Climatic Conditions.

Kashmir lies between 32° and 36° latitude, and is roughly at the same distance from the equator as Southern Spain or Morocco. The city of Srinagar lies in the valley through which the River Jhelum flows, and the town is built on each side of the river. The valley lies at an altitude of 5,000 feet. The hills round this valley are 7,000 or 8,000 feet in height; further away are hills of 12,000 to 13,000 feet, and still higher peaks overtop these in the distance.

All English flowers and fruit grow well. The temperature may rise to 90° or over in the hottest days of July and August; and again in winter the thermometer falls 10° and more below zero; yet on the whole it is a temperate and equable climate for eight months of the year. In the winter months osteomalacia becomes much worse. Wood is the fuel burnt, and during the four winter months a thick pall of fog and smoke hangs over the city in the early morning and evening.

The streets leading from the river are narrow and tortuous, and the houses, which are of wood, are high and built round small courtyards, where in the winter the sun never shines. Nor does it reach the ground of many of the streets where the aspect faces north. Icicles ten feet and more in length hang for weeks in such places from the roof, and snow to a depth of four or five feet lies in the streets. The roofs have to be cleared of snow or they would give way under the weight; men shovel it off, and it lies in the streets until spring comes. Owing to reflection there is some slight improvement in the light in the dwellings when the snow comes.

The women wear but one garment and go out in the winter as little as possible. They live in the lowest rooms of the high wooden houses in the winter, so as to be on the same floor as the water supply and the fire. The ground floor is the warmest. The windows are sometimes less than half a yard square, and protected against thieves by being near the ceiling and closed by wooden lattice-work. All windows are so made, but on the upper floors are larger. In winter they are covered with oiled paper to keep out the cold. The minimum of available light is thus admitted, and some rooms, specially liked for warmth, have no windows at all.

That the light supply is sufficient for health in all ordinary life is proved by the rarity of rickets and the healthiness of the boat women and the country women working in the fields, but a degree of seclusion which would have little effect on the plains of India produces osteomalacia in Kashmir. A photographer who lived for many years in Kashmir said that he always gave twice the exposure he would in England to get a good result in Kashmir, which looks as if the actinic rays might be deficient. Most of the oblique rays of the sun in mid-winter are cut off by the mountains encircling the valley.

Sunlight alone can cure the disease, and cod-liver oil without sunshine is of very little use. The seasonal incidence above described points to the same cause—absence of sunlight. In spring and summer the women go out and improve in health. The disease only occurs in those deprived of sunlight, and one meets women walking about who have evidently had the disease, and who will tell you they were shut up as young women, but on the death of the husband were free to go out. One woman told me she only began to suffer in her later confinements when her husband had moved from a house facing an open space to the crowded quarters of the city. The fact that the men of the families where the women have osteomalacia are so often tuberculous points to the same thing.

Reports from places in India where cases of osteomalacia occur would indicate lack of sunlight as the cause.

At Islamabad, higher up the valley than Srinagar, the doctor tells me that wherever she goes she sees cases, especially among the wives of priests, shopkeepers, and butchers—all men having some means and able to keep their young wives in seclusion during their early married life. At Ladakh, 11,000 feet, with long cold winters, it is unknown, except for one case in a Kashmiri woman. The women there go out freely. At Peshawar among the Afghan women, who go out freely and live an open-air life, none were known; the only cases reported were in Hindu shopkeepers' wives, who married young and were kept

in purdah. In Lahore the disease is uncommon; the worst cases occur among those who seclude their women and are rich enough to have glass windows, sometimes made so that they cannot be opened.

The most instructive notes come from Bombay, where the Parsee women are completely free from it, and yet the women of the weaver class have it, and were they not recruited from the outside country villages would die out in a generation. A Parsee doctor tells me that out of 25,000 deliveries he did not encounter one case of osteomalacia among Parsees. They have great freedom, and do not marry until about 20 or 22. The weaver class, on the other hand, living in the same town are almost all affected. The superintendent of the Cama hospital tells me they suspect osteomalacia in every weaver woman coming for her confinement. These women live in buildings eight stories high. The loom is on the ground floor in the room facing the street, because all available light is needed for the work, and the women live in dark rooms behind that; the mortality rate is 678 per 1,000 infants under 1 year.

In Chamba, in the Himalayas, the village women do not suffer, but in the hill town there is "hardly any sunlight" in their houses, and those in purdah, the richer women, suffer badly. In Hyderabad the disease is very rare, but cases are known in Hindu women, who eat fuller's earth to cure it.

I also have some notes of the occurrence of the disease in cows in places as distant from one another as Norway, New Zealand, and Australia. I have never seen a case in cattle in Kashmir, but there the cows living in the city are turned out to pick up any garbage they can find in the streets. They thus get any sunlight and air available. In Norway fractures of the bones of affected cattle were reported. Its occurrence in male animals, and its appearance after drought when artificial dry feeding had to be resorted to; the absence of the disease in cows at the sea where they consume fish, and in the extreme north where there is darkness for several months in winter, are all points of interest. Professor Per Tuff of Aas, Norway, says the disease, which led to fractures of bones, is much less common than it was fifty years ago, and he attributes this to the better lighting and hygiene of cattle sheds.

My best thanks are due to those who have so kindly answered my inquiries during the past few years as to the conditions in their districts where osteomalacia occurs either among the women or the cattle.

These rough notes are published in the hope that something may be done in Kashmir to investigate still further the conditions of the sunlight there, with a view to the prevention of this disease, to which the lives of hundreds of women and children are sacrificed every year.

NOTES ON THE USE OF LEAD COLLOIDS IN THE TREATMENT OF CANCER.

BY

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THE question of the treatment of cancer by lead is now so much before the profession that our experiences with this metal may be of interest.

For some years past we have independently tested new cancer cures as they have appeared in the English and foreign journals. The article by Professor Blair Bell in the *Lancet* of 1922 (vol. ii, p. 1005) seemed to be of such importance and to stand on such a rational basis as to invite an early trial of the effect of lead on cases of inoperable cancer. As we did not find it possible to obtain information from Dr. Blair Bell beyond that which had appeared in his articles, a convenient source of lead had to be secured. The aim has been to find a combination of lead with a suitable radicle, the latter, if possible, assisting the absorption or adsorption of the lead. One of the chief difficulties was to obtain a colloidal suspension of the

dispersed lead compound capable of remaining dispersed long enough for general use and of the correct composition for intravenous injection.

The first colloid used was lead oleate. This was freshly made for us at frequent intervals, as it did not keep dispersed very long. It was given intramuscularly. The results gave little encouragement, except that one man with cancer of the fauces seemed to remain stationary; he was neither better nor worse a year afterwards. He died eventually, but the probability seemed that he would have died more quickly without the lead injections. It must, of course, be noted that when first we used these lead compounds we were giving them in very small doses.

The second compound tried was a lead nitro-benzoate, referred to in what follows as "lead N." The use of this was discontinued because we were not able to give any but very small doses without causing some discomfort, chiefly gastric, during the day after the injection.

Next a combination of lead with a very complex radicle of high molecular weight was made. This contained mercury in the same proportion as the lead, but in a non-ionized form. As it was thought that the mercury might add some antiseptic properties if liberated amongst dead cancer cells, it was retained in the compound. A colloidal suspension of these drugs has been used, and will be referred to as "lead M.A.," the M denoting mercury and the A an amino group. It has been found convenient to refer to these complex bodies by such simple terminology. These colloids have been fully tested on animals as to their immediate toxicity, and found to be harmless. The colloidal suspension of lead M.A. contains 0.1 per cent. of mercury and 0.1 per cent. of lead—that is, one-tenth of a gram, or $1\frac{1}{2}$ grains of lead per 100 c.cm., and similar quantities of mercury.

Some twenty cases of cancer have been treated. All of these were naturally inoperable, either from the magnitude of the growth or from its position. Cases were selected in which the cancer was on the surface in some easily observable position. In none of them could the diagnosis be doubted, whilst most had had operations performed on them and the diagnosis confirmed histologically. The results can be divided into four groups.

In the first group of patients are those on whom the lead does not appear to have made the slightest difference, many of them so desperately ill or so full of enormous masses of cancer that no drug could have been expected to influence them, added to which many of them had very small doses.

In the second group temporary improvement was shown. This was manifest by the patients' weight, which had been falling, remaining stationary over a period of many months, or even improving to the extent of a few pounds. The growths often showed considerable decrease in size, firm masses of glands becoming smaller, each gland becoming discrete and freely movable on its fellows. This was due, perhaps, as much to a subsidence of the surrounding inflammation as to any effect upon the growth itself. We may briefly consider five such cases.

1. In an old lady of 76 a hard ulcer firmly adherent to the ribs healed over fairly quickly, and she put on a good deal of weight. She died some months later from hemiplegia; 30 c.cm. of lead N. and lead M.A. were given in twelve doses.

2. A lady with very extensive cancer *en cuirasse*, with many glands in the neck, lost the whole of the hard oedema of the skin. The glands became discrete and freely movable in all directions. For six months she was able to lead a normal life, and took a holiday abroad of seven weeks' duration. During this time she lost ground, which subsequent injections failed to regain; possibly the interval was too long. The cancer cells may have some power of protecting themselves against the lead if

given time to do so. In all, 195 c.cm. of lead N. and lead M.A. were given in forty-two doses.

3. A man with cancer of the larynx, who was given three months to live, and in fact died fifteen months later, showed marked improvement during the first few months and maintained his weight for six months; 216 c.cm. of lead N. and lead M.A. were given in forty-one doses.

4. A very emaciated man who had had his upper maxilla removed at St. Mary's Hospital for a squamous-celled carcinoma showed every sign of healing. Red spots on his face began to disappear and pucker. The stench from his mouth lessened markedly after large pieces had sloughed away. He showed some slight gain in weight, but died suddenly without any very apparent cause. He received 16 c.cm. of lead N. in ten doses.

5. An old lady with a growth in the breast showed a diminution in size of the growth at the end of a year. At one place where it looked very red, like an abscess pointing, the skin became darkened, then almost stained black, and soft as though subsiding. She died from bronchitis. She had had 18 c.cm. of lead N. in seven doses, and 178 c.cm. of lead M.A. in thirty doses.

In the third group are two rather peculiar cases, in which the cancer seemed to abort, the whole of the growth apparently falling out.

The first of these was a woman with a growth springing from the lower jaw involving the cheek and neck. After a few days' apparent improvement the whole cancerous area sloughed out, leaving the bare ends of the lower jaw-bone and a huge fistula opening into the mouth. She received 33 c.cm. of lead N. in ten doses.

The second was a man with a hard, brawny growth filling in the area under the lower jaw-bone. He was getting about the ward, and was not in any way in *extremis*. There was no breaking of the skin. After a few doses of the lead colloid the whole of this area sloughed away, leaving a huge gaping "cut-throat" wound. The edges were thickened, inflamed, and oedematous, and his face swelled above it, possibly from interference with the lymphatics. He had had 29 c.cm. of lead M.A. in five doses.

Both of these patients died from sepsis soon after the abortion of the growths brought about by the lead.

In the fourth group is the case of a patient whose history and treatment will be considered in some detail. This was a man, 56 years of age in 1925, a worker in a railway electrical department.

Previously to 1920 for many years he had had a wart or mole on the side of his head. This became very sore and somewhat enlarged; it bled slightly at first, then very profusely. He ceased work in 1921. The growth increased continuously. He had no treatment except medicine until 1924, when he came into hospital.

When first seen he was a thin, emaciated, poisoned-looking man, very anaemic, with the skin and sclerotics of a lemon-yellow tint. On the left side of his head, above the ear, he had a huge cauliflower growth, protruding about two inches above the level of the scalp, covered with pus, and very foul-smelling. No glands or metastases were to be found. To-day he is a strong, well nourished man, wishing to leave the hospital and return to work. The growth on his head is not healed and much is still present, but it has become progressively smaller and smaller. It disappeared by minute portions at the periphery, turning to black points and sloughing off.

During the early part of his treatment the growth, after becoming less septic and cleaning up, poured with exudation; later it became quite dry. About this time he also had considerable oedema of the legs and some albuminuria, both of which were considered to be symptoms due to the lead.

The chart reproduced herewith has marked on it this man's progress over many months. The top black line shows those times at which he was receiving doses of x rays. This treatment was given to him by Dr. D. Arthur, radiologist to the West Middlesex Hospital, who has kindly supplied the following details.

"A Sabouraud and Noiré's pastille dose with a water-cooled x-ray tube of $4\frac{1}{2}$ inch equivalent spark-gap has been given once or more usually twice a week during those times marked on the chart by the top black line. The rays were filtered through 2 mm. aluminium filter and the growth treated from different aspects (multiple port of entry), no area being treated twice in succession."

Dosage and body weight.

We consider it difficult to apportion the exact amount of credit due to this treatment and to the lead injections, though each may well have assisted the effects caused by the other.

Below this runs a graph of his weight, conforming to the scale on the right-hand side. Taking 12 st. as his normal weight when well, it will be seen that he had lost over 3 st. before treatment commenced; that he rose in weight steadily until he had regained his normal weight, and that he has remained at this for the last nine months.

The vertical lines rising from the base of the chart denote the weekly doses in numbers of cubic centimetres of the lead colloid in use at that time. Weekly intervals on these lines are dated by the months and years at the top of the chart. The numbers underneath the chart are used for reference to this article.

The injections given between (1) and (2) were of lead N. From (3) onwards he was having weekly doses of 10 c.cm. of lead M.A. pretty regularly, and he was putting on weight at a great pace. Part of this increase was due to the very considerable oedema of the feet and legs, as already mentioned, and at (5) he appeared to be suffering from early symptoms of lead poisoning. The injections were therefore discontinued for a short time. At (6) the lead M.A. was recommenced. From there till (7) doses were given intramuscularly; from (7) onwards the intravenous route was used. Owing to the fact that he appeared to be doing quite well as he was, doses were given less frequently from (8) to (9). He was having doses of α rays regularly at this time, but the growth showed signs of increasing in size rather than diminishing, and he was not feeling quite so well. At (9), therefore, full treatment was commenced again, and he at once became better in every respect.

On November 14th, 1924, he gave a *plus* two Wassermann reaction. On November 7th, 1924, Dr. Fletcher examined a portion of the growth, and reported as follows:

"This is undoubted squamous-celled carcinoma. The cancer cells are arranged in solid masses, freely infiltrating the sub-epithelial tissue. There are no cell nests."

This man has had up to the present 368 c.cm. of colloidal lead containing 0.36 gram, or $5\frac{1}{2}$ grains, of lead.

The condition of his blood has been extremely interesting. At the commencement of treatment the blood counts, taken several times, showed an average red count of 2,500,000 and a white count of 12,000. The blood on withdrawal looked like thin washy damson juice of a peculiar purplish colour. No normal red cells were to be seen, extreme poikilocytosis being present. His red cell count has increased to 3,600,000 and the white count is 10,000 odd. The differential white count is normal. The freshly shed blood is bright red, and the red cells are remarkably even and regular, though somewhat oval. It is noteworthy that, in spite of the large amount of lead which he has received, his red cells have increased in number and become normal in shape. No stippled cells have been found in his blood.

Full blood counts must be made in all cases, and stippled cells must be frequently sought for. They are quite common, together with polychromasia, in the blood of many cases, often after quite small doses of lead. We are accustomed to record them as the number of stippled cells counted over the number of fields examined, using a 1/12 oil-immersion and a No. 3 eyepiece. Urinalysis is essential when giving full doses.

Occasionally some protein shock has occurred a few hours after an injection—slight shivering, sweating, some rise of temperature, and more rarely some vomiting.

During the cold weather the preparation of lead M.A. is liable to form a gel, but in any case it should always be thoroughly warmed before being injected intravenously.

The injections have all been made with Record syringes of convenient capacity and No. 17 needles. The syringes can be boiled and used immediately while still hot.

No special technique is necessary, but in comparison with similar injections in the case of asthmatics and other patients the giving of an intravenous injection to a cancer patient is often a matter of extreme difficulty. The veins become much shrunken as the patient wastes, and there is a shortage of blood to distend them; they sometimes become hardened pipes of greater substance than an ordinary artery. The lack of supporting fat allows the vein to roll away from the needle as it attempts to pierce the vessel through the leathery skin.

In the series of cases here dealt with the dosage has on the whole been small, and we consider that there is a large margin of safety within which injections of lead can be increased in size and frequency before toxic symptoms from the lead need be expected. But the dosing of any particular case will depend upon a great many different

factors. Patients of large weight with no cachexia will call for large doses. Males will take larger doses than females. Emaciated patients and those with growths which have ulcerated to the surface will require small doses, at any rate to commence with. As any growth may abort, special care must be taken to make such abortion as aseptic as possible. In this connexion the blood supply to the part is probably an important factor. In growths of the gut abortion must be particularly guarded against.

Summary.

We are using a very stable colloidal suspension of lead and mercury (lead M.A.). This can be injected intravenously with the minimum danger of immediate shock or toxicity from the lead. It has undoubtedly had a beneficial effect upon the patient whose case is reported in full in this paper.

We now have a series of cases under treatment with much heavier doses, and the results obtained will be published at a later date.

Arrangements are now being made whereby a supply of lead M.A. will shortly be available for general use.

THE SURGICAL TREATMENT OF TIC-DOULOUREUX.*

BY

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Of the various procedures which have been devised for the cure of this most distressing malady two only have stood the test of experience. They are: (1) Some form of alcohol injection. (2) Operation on the Gasserian ganglion by the Hartley-Krause method of approach.

Injection treatment has obvious advantages: it is a minor operation which involves no long convalescence, there is no risk to life, and serious complications are very rare. On the other hand, it is always more or less uncertain in its effects, and the relief from pain is often only temporary.

Open operation on the ganglion has one advantage only, but an important one—with the rarest exceptions it cures the patient, and cures him permanently. My own practice has been to try injection first, and, if this proves unsatisfactory, to operate. During the last five years I have performed fifty-two injections and thirteen operations. In most of the operation cases I had tried injection previously, but in a few cases the patients had been injected elsewhere and refused to have any more. Consequently it would appear that, out of every four cases, three have been reasonably comfortable with injection and one has needed open operation.

TECHNIQUE OF INJECTION.

There are two distinct routes of approach in attempting to inject the Gasserian ganglion—from the front and from the side. From the front it is rather difficult to find the foramen ovale, but, when found, the needle enters easily. It tends, however, at this angle to enter the subarachnoid space rather than the ganglion, and at least one serious disaster has followed injection by this route. The alcohol was evidently injected into this space, and paralysis of a number of important cranial nerves followed.

From the side it is easier to find the foramen ovale, but, on account of the obliquity of approach, the needle tends to stick in the orifice. In some skulls, even with the soft parts removed, it is impossible to pass a needle through the foramen. I believe, however, that alcohol injected into the mouth of the foramen infiltrates through into the ganglion, for after such injections anaesthesia has occurred in the first and second divisions as well as in the third.

I have confined myself to lateral injections, largely on account of the serious disaster already referred to as following an anterior injection. A local anaesthetic is employed so that the sensations of the patient may be

* Abbreviated from a paper read before the Midland Medical Society on November 25th, 1925.