remedy cannot always be relied upon to accomplish the desired result, for a recurrence may follow when the nail grows again. A more simple method is to pare and scrape the nails to the utmost limit of the patient's endurance, and then apply a 2 per cent. solution of silver nitrate or Fehling's solution. It is essential to keep the fingers dry, for the disease is most common in those whose occupation entails the immersion of the hands in water. It is also advisable to continue the treatment with a weaker solution after the disease is apparently cured.

In conclusion, I would emphasize the point that these diseases are more common than is generally supposed; they are of sufficient medical and social importance to deserve recognition and study by medical practitioners.

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Report

ON

THE TREATMENT OF MALIGNANT DISEASE BY COLLOIDAL LEAD.

BY

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IN view of the success claimed in the treatment of malignant disease by means of injections of colloidal lead I visited Liverpool in April, 1926, and, with Professor Blair Bell's permission, saw some of the patients who had there been submitted to the treatment, and observed the technique of the process. Although I was unimpressed by the results which were shown it was considered necessary by the Cancer Hospital that the method should be fully investigated. Dr. Lorna King was therefore appointed to assist me, and together we have treated a total of 88 patients in this way. Of these, however, 32 were given a preparation of colloidal lead hydroxide, and I omit details of them for three reasons—namely: (1) the preparation differs from that used by Professor Blair Bell in that all the lead has been converted to hydroxide, whereas in the latter only a variable and unknown proportion is in that form; (2) it is extremely toxic—ill effects so frequently follow its use, and are so marked, that I consider its employment unjustified; (3) no evidence of benefit was obtained in any case. Moreover, it has often been emphasized that satisfactory results could be obtained only if the lead be prepared in a particular manner, and if its pharmacological effects be closely watched in each patient. That much importance need be attached to such a statement is more than doubtful—the method used in Liverpool for preparing the metal has been many times changed, and there is no evidence whatever that one method is more successful therapeutically than another—but it was obvious that, in the first place, the original technique must be strictly followed.

Fifty-six cases were treated strictly by the Liverpool method—namely, 35 at the Cancer Hospital, 18 at St. James's Hospital, S.W., and 3 privately. In describing the results no differentiation is made between these series.

Method of Preparing the Colloidal Lead.

When this work was commenced it was impossible to obtain colloidal lead except by preparing it for oneself. The necessary apparatus was erected by Mr. C. E. Phillips, consulting physicist to the Cancer Hospital, and consisted essentially of a circuit containing a voltmeter and an ammeter together with an adjustable resistance, such that a current of 70 volts and 10 amperes passed when an arc was established between two pure lead electrodes immersed in distilled water. The water was placed in a porcelain

bowl with a few small lead shot. One electrode was then fastened so that its lower end was in contact with the shot, which were constantly stirred with the other electrode while the current passed. In twenty minutes a colloid suspension of lead (about 0.5 per cent.) was obtained. Its concentration was estimated by a modification of Nessler's method—a not very accurate one for such quantities, but the most practicable in the circumstances. For use, the suspension was diluted to exactly 0.5 per cent., and 0.4 per cent. gelatin, 2 per cent. sodium chloride, 0.05 per cent. potassium chloride, and 0.027 per cent. calcium chloride were added. The preparation is very unstable, sedimentation quickly occurs, and oxygen is rapidly absorbed from the air with the formation of very toxic lead hydroxide. It must consequently be used at once, and cannot be prepared in bulk for use at a later date.

From time to time certain slight modifications were made. First, 4.0 per cent. of gelatin was added instead of 0.4 per cent., so that the preparation was solid at ordinary temperatures. In this condition it could be stored in sealed ampoules, and remained stable for several months. Then iso-electric gelatin was substituted for the ordinary substance, and had the same stabilizing effect without becoming solid. Sometimes a trace of a reducing agent was added to hinder the formation of hydroxide. Finally, we reverted to the original preparation.

All these preparations are essentially the same, and there is no reason to suppose that their therapeutic action differs.

Type of Patient Treated.

Most types of malignant disease have been treated—epithelioma, carcinoma, and sarcoma. In every case the disease was inoperable when first seen, or was recurrent after operation. Many of them were in an advanced stage of the disease. To obtain suitable patients for such work is far more difficult than appears on the face of it. A large majority of the inoperable patients admitted to hospital are having, or have had, some other form of treatment (for example, radiation), and are therefore unsuitable for this, since any change observed could not be certainly attributed to either method. If the patient be not already under some form of treatment he or she is generally too near the end for any form. Another difficulty is that very often the patient refuses to remain long enough in hospital to give the method a chance. No patient in this series had received any but surgical treatment.

Dosage.

In deciding on the dose to be given an attempt was made to give the maximum amount of lead which did not endanger life, and to keep the patient as long as possible under the influence of this quantity. With six exceptions the initial dose was 0.08 to 0.1 gram. In one case this was repeated after seven days, with the result that the patient became very ill; there were several rigors, repeated vomiting, and marked jaundice. From these effects she eventually recovered, and survived about seven months, but it was not considered justifiable in any other case to repeat the dose at so short an interval. In seven cases the second dose was given a fortnight after the first, but again the reaction which followed was generally intense, so intense that it was decided to allow an even longer interval. In six cases an initial dose of 0.05 gram was given, and repeated in approximately a week. While these showed no better therapeutic results than the others, the reaction following each injection was reduced to a minimum, and never amounted to much. For the remainder an initial dose of 0.1 gram was followed by the same dose at the end of three weeks. Even after this interval some reaction was almost invariable, but was in no case serious.

Subsequent doses must depend, both as to the quantity and interval, upon the reaction of the individual patient. Our aim has been to administer a total of 0.6 gram to each patient, and we commenced by repeating the original dose of 0.1 gram at intervals of three weeks to six doses. This proved disastrous, for the only two patients who were so treated (one with five and the other with six doses) both died of uraemia within eleven days of the last dose. We therefore changed the procedure and gave three doses of 0.1 gram at intervals of three weeks, and then continued

with doses of 0.05 gram at intervals varying from a fortnight to a month, according to the condition of the patient, and no other instance of renal complications clinically discoverable was encountered amongst those who received the latter doses.

The two cases mentioned above called attention to the importance of determining, if possible, how near one has approached to the patient's tolerance. But no method of doing so was discovered. In both cases, before the last dose, the urinary urea was adequate; the blood urea was well within normal limits, there was no marked anaemia nor deficiency of haemoglobin, and little or no punctate basophilia in the erythrocytes. Lead is, of course, a cumulative poison, and it seems as though it accumulates up to a point without causing any appreciable damage to the kidneys, but immediately that point is passed there is a sudden or rapid destruction of certain of the renal elements, so that the urinary urea falls, the blood urea rises, and the patient becomes uraemic. In one of these cases the blood urea was steady between 18 and 36 mg. per 100 c.cm., but four days after the last injection it had risen to 146; in the other it was 28 to 34 until the last dose, whereas two days later it was 77, and another five days later 111.

Observations were made on certain of the cases with phenolsulphonephthalein, as well as on the various nitrogenous constituents of the blood—for example, uric acid, creatinine, etc.—with the object of determining whether any change could thereby be discovered which would indicate damage to the kidneys before evidence was afforded by the urine or blood urea. No significant change was found, nor did any other case of uraemia occur (though one other patient had died of this condition after a comparatively small dose of lead before these observations were commenced).

Probably the best method of deciding whether, and when, another dose shall be given is by clinical experience. The patient's colour is important—too marked pallor contraindicates immediate treatment. A very severe reaction suggests a longer interval. A reaction, even though moderate or slight, if long drawn out, calls for delay in administration of the next dose. Examination of the blood really helps very little. There is a more or less marked fall of haemoglobin within a few hours of each injection, but as a rule recovery takes place. If the haemoglobin falls very much, or if it fails to recover its previous figure, treatment must be discontinued or delayed. We found that the number of red cells showing punctate basophilia was no evidence whatever for or against continuation of treatment.

Immediate Reaction.

Following the injection there is usually some general reaction, but very rarely does it amount to much. It is either of two main types: (1) rise of temperature and pulse frequency, rigor, generalized pains (head, back, and limbs); (2) nausea, diarrhoea and vomiting, and abdominal pains. It may come on in a few minutes or be delayed for two or three hours. A sensation of chilliness without actual shivering is the commonest reaction, though not infrequently there is a slight rigor. Both of these symptoms remain but a short time, and as a rule pass off within ten to sixty minutes. Occasionally there is no rise of temperature, more often it rises to about 100° F., in a few cases it will reach 103° F. or thereabout; but 100° to 101° F. is usual. There may be a feeling of malaise—the sensation is apparently indescribable; there may or may not be some headache. Nausea is commonly experienced. Abdominal pain and discomfort were observed once or twice, and definite colic once. Abdominal symptoms may be accompanied by diarrhoea. Only three times was a severe reaction seen—temperature 102° to 103° F., dyspnoea, cyanosis, a small frequent pulse, and pain in the head and back. In only two cases was there any local reaction, shown by swelling and pain in the growth.

In some cases the types have been combined. Recovery was quick and appears complete from the first type of reaction. In the second type the patient felt ill for a considerable time—in two cases the abdominal discomfort lasted for five weeks, and in one of these was followed by a blue line on the gums, a metallic taste in the mouth,

and sluggish knee-jerks. Both eventually recovered, and treatment was continued. In no case has death occurred as an immediate result of an injection of lead.

Occasionally a prolonged reaction was observed. Slight headache commenced an hour or two after the injection, but disappeared after a night's rest. In the morning, however, there was slight nausea, and the patient might even vomit. This condition of discomfort—there is an indefinable feeling of malaise, a suspicion of nausea, loss of appetite—may persist and only pass off in six or seven days.

It is quite impossible to foretell the occurrence of a reaction; it is no more likely after a first than after any subsequent injection.

Late Reaction.

Rarely was there any apparent effect upon the growth itself—there was no swelling of the mass, no increase of pain in it, and no breaking down; but in two cases swelling of the growth, and pain in it, were noted. It is difficult to say whether these effects were the direct result of lead, or merely that of the natural progress of the disease.

Effect on the Blood.—Some degree of anaemia generally follows the injections, though the effect on the erythrocytes is not extreme. The number of the latter falls, often considerably, but rarely below 3.5 million. Even after considerable doses of lead they may remain well up (5 to 5.5 million). A more marked effect is exerted upon the haemoglobin, which falls more rapidly and to a greater extent. In spite of this, only once had we to cease treatment on account of the condition of the blood. Stippling of the red cells was found to a greater or less extent in all cases, but appeared to have no special significance from a prognostic point of view, and after a short time little or no importance was attached to this finding. The white cells did not appear to be affected in any way. Except in one case, when a carcinoma of the breast was complicated by diabetes, the injection of lead did not influence the sugar content of the blood. In the diabetic, however, it seemed to increase the circulating sugar and exert an adverse influence on the course of the disease. Three cases of uraemia have already been mentioned; in no other case was clinical evidence of renal damage obtained—the urine remained normal and the blood urea showed no significant change. In a few cases the excretion of phenolsulphonephthalein was tested, but no abnormality was found. In some others the nitrogenous constituents of the blood, other than urea, were also estimated, but without demonstrating any pathological change.

Effect on the Urine.—The urine in non-fatal cases has shown variable alterations. In many cases the amount excreted in twenty-four hours has been very much diminished for seven to fourteen days after an injection, usually (but not always) with diminished urea excretion. Cases with reduced urea excretion (even though this be marked) have shown no clinical signs of renal incompetence, have had no rise of blood urea, and have had further injections of lead without ill effect.

Uraemia.—Three cases of uraemia occurred. One of these must certainly be attributed to the direct effect of treatment, and is, indeed, a case of acute lead poisoning. This patient received in all 0.6 gram of lead in the course of three months, and eleven days after the last injection she died presenting the typical picture of uraemia. Towards the end the excretion of urine diminished, albumin (at first a trace, later in considerable quantity) and casts appeared in it, and the blood urea rose from 0.034 to 0.111 per cent. At autopsy the kidneys showed well-marked changes in the tubules, but none in the glomeruli. It is more than doubtful whether the other two can be attributed in any way to the lead administered. In one the original lesion was a carcinoma of the cervix, which eventually penetrated the bladder and involved both ureters. The blood urea rose from 0.036 to 0.146 per cent. At necropsy the pelvis of each kidney was dilated, and the kidneys showed numerous minute abscesses scattered throughout. The other died of uraemia after a total of 0.25 gram of lead. A carcinoma of the rectum had been excised some time previously, but a local recurrence appeared and, spreading to the bladder, involved both

ureters. The kidneys showed extensive interstitial fibrosis with tubular changes superimposed. In both these cases ureteric obstruction and subsequent bacterial invasion of the organs are sufficient to account for the microscopic lesions.

No case of typical chronic lead poisoning occurred—constipation, colic, peripheral neuritis, encephalopathy, were never seen—but one patient presented a blue lead line on the gums after 0.25 gram of lead given during a period of eleven weeks.

Autopsies were made on 17 of those who died, and the post-mortem findings were remarkably constant. In no case was any sign of regression observed in the growth. In some cases it showed advanced degeneration (but no central

necrosis, and no change which is not commonly seen when no lead at all has been given), in others there was no degeneration whatever, and in every case the mass of growth was larger than when treatment commenced. In nearly every instance the brain, liver, and kidneys showed evidence of damage as follows. In the brain there was extreme superficial (subarachnoid) oedema, with free fluid at the base. The choroid plexuses were markedly oedematous. The liver showed extreme fatty degeneration. Apart from the cases of uraemia, the kidneys showed no macroscopic change. In most the cells of the convoluted tubules stained badly and showed some degree of desquamation, but it is possible that this is largely, if not entirely, a post-mortem process. But the localization of the changes is noteworthy: in no case was any abnormality discovered in the glomeruli or the cells of the loop of Henle or the collecting and straight tubules. In view of the fact that these appearances are not such as are met with in cases of malignant disease treated by other methods it is fair to presume that they directly result from the toxic action of the lead preparation employed.

Final Results.

Of the 56 patients treated one only—with a small supra-clavicular gland which appeared one year after amputation of the breast for carcinoma—showed definite improvement, the gland being now only just palpable, whereas before it was about the size of an almond, and quite visible. Although clinically a definite diagnosis of secondary malignant disease was made, there is no proof that the gland was in fact malignant.

No appreciable change took place in 12, but of these 7 received admittedly inadequate treatment—2 because they were so ill that it was decided to leave them in peace, 5 because they refused further injections. Five received from 0.3 to 0.6 gram of lead in all, but the local condition remained unchanged. Another 11 were actually worse after treatment, of whom 2 received less than 0.3 gram of lead in all (one was considered too ill to receive more, the other refused). Nine received from 0.3 to 0.6 gram, in spite of which the malignant growth progressed. Thirty-two died, of whom 8 had received only one injection each. In other words, of 40 patients who received sufficient lead to warrant the expectation of some benefit, if any ever occurs, 22 died, 11 were clearly worse, 6 showed no change in either direction, and only one in any way improved. (Full results, with total dosage, are given in the accompanying table.)

Conclusion.

Of 40 patients who have received 0.2 gram or more of colloidal lead intravenously, only one has shown any improvement, while the majority are dead or obviously much worse than before treatment. So far, then, as my observations go there is no support for the statement that colloidal lead exerts a beneficial influence upon the progress of a malignant growth. Moreover, it is certainly a difficult and dangerous therapeutic method.

SYPHILIS OF THE HEART.

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It is of the utmost importance to recognize syphilis of the heart, this being one of the few heart affections which almost invariably yield to treatment. In many cases, it is true, the improvement due to antispecific treatment is not pronounced, but there are doubtless numerous cases of cardiac syphilis in which proper treatment has effected a complete cure. To overlook a case of syphilis may mean the whole difference between normal health and permanent disability, and sometimes even between life and death.

The incidence of syphilis in heart disease has been greatly underestimated in the past, and there are but scant references to it in the older textbooks. Mackenzie,¹ for instance, dismisses it with a few words, and authors like Romberg² actually express the opinion that syphilis of the heart is rare. As a matter of fact syphilis is a

Table showing the Results in 56 Cases of Malignant Disease treated by Colloidal Lead.

Patient.	Disease.	Duration of Treatment.	Total Dose.	Results.
A. C. ...	Ca. thyroidei	169 days	0.55 gram	Died.
A. F. ...	Ca. thyroidei	15 "	0.2 "	Died.
C. P. ...	Ca. recti	43 "	0.25 "	Died.
C. H. ...	Ca. mammae	225 "	0.45 "	I. S. Q.
E. S. ...	Ca. mammae	106 "	0.3 "	Worse.
A. H. ...	Ca. mammae	107 "	0.35 "	Worse.
L. A. (a) ...	Ca. mammae	107 "	0.05 "	Died.
R. D. ...	Sarcoma femoris	132 "	0.57 "	Died.
I. D. ...	Ca. ventriculi	45 "	0.17 "	Died.
A. B. ...	Ca. mammae	63 "	0.3 "	Worse.
W. A. S. (b) ...	Ca. ventriculi	46 "	0.22 "	Died.
S. H. ...	Ca. oesophagi	—	0.1 "	Died.
R. S. (c) ...	Ca. soli oris	—	0.09 "	I. S. Q.
E. T. ...	Ca. cervicis	—	0.1 "	Died.
S. G. ...	Ca. cervicis	—	0.08 "	Died.
E. C. (c) ...	Ca. cervicis	—	0.08 "	I. S. Q.
D. N. ...	Epith. oris	—	0.08 "	Died.
S. W. (c) ...	Ca. ovarii	—	0.07 "	I. S. Q.
T. G. ...	Melanomatosis	—	0.104 "	Died.
M. H. ...	Ca. mammae	49 days	0.3 "	I. S. Q.
W. K. ...	Epith. pharyngis	115 "	0.508 "	Died.
T. B. ...	Ca. vesicae	77 "	0.254 "	Died.
H. D. ...	Ca. recti	21 "	0.2 "	Died.
E. S. ...	Ca. mammae	88 "	0.35 "	Worse.
C. S. R. ...	Ca. nodorum cervicis	84 "	0.45 "	Died.
M. A. ...	Ca. vesicae	42 "	0.295 "	Worse.
A. B. P. (d) ...	Ca. mammae	105 "	0.53 "	Worse.
A. W. H. ...	Epith. oris	22 "	0.2 "	I. S. Q.
C. J. ...	Epith. labii	166 "	0.6 "	Worse.
B. A. ...	Epith. soli oris	166 "	0.075 "	Worse.
M. B. ...	Ca. cervicis	54 "	0.4 "	I. S. Q.
R. H. ...	Epith. soli oris	36 "	0.3 "	Died.
A. B. B. (c) ...	Ca. oesophagi	36 "	0.1 "	I. S. Q.
E. D. ...	Ca. ovarii	65 "	0.35 "	Died.
C. C. ...	Epith. soli oris	176 "	0.575 "	Died.
K. P. ...	Ca. ovarii	176 "	0.1 "	Died.
E. N. ...	Ca. mammae	207 "	0.26 "	Died.
M. R. ...	Ca. mammae	28 "	0.3 "	Worse.
W. C. ...	Epith. labii	55 "	0.3 "	Died.
A. G. B. ...	Ca. oesophagi	43 "	0.3 "	Died.
M. C. ...	Ca. ovarii	35 "	0.25 "	Died.
W. G. (c) ...	Ca. soli oris	35 "	0.1 "	I. S. Q.
F. B. ...	Ca. oesophagi	35 "	0.1 "	Died.
W. P. ...	Ca. recti	35 "	0.1 "	Died.
M. N. ...	Ca. vesicae	41 "	0.29 "	Worse.
E. M. ...	Ca. vesicae	41 "	0.29 "	Worse.
D. N. (c) ...	Ca. mammae	98 "	0.4 "	Worse.
G. S. (e) ...	Epith. tonsillae	20 "	0.2 "	Died.
F. O. ...	Ca. cervicis	74 "	0.5 "	Died.
A. G. ...	Epith. soli oris	86 "	0.6 "	Died.
J. C. ...	Epith. oris	147 "	0.5 "	Died.
A. L. ...	Ca. vesicae	58 "	0.4 "	Died.
A. N. B. (c) ...	Ca. mammae	94 "	0.45 "	Improved.
R. M. ...	Ca. mammae	36 "	0.2 "	Died.
F. T. ...	Ca. mammae	197 "	0.6 "	I. S. Q.
G. S. B. (c) ...	Ca. prostatae	21 "	0.32 "	I. S. Q.

(a) This patient also had diabetes. (b) Died of haematemesis. (c) Left hospital at own request. (d) Still under treatment. (e) Refused further treatment.