed milk or broth. It is certain that the danger of causing gastric irritation is much lessened when this drug is thus given, instead of being given on an empty stomach before meals. In cases where the diet allowed is not so rigidly restricted, and considerable quantities of food are taken at each meal, and yet the administration of the silver on an empty stomach causes irritation, I have found it useful to give a few spoonfuls of light arrow-root a couple of hours before the regular meal, and to administer the silver immediately after this.

The second great difficulty attaching to the internal administration of nitrate of silver is the tendency to

discoloration of the skin by the deposit of the silver in its tissues. This discoloration of the skin has long been known. Fourcroy (*Médecine éclairée par les Sciences Physiques*, tome i. p. 342) was among the first to call attention to it; Dr. I. A. Albers, of Bremen, communicated a case to the Royal Medico-Chirurgical Society of London, in 1815 (*Med.-Chir. Transactions*, vol. vii. p. 284); and since that time numerous cases have been placed upon record.

The skin first presents a peculiar, bluish-slate color which may deepen until the patient acquires a hue of the deepest lividity. In some cases, where the discoloration has become very intense, the color is described as bronzed. This discoloration is usually said to be deepest in parts exposed to the light, as the face and hands. The whole surface is, however, involved, and in severe cases the sclerotic coats of the eyes, the mucous membrane of the mouth, and even the internal organs, as the liver, spleen, and kidneys, have been found to be discolored. So grave is the danger of inducing this condition, and so universally is it regarded as a serious contra-indication to the use of this valuable remedy, that it is important to consider somewhat more in detail (1) the cause of this discoloration; (2) the shortest period of administration and the smallest quantity of the nitrate of silver after which it has been known to occur, and (3) the best mode of avoiding this unfortunate result.

In regard to the first of these points, the fact that the discoloration is not limited to the external surface, but affects also the internal organs, goes far to prove that it is not due to the chloride of silver, but to a

deposit of the metal itself or its oxide, and this view is further confirmed by chemical examination.

The amount of silver in the tissues required to produce this discoloration is extremely small, thus H. C. Wood quotes the analysis of the organs in a case of Versmanns (Virchow's Archiv, xvii., 1859), who in 14.1 grammes of dried liver found only 0.068 gramme of metallic silver (0.047 per cent.), and in 8.6 grammes of dried kidney, 0.053 gramme (0.061 per cent.).

The smallest amount which has ever been known to produce general discoloration is difficult to determine. It has been known to follow the use of one hundred and twenty grains, given in the dose of half a grain daily for eight months consecutively; while again, in a case reported by Bertini (*De usu interno preparationum argenti, Thesis inauguralis. Geneva, 1814*), thirty-three and a half drachms were taken in a period of two years and a half, averaging two and a half grains daily. These cases may perhaps be taken as representing about the extremes; but in the latter instance it is not stated how long the drug had been taken before the discoloration was first noticed, nor is it possible, of course, to form any idea of how much of the great amount given passed through the alimentary canal unabsorbed.

With regard to the length of time necessary for the development of the discoloration, Dr. James Johnson asserts that there is no case of discoloration on record in which the use of the medicine had not been continued beyond three months. Much more frequently, however, when argyria, or discoloration of the skin by silver, is produced, it will be found that the patient has continued the use of the remedy with or without

the advice of the physician for a much longer period of time than the above, usually eighteen months or over. It is interesting to note, in this connection, that so large a proportion of the recorded cases of argyria has occurred in epileptics. It is well known that, before the discovery of the peculiar powers of the bromides, the long-continued use of large doses of nitrate of silver was strongly recommended in this disease.

Another peculiarity connected with argyria, according to some observers, is that the discoloration continues to deepen for some time after the use of the remedy has been suspended. It is even asserted (Sigmund, *Lancet*, March 31, 1838) that in some instances the discoloration does not occur until some months after the remedy has been discontinued, but this appears to me very improbable, and certainly needs confirmation.

In regard to the mode of avoiding this unfortunate result, various suggestions have been made. Thompson proposed the simultaneous administration of nitric acid, with a view of preventing the conversion of the nitrate into the chloride. This, however, has been shown, both theoretically and practically, to be useless. The majority of authors content themselves with recommending that the administration of the silver salt should be suspended after a period which, according to different authorities, varies from three weeks to three months. It is evident, however, that this is altogether too vague to be depended upon. It would be more valuable could some safe limit as to the quantity to be used be determined. My own rule, for a number of years, has been to continue its administration in doses

of from one-fifth to one-third of a grain thrice daily until thirty grains have been taken; to then suspend it for one month; after that interval to resume and continue its administration until fifteen grains more have been taken; and again to withdraw it either permanently or for another month, to be then followed by a final course of fifteen grains, making sixty grains in all. One great defect, however, of such rules, is that they only fix a minimum dose without reference to the individual features of the case, and, of course, without any accurate knowledge of the proportion of the remedy absorbed in different instances. Thus, among other considerations which deserve attention, is the weight of the patient. In the case of nitrate of silver, as of many other drugs capable of producing an effect on the whole body, it cannot be doubted that one of the factors, in determining the amount that can be tolerated in any given case, is the weight of the subject. But when we consider the extreme value of this remedy in certain conditions, it becomes evident that what we need, is a rule which will enable us to administer, in any given case, the maximum dose consistent with entire safety. It is with the hope of establishing such a rule that I venture to bring forward the results of certain recent observations that I have made, which go to show that *the earliest sign of argyria, occurring before there is any danger of the slightest discoloration of the skin, is a peculiar blue line on the gums.*

The following cases are given in illustration of this position. It may be premised that crystals of nitrate of silver were used exclusively in compounding the

pills administered in these cases, and that consequently there is no chance of any lead having been admixed. This is mentioned because the nitrate of lead is sometimes associated with the nitrate of silver in the form of stick.

CASE I. *Chronic Gastro-hepatic Catarrh*.—Mrs. W., æt. 60, of unusually large frame; had suffered from deep jaundice of six months' standing, subject to marked variations in intensity, and associated with frequent spells of hepatic colic from closure of the common duct owing to swelling of the mucous membrane. Treated by nitrate of silver and Carlsbad water, with restricted diet. Complete cure at end of eight months. About sixty grains of nitrate of silver were given in all, in doses of one-sixth to one-fourth of a grain three times a day in pill form. Thirty grains were given at first, then, after an interval of a month, fifteen grains more; and later, after a longer interval, fifteen grains more. No trace of discoloration of the skin, and no line on the gums.

CASE II. *Chronic Gastro-hepatic Catarrh*.—Mrs. G., æt. 58, of medium size, was desperately ill for many months, with deep jaundice, clay-colored stools, irregular chills and fever, frequent vomiting, extreme emaciation, intense attacks of hepatic colic: no gall-stone. Complete cure resulted from the use of nitrate of silver, given in doses of one-fourth of a grain with a small dose of opium three times a day. About fifty grains were given. At the close of this time a blue line made its appearance on the lower gum corresponding to the two incisors, canine, and first premolar teeth on right side of jaw. The line was close to junction with teeth, and closely resembled the lead line. The nitrate of silver was dispensed in form of crystals.

CASE III. *Gastric Ulcers*.—Mrs. B., æt. 30, rather small-sized, slender woman. Gastric ulcer, profuse hemorrhage, intense gastralgia and heartburn. After controlling the hemorrhage, nitrate of silver was given in pill form, in doses of one-fourth of a grain, thrice daily, taken immediately after

taking small quantities of milk. Rapid improvement. About forty-five grains of nitrate of silver were taken in all, extending over a period of about two months. One month afterwards, examination of her mouth showed a very marked blue line on lower gum, corresponding to the five or six teeth to the right of the median line. The nitrate of silver was given in the form of crystals.

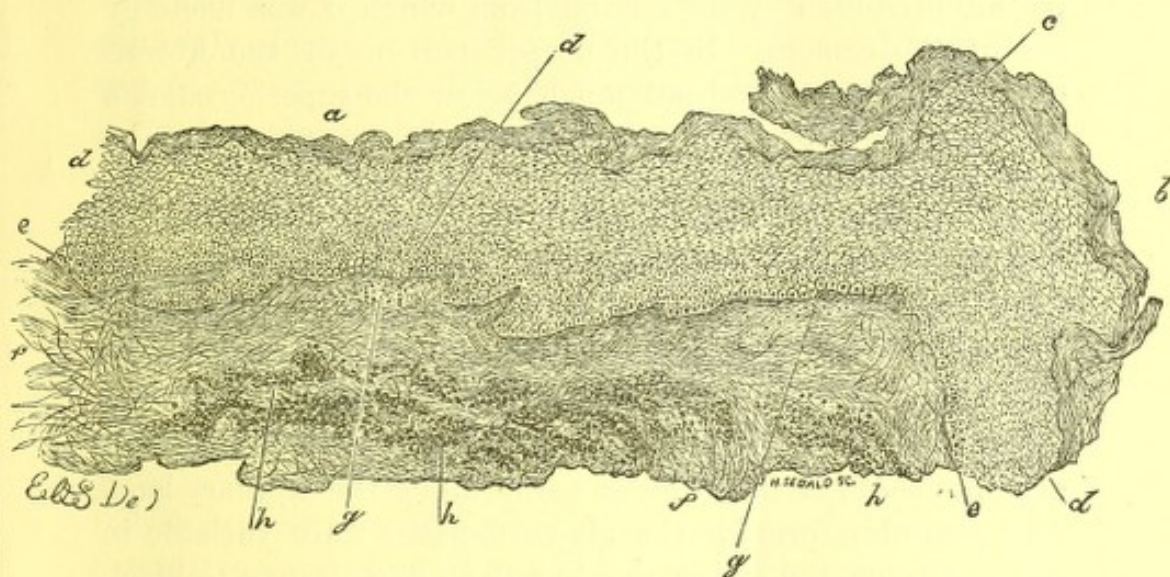
CASE IV. *Chronic Perityphlitis*.—H. W., æt. 25, suffering with chronic perityphlitis from a strain; seen in consultation with Dr. Santee; was treated with restricted diet and nitrate of silver in pill form. About fifty grains in all were taken between July 5, 1876, and October 1, 1876. After the above period it was discovered that there was a very marked blue line on the gums, closely resembling the blue line of lead-poisoning.¹ This chiefly affected the lower jaw, where it corresponded to about six or seven teeth counting to the right from the left lateral incisor.

The line was quite broad, in places nearly one line. On the upper jaw a slightly developed line was noticed, corresponding to the right lateral incisor, canine, and first premolar. In addition to this, there was some excessive pigmentation of the mucous membrane of the lower lip near its junction with the gum. There was no trace of discoloration of the skin. A small piece of the discolored portion of the gum was cut out and placed in the hands of Dr. E. O. Shakespeare, who has kindly furnished the following report of the microscopical and micro-chemical examination of the specimen:—

The small portion of tissue from the gum was hardened in dilute alcohol, and, when of sufficient consistence for cutting, the piece measured in length $\frac{1}{2}$ inch, in breadth $\frac{1}{4}$ inch, and in thickness $\frac{1}{16}$ inch. It was imbedded in paraffin in order to make thin sections from it. Cuts were intended to be made vertical to the upper edge of the gum and to its anterior epithelial surface, but, when placed under the mi-

¹ The painting, which was exhibited in connection with this case, has not been reproduced, on account of this close resemblance between the silver line and the familiar blue lead-line on the gums.

roscope, they were found to be somewhat oblique to the latter surface. Some of these sections were stained with carmine and mounted in balsam, others were mounted in the same medium unstained. The accompanying drawing, by Dr. Shakespeare, represents one of the former, enlarged one hundred and fifty diameters. (See wood-cut.)



Section of gum, showing supposed silver deposit along course of vessels.—
a. Anterior epithelial surface. *b.* Upper edge of gum. *c.* Corneous layer of epithelium. *d.* Rete mucosum. *e.* Layer of cylindrical cells. *f.* Fibrous substance of gum. *g.* A few black granules deposited along vessels of papillæ. *h.* Dark granular deposit covering and occupying the vessel walls.

Under the microscope, the stained section exhibited the following appearances: The epithelial layer of the gum was a little thickened. The layer of cylindrical cells covering the papillary surface was so entirely free from pigment as to lead to the assumption that the patient was very light-complexioned. The outlines of these palisade-like cells were slightly indistinct, the contents finely granular, and the nuclei large and deeply stained. The cells of the rete Malpighii presented large, deeply stained nuclei, granular contents and ill defined outlines. The squamous epithelium near the corneous layer, which was not increased much in thickness, also showed nuclei very distinct and well stained. Through-

out the sub-epithelial, dense, fibrous tissue of the gum, as well in the papillæ as in the deeper portions, but particularly in the latter, was to be observed a very considerable and diffuse cellular infiltration. This cellular infiltration has not been represented in the drawing, but in other respects the latter is as nearly as possible an accurate copy of the microscopic picture presented by the section from which it was made by aid of the camera. In the deeper portion of the fibrous tissue of the gum, and not much below the superior edge, a dark granular deposit was very distinctly seen to occupy the position of the large veinules and capillaries, which here mainly pursue a course parallel to the anterior epithelial surface. Under Hartnack's No. 11, à, Immersion, no crystalline forms could be detected in the deposit, nor could it be discovered that the granular particles were contained within the bodies of cells of the surrounding cell infiltration. In one or two of the papillæ, scarcely visible traces of these dark granules could be made out at points along the capillary loop. The granules forming the above deposits were variable in size and color, the latter ranging from dark brown to black by transmitted light, and the former not differing from that of the granules often found in silver staining. They were sufficiently numerous to mask the vessel wall where they occurred.

The next point to be determined was, whether this dark granular deposit so distinctly limited to the course of the deeper vessels of the gum, was some form of the blood pigment, or was silver in some shape. Of the coloring matters of the blood, hæmatin and melanin are granular and dark-brown or black. The others are crystalline, and may be excluded from further notice here. Hæmatin is soluble in either an aqueous or a spirituous solution of ammonia. Melanin is not at all or only slightly soluble in a strong solution of cyanide of potassium. Oxidized silver is readily soluble in the latter solution. In order to distinguish between these three substances, the following tests were applied to several sections of the small portion of gum:—

Several sections, in which could be well seen the dark, previously described deposit, were macerated for a considerable time in an aqueous solution of ammonia, rather strong. Upon subsequent examination under the microscope, the deposit appeared not to have decreased in density or to have changed at all. Other sections were macerated a few moments in a strong solution of cyanide of potassium, and were subsequently placed in the field of the microscope. From these sections every trace of the granular deposit had vanished. A fresh piece of the choroid coat of the human eye, after staining with silver, and exposure to light, was placed in an equally strong solution of cyanide of potassium, and the effect was observed under the microscope. The black silver lines rapidly disappeared, but the pigment in the hexagonal cells and in the stellate cells of the stroma of the choroid remained untouched. One other micro-chemical test was applied. Either the chromate or the bichromate of potassium gives, with nitrate of silver, a precipitate which is red by reflected light. Several sections showing clearly the granular deposit, were macerated a moment in a drop of nitric acid, rather strong. The nitric acid was then removed, and the sections were covered with a drop of a solution of bichromate of potassium, in which they were permitted to remain a few moments. They were subsequently well washed and mounted in glycerine. Viewed by reflected light, and under a low magnifying power, the formerly dark deposit now gave a distinctly red reflex when seen in sunlight. The bichromate had, as usual, stained the mass of the tissue yellow, and this color had the effect of slightly modifying the red so as to produce a yellowish-scarlet or an orange tinge of red. Microscopic examination by reflected light, of the previously-mentioned unstained section mounted in balsam, showed a whitish or grayish reflex from the position of the deposit, which, by transmitted light, appeared dark and granular. From the preceding examination I am, therefore, inclined to think that it is highly probable that the mass of the dark granular deposit above alluded to, consists neither of hæmatin nor of melanin, but that it is composed of silver.

At the time the above cases were examined, as I had never happened to see any allusion to such early staining of the gums in advance of general argyria, I fancied that the observation was an original one. On coming to examine the literature of the subject, however, I soon found that this was far from being the case. Dr. George B. Wood states (*Treatise on Therapeutics, etc.*, 2d ed., 1860, vol. i. p. 401), "happily, before the skin begins to exhibit this hue, a similar dark discoloration usually appears upon the gums and tongue and in the fauces, and serves, if observed, to put the practitioner upon his guard." This statement appears to rest upon the authority of the original observer since, in the *United States Dispensatory* (thirteenth edition, 1870, p. 1049), Dr. Wood states again, "according to Dr. Branson, an indication of the approach of discoloration is furnished by the occurrence of a dark blue line on the edges of the gums, very similar to that produced by lead, but somewhat darker." I have been unable to find Dr. Branson's communication on this subject, nor do I find that his observation attracted lasting attention, since, with the two exceptions above given, I have not discovered any allusion to this important phenomenon occurring as a premonitory sign of argyria, in any of the numerous recent works on *Therapeutics* which I have consulted. I am glad, therefore, to have been led, by observing anew this blue silver line on the gums, to call attention to Dr. Branson's original observation. The practical importance of this sign is considerable. I believe that it enables us to administer nitrate of silver internally with safety so far as any danger of discoloration of the skin is concerned,

provided that the gums be examined every few days, and that the use of the remedy be suspended as soon as the characteristic blue line is observed.

Another point of importance is its close resemblance to Burton's blue line on the gums, due to the saturation of the system with lead. Indeed, in some of the cases I have recorded, it would have been impossible to determine, by inspection alone, whether the blue line was due to lead or not. It may be said, however, that in other instances the color of the silver line is darker and more decidedly blue, and also that there is a tendency for the discoloration to extend to a greater distance on to the gum from the line of junction with the teeth, and also for it to affect the mucous membrane of the lips near the junction with the gums. It will hereafter be necessary, however, in any case where a blue line is observed on the gums, to investigate the history of the case not only with regard to the action of lead, but also of silver.

The safeguard which I have above proposed, and which, I trust, will prove to be a constant and reliable phenomenon, becomes of greater importance when it is borne in mind that the discoloration of the surface is, as a rule, permanent. I have known several cases where it continued unchanged after the lapse of twenty years, and similar instances are not scarce in medical records. It is true that Orfila (*Medical Times and Gazette*, March, 1852, p. 279) found silver in the liver of animals, to which the nitrate had been given, six months after its administration; but found that in seven months it had disappeared from the tissues of animals similarly treated. And so, in certain cases, argyria has been stated to gradually diminish with

the progress of time. So, too, success has been claimed for various remedies in the treatment of argyria. Thus repeated blistering, alkaline baths, the prolonged use of cream of tartar and iodide of potassium, have all been recommended. Of these, iodide of potassium has most evidence in its favor, and is the one on which I should myself rely; but still in several instances it has been vigorously employed without success.

After the discontinuance of nitrate of silver in Case IV., iodide of potassium was directed with a view of favoring the absorption of the indurated cellular tissue surrounding the cæcum. This has given the opportunity of observing the influence of time, in connection with the use of the iodide, upon the blue line on the gums. At the present time, six months after discontinuance of the nitrate of silver, the line has perceptibly, though slightly, faded in intensity.

It is very possible that the difference in the persistence of the argyria, and in the results of treatment in different cases, may depend somewhat upon the amount of silver which has been absorbed and fixed in the tissues.