These drugs exert their peculiar action only on subjects, either male or female, who have passed the "change of life."

Susceptibility to this action is probably associated with an alteration in the nature or balance of the sex hormones.

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ALKALI POISONING

A DANGER IN THE TREATMENT OF GASTRIC ULCER

BY

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During the past few years several drugs which have been employed without suspicion of seriously harmful effects have been discovered to produce profound toxic disturbances in certain susceptible individuals. Among such drugs prominence has been given to the dangers of dinitrophenol, and more recently to those of amidopyrine. Dinitrophenol was for a time recommended for reducing weight in cases of obesity, but its use had to be given up because it was liable to cause cataracts, peripheral neuritis, liver damage, and other undesirable effects. Amidopyrine has long been a constituent of many sedative and analgesic powders, but has been found to cause in some people a dangerous toxic state associated with a serious fall in the number of polymorphonuclear leucocytes in the blood. The fact that this drug has been easily accessible to the public without medical prescription, and was indeed a constituent of some proprietary remedies, has increased its dangers, and a number of cases of death from its use have appeared in the coroners' courts.

It is the purpose of the present article to call attention to the occasional toxic effects of yet another common type of substance which is widely used without medical prescription. This is the group of alkaline powders which, in various mixtures, are prescribed and sold as "stomach powders" for the relief of gastric ulcer and other similar gastric complaints.

It may be considered remarkable, in view of the extremely widespread use of these alkaline powders, that reports of untoward effects have not been published more frequently. Two reasons are probably responsible for this. The first is the relative infrequency of susceptible subjects, and the second the peculiarly insidious nature of the symptoms, which may render the recognition of alkali poisoning difficult to those not well acquainted

with the condition. But the recognition of alkali poisoning in the treatment of gastric ulcer is by no means new. Discussions of the subject have from time to time appeared in medical literature. As long ago as 1923 Hardt and Rivers in America reported a series of cases in which toxic symptoms developed during the routine treatment of gastric ulcer by the Sippy method, which includes the ingestion of alkalis. They were able to show that the sensitive individuals reacted biochemically in a different manner from the normal to the ingested alkali.

But until relatively recently the condition does not appear to have been well recognized in England. Indeed, in 1928 MacLean definitely denied that alkali ingestion, in the quantities recommended by him at least, ever led to the development of serious undesirable symptoms. And this pronouncement by MacLean probably went far to encourage the belief that alkali administration was as harmless in all individuals as it still appears to be in the great majority.

But there is now no doubt that a small group of persons does exist who are abnormally sensitive to some constituent of the alkaline powders. Cases of alkali poisoning do from time to time occur among patients under treatment in hospital, and a certain number are also admitted to hospital with toxic symptoms which have developed at home. It is because the histories given by the latter group often show clearly that the toxic condition was not recognized as such by their medical attendant that the present attempt is made to define more adequately the symptoms and signs by which such poisoning may be detected. The nature of the symptoms in these cases is often such that chronic alkali poisoning may persist for several weeks without the nature of the condition being appreciated unless the possibility of it is definitely borne in mind.

Symptoms of Alkali Poisoning

The condition develops typically in sufferers from gastric ulcer or other similar gastric disorder who are taking one of the usual alkaline mixtures for their complaint. These powders generally contain varying proportions of sodium bicarbonate, calcium carbonate, magnesium oxide or carbonate, and bismuth oxycarbonate. Whether one of these constituents is more likely to cause toxic symptoms than the remainder has not yet been determined. Occasionally it can result from other causes, and we have seen one case in which typical symptoms resulted from large doses of potassium citrate during the treatment of a pyelitis.

The mode of onset is nearly always insidious, but may be fairly rapid, reaching serious intensity in a day or two, or it may be much more chronic, developing progressively over a period of several weeks. It is the latter type of case which in general practice is most likely to be missed.

The relation to the amount of alkali taken is also variable. In very sensitive individuals it may come on within a few days of commencing alkali therapy, in others it may develop relatively rapidly in a person who has been taking alkalis without apparent ill effects for years. In the latter type of case it is not infrequently provoked by an increase in the alkali dosage.

During the early stages of the development of symptoms of alkali poisoning a marked deterioration in appetite is frequent. It appears to be directed against all types of foodstuff, but Cooke has noted a special antipathy to the taking of milk. This anorexia is frequently associated with attacks of vomiting of moderate severity. This vomiting is not necessarily associated with epigastric pain, which may be completely absent at the time. Nor is it of the severity and insistence encountered in pyloric obstruction, unless, of course, as may occasionally happen,

actual pyloric obstruction coexists as an independent lesion.

These early symptoms are in no way characteristic of alkali poisoning, and it is not usually possible even to suspect its existence from their presence. But the most typical and valuable symptoms are of a different nature. They are concerned essentially with a change in the character of the patient and in his mental outlook. His friends notice that he is becoming difficult, irritable, thoughtless, and unreasonable. Previously cheerful, he begins to suffer from attacks of melancholy and depression. Irritability and the occurrence of delusions may lead him to spread scandalous and frequently untrue stories about his friends and acquaintances, thus making life difficult also for those who are associated with him. He himself may note that his mind is not as clear as it was, and that his powers of consecutive thought and of concentration are diminished. Because of this he becomes less able to carry on his work, and this again increases his depression. Consulting his medical adviser, he may be told that he is in danger of a nervous breakdown, or he may be suspected of some more severe nervous disease.

These symptoms continue, as a rule, to increase in intensity until a definite drowsiness appears. There may be complaint also of vague headaches and of general muscle pains. The headaches tend to be worse in the evening than in the morning, being aggravated probably by the alkali taken during the day. Somnolence and drowsiness become an increasingly prominent feature, until finally the patient may even pass into a deepening coma.

The rapidity with which these successive stages are passed through varies considerably. In acute cases the transition from apparent normality to definite drowsiness may only take a few days; in chronic cases the patient may remain for weeks in a state of depression and mental inefficiency without the appearance of any drowsiness.

A further peculiar symptom which has been present in all the cases which we have seen, but is probably not invariable, is the complaint of soreness of the eyes. This is due to a red and inflamed conjunctiva. Vision may be slightly blurred, but is not as a rule appreciably interfered with.

Physical Signs

The physical signs of alkali poisoning are scanty. The presence of the above-mentioned conjunctivitis is a useful one. In severe cases bordering on coma the breathing may be rather slow and shallow—a point of contrast with typical diabetic and uraemic comas. But in most cases no definite change in respiration can be noted. The skeletal muscles are sometimes abnormally excitable to direct percussion, but actual tetany appears to be decidedly uncommon. The blood pressure is not raised above its previous level, and there is no rise in temperature. The daily urine volume is frequently increased in amount, and such a polyuria has been thought to be of diagnostic value, but it is probably due largely to the diuretic effect of the ingested alkalis. This polyuria is by no means invariable, but when present is another point of contrast to other forms of alkalosis which are due to severe vomiting. But in some cases of alkali poisoning the urine volume is reduced below the normal.

The urine is in the great majority of cases alkaline to litmus, and owing to its high content of bicarbonate effervesces readily on the addition of acid. Only rarely are cases encountered in which the urine is acid when fresh. It always contains albumin, the amount varying from a definite trace to the more usual good cloud on boiling with acetic acid. Hyaline casts are usually present in fair numbers if the urine is examined while fresh, and the more finely granular casts may also be numerous. Very characteristic of all conditions of this

type in which the body contains an excess of alkali is the extremely low concentration of chloride in the urine. This may be very simply demonstrated by the addition of nitric acid and a small quantity of silver nitrate solution. Normal urine gives a heavy precipitate of silver chloride under these conditions, but the urine from a case of alkali poisoning may give only a faint turbidity.

Blood Changes

From the diagnostic point of view the most important changes are to be found in the blood itself. These blood changes may be divided into three groups:

1. *Those referable to the failure of the kidney to excrete nitrogenous waste products of metabolism.*

The presence of casts and albumin in the urine implies some renal involvement, and this is shown by the blood to be of serious degree. The blood urea is greatly raised, and may even exceed 300 mg. per 100 c.cm. There is a general nitrogen retention involving also the total non-protein nitrogen and the plasma creatinine. As so often happens in advanced renal damage, plasma phosphate is also above normal in most cases.

2. *Changes due to the failure of the kidney to excrete the ingested alkali.*

The reaction of the blood is more alkaline than normal, its pH being 7.6 or higher instead of the normal 7.4. This change is, however, not readily detected without the use of a special technique such as the glass electrode.

The bicarbonate content or alkali reserve of the plasma is much increased. This is measured as the number of volumes of CO₂ evolved from 100 volumes of plasma on the addition of excess of acid. In the normal it is usually between 55 and 75 volumes, but in alkali poisoning values of over 100 volumes per cent. are not infrequent. The plasma chloride concentration is much reduced. Such a reduction is usually found in all conditions in which the bicarbonate is increased, the two tending to bear an inverse relationship to one another. It is, no doubt, this low plasma chloride which accounts for the almost complete absence of chloride from the urine.

The changes included in this second group are all those typical of an uncompensated alkalosis. They appear to result directly from the failure of the normal renal ability to keep constant the reaction of the blood under conditions of excessive alkali intake.

3. *Changes referable to an inability of the kidney to excrete the basic radicals of the alkaline stomach powder.*

All forms of severe vomiting result in the loss of considerable amounts of sodium chloride in the vomitus, and as a result tend to produce a fall in the concentration of sodium in the blood. But in alkali poisoning the ingested alkali is, as a rule, more than sufficient to replace that lost in the vomit, so that no such reduction in serum sodium takes place. Indeed, its concentration may actually be above the normal. In this respect alkali poisoning stands in marked contrast to the somewhat similar condition of alkalosis encountered in pyloric obstruction.

If, as is usually the case, the alkaline powder contains calcium carbonate, then calcium also tends to accumulate in the blood stream, and the serum calcium may be raised from the normal level of 9 to 11 mg. per cent. to 16 mg. or even higher. Except in the presence of alkali poisoning or parathyroid tumour, such high values for the serum calcium are rarely if ever encountered in man in disease (Cope).

The alkaline stomach powder usually also contains magnesium, in the form of either the oxide or the carbonate. If this is so then retention of the magnesium in the blood stream is frequently found. The normal concentration of magnesium in the serum is 1.5 to 2.5 mg.

per 100 c.cm. In alkali poisoning figures in excess of 6 mg. have been encountered (Cope).

The changes in the composition of the blood in alkali poisoning may thus be summarized as: (1) a severe degree of nitrogen retention; (2) a definite uncompensated alkalosis; and (3) hypercalcaemia and hypermagnesaemia.

Diagnosis of Alkali Poisoning

Since the most marked and characteristic symptoms of alkali poisoning are those referable to change in mental state, a previous knowledge of the patient and his character is of the greatest help in early diagnosis. It is by recent definite changes in his character that a suspicion of alkali poisoning will frequently be first aroused. In some cases the patient himself may complain of an increasing impairment of mental efficiency, in others his relatives and friends may be the first to note a change in his behaviour. Any such change in a person taking alkalis for a gastric ulcer should lead to a suspicion of possible alkali poisoning, especially if it is associated with a recent anorexia or with attacks of vomiting. The fact that the patient may have been taking alkalis for a long time without apparent ill effects does not eliminate the possibility of alkali poisoning occurring later. The presence of an unexplained conjunctivitis is a sign of considerable confirmatory value.

The urine should be tested for albumin, and the presence of this provides additional support for the diagnosis, especially if the albuminuria is known to be of recent development. The urine should also be tested for the presence of chlorides in the manner previously mentioned, and if only traces are found this is a strong point in favour of the diagnosis. An alkaline reaction of the urine with effervescence on the addition of acid is of no diagnostic value. It is frequently found in persons who are taking considerable quantities of alkalis, in the complete absence of all toxic symptoms.

Although alkali poisoning does not itself cause a rise of blood pressure, the presence of this or of other signs associated with chronic nephritis, such as enlarged heart or fundus changes, does not eliminate the diagnosis. For although alkali poisoning often occurs in persons who have shown no previous evidence of renal damage, it may also occur in chronic nephritics. In the latter case the diagnosis is not quite so readily made.

Greater certainty of diagnosis can as a rule only be obtained by recourse to blood analysis. In this respect two estimations are of the greatest value. Estimation of the plasma bicarbonate or alkali reserve is the most certain of interpretation. A rise of this above 80 volumes per cent. is practically diagnostic of alkali poisoning, even if the patient is known to have suffered previously from a chronic nephritis. A rise of the blood urea is also invariable, but is not quite so specific, as it may be due to a previously present chronic nephritis or to dehydration produced by severe vomiting. It would seem to be a safe general rule, however, to regard all suspected cases showing a rise in blood urea about 80 mg. per cent. as cases of alkali poisoning unless an independent cause for the high value can be definitely found. In cases of doubt a plasma bicarbonate determination will generally provide a definite answer. Occasionally the demonstration of a low plasma chloride may furnish useful confirmatory evidence, but estimations of blood constituents other than those mentioned are of greater scientific interest than diagnostic value. Although a close approach to certainty of diagnosis can be made without recourse to plasma bicarbonate determination, final proof in such cases is only obtained by the subsequent course in response to treatment.

Treatment and Course of Recovery

The essential and often the only necessary point in treatment is to stop at once the administration of all alkalis. In this regard it should be remembered that ulcer patients are not infrequently taking milk to which citrate has been added. This citrate is also to be classed as an alkali, and should not be given.

The period of recovery involves two main processes. First, the elimination of retained bicarbonate and the restoration of a normal blood reaction; and secondly, the restoration of normal renal function with resultant elimination of retained products of nitrogen metabolism. The successful establishment of the first process enables the second to take place spontaneously. After stopping the alkali administration the plasma bicarbonate and the blood reaction return to normal, usually in a few days. The process may be encouraged in two ways. The alkalosis of alkali poisoning is associated with a lack of sufficient chloride in the plasma, and probably also in the body as a whole. In such circumstances the elimination of the excess sodium bicarbonate is made difficult for the kidney. The administration of saline per rectum, by correcting this lack, facilitates considerably in some cases the excretion of the bicarbonate, and is therefore in severe cases a valuable method of treatment. The second substance which may occasionally be of value is ammonium chloride. This has an acidifying action in the organism, and therefore tends to combat the state of acidosis. But it must be used with extreme care, for in all cases of alkali poisoning the kidney is severely damaged, and in such circumstances it is very easy to convert the state of alkalosis into one of severe acidosis. It should never be used in treatment unless facilities are available for examining the reaction of the urine at frequent intervals. Indeed, its use is best controlled by frequent estimations of the plasma bicarbonate.

In a few days by such simple means the alkalosis can usually be cured, and this results as a rule in a very definite improvement in the patient's general condition. But the second part of the recovery process—the restoration of normal renal function—is much more slow. So far as is at present known nothing further can be done to hasten its progress. The blood urea takes from two to several weeks to return to normal, and albuminuria almost as long. Symptomatically the patient is usually restored to normal in a week or ten days at most, although the blood urea may still be high and albuminuria persist for considerably longer. But ultimately the urine, which has already become acid, becomes also albumin-free, and when the blood urea has returned to normal the renal function is fully restored. Although the damage which the kidney suffers in alkali poisoning is severe, there do not appear to be any permanent ill effects upon its function.

After-treatment

It is desirable that any person who has once been found to be alkali-sensitive should in future avoid the stronger alkalis of the type found in the usual "stomach powders." Epigastric pain may as a rule be much relieved in such individuals by disodium phosphate. This is a weaker alkali than those generally used, and appears also to be rather less efficacious in relieving symptoms. In mildly sensitive individuals who develop toxic symptoms only after very large doses of alkalis, it may often be possible to give these in restricted quantity, but a careful watch is necessary for the fresh development of signs of poisoning. In the more sensitive cases all such alkalis should be avoided, and it is important to impress this point strongly on the patient himself, for if he should at any

time seek medical advice elsewhere he will probably be given a prescription for the very alkalis to which he is sensitive.

It is possible that the recently introduced hydrated magnesium silicate will solve the problem of the treatment of gastric ulcer in persons who are very sensitive to alkalis, but I have no experience with this substance.

Illustrative Case

Cases of this type of alkali poisoning have been reported elsewhere by Cooke and by Cope. The following case is recorded here because it is of a type likely to be encountered in general medical practice.

A married man, aged 57, was admitted to St. Thomas's Hospital on June 3rd, 1935. For the last fifteen years he had suffered from "gastric trouble," for which he had at times taken alkalis. In 1930 he had been operated on for gastric ulcer. The precise nature of the operation was not determined. Since this operation he had regularly taken about 4 drachms of alkali daily, and had remained fairly free from symptoms until six months before admission. At that time a recurrence of epigastric pain led him to increase his dose of alkaline "stomach powder." During the last few months he had noticed the onset of a general weakness. His appetite, which previously had been good, became poor, and he became irritable and depressed. He began to quarrel frequently with his wife, and complained of a diminishing mental efficiency. In this state he consulted his doctor, who considered him to be suffering from a "nervous breakdown," and advised a holiday. During this holiday, which was taken in the fortnight previous to admission, he continued to take his alkalis regularly. The holiday appeared to do him no good, and during it he vomited several times. On his return home he was beginning to feel definitely drowsy, and in this state presented himself at hospital.

He was found to have a moderate albuminuria and a definite conjunctivitis, and was admitted as a typical case of alkali poisoning. His blood urea on admission was 201 mg. per 100 c.cm., and his plasma bicarbonate 101 volumes per cent.

No treatment other than the complete withholding of all alkalis was employed, and he made an uninterrupted recovery. The albuminuria ceased seven days after admission, the blood urea being then 82 mg. and the plasma bicarbonate 63 volumes. In another week his blood urea had fallen to 57 mg. and the bicarbonate to 57 volumes. So far as could be judged his mental condition was normal, and he was discharged from hospital a few days later.

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Dorothy Viscountess St. Cyres, who died on September 20th, left many bequests, public and private, including £3,000 to the National Hospital for Diseases of the Heart, as to £1,000 to endow a second bed in memory of her husband, £1,000 to endow a bed in memory of Dr. J. Strickland Goodall, £500 for scientific or technical equipment, and £500 as a further endowment to the "St. Cyres Lecture"; £1,000 to the Cottage Hospital, Lymington, to endow a St. Cyres bed; £1,000 to Salisbury Infirmary, to endow a James Archibald Morrison bed, in memory of her brother; £1,000 to Charing Cross Hospital, to endow a Mabel Morrison bed, in memory of her mother; £1,000 to St. Bartholomew's Hospital, to endow a free bed in the women's cancer ward, in memory of her aunt Amy Mackarness; £500 to Lord Horder, for the benefit of St. Bartholomew's Medical School or Hospital; £500 to the Florence Nightingale Hospital; and £5,000 upon trust for use in furthering the prevention, cure, and relief of diseases of the heart by assisting existing institutions or promoting, founding, or assisting the formation of new institutions.

THE EYNESBURY QUADRUPLETS: FIRST NINE MONTHS OF LIFE

BY

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A short description of the birth of the Eynesbury quadruplets was published in the *Journal* of December 21st, 1935 (p. 1207). I feel sure that an account of the subsequent history of the rearing of these babies will prove of interest.

The quadruplets were due to be born on January 20th, 1936, and their arrival on November 28th, 1935, shows them to have been seven and a half weeks prematurely born. They presented the usual signs of prematurity—namely, absence of finger-nails and toe-nails, and, in the case of the boys, undescended testes. Their skins were wrinkled, their abdomens protruded, and their bodies resembled skinned rabbits and were about the same size. They were a purplish-red in colour. They had cried well at birth, with the exception of Michael, who cried after a period of artificial respiration. Their heart sounds were clear, except that Paul had a soft systolic murmur heard at the apex; this murmur disappeared after the first week.

Nourishment During the First Month

Their diet consisted at first of sterilized water only, and sugar was gradually added. For the first two days the babies were oiled with warm olive oil, wrapped in gamgee, placed in two armchairs in the living room, and attended by the two district nurses. It was impossible to maintain an even temperature in the room, which was in a council house, and I therefore decided that the babies would have to be moved, and this was done on November 30th at 6 p.m. We had prepared a room in my home for their reception, and the services of four trained nurses from Great Ormond Street Hospital for Sick Children, London, were obtained. The room is 15 ft. 6 in. square, facing south, and was heated by an open fire, an electric steam radiator, and an ordinary electric fire. It was kept at a steady temperature of 78°. The babies had two hot-water bottles each in their cots, and were oiled each day, and wrapped in gamgee. A separate thermometer was kept under the blankets and over the gamgee covering, and by experiment we found that when these thermometers registered 102° the babies' temperatures were 98.4°. During this experimental stage the babies' temperatures had varied from 102° to 97°. As the babies were prematurely born their suprarenal and thyroid glands had not sufficiently developed to be able to maintain a temperature, and so heat had to be supplied and carefully regulated. Moisture in the room was kept up by means of a boiling kettle. Oxygen cylinders, and a special oxygen tent, kindly lent by the British Red Cross Society, were at hand, but, fortunately, they were not required.

A point of interest is that the finger-nails and toe-nails developed and the testes descended at an earlier date *ex utero* than they would have done normally *in utero*. The finger-nails appeared on December 2nd, and the toe-nails a few days later. They reached the ends of the fingers and toes on about December 25th, and both testes were in the scrotum on that day. All four babies were constipated at birth, but Michael passed meconium better than the others, probably due to the artificial respiration stirring him up. When they began to take food more freely, and with the help of petrolagar in 1/4 drachm doses at bedtime, they passed their motions better and the meconium finished on the sixth day after birth. Supplies of human breast milk were fetched twice daily