Radium Emanation and Goitre.

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[*Read before the Canterbury Philosophical Institute, 2nd November, 1927; received by Editor, 18th April, 1928; issued separately, 30th August, 1928.*]

IN 1925 Rogers (1) estimated the amount of Radium emanation in several drinking-waters of this district, with a view to determining if any correlation exists between the percentage incidence of goitre and the amount of emanation in the water of the localities under observation.

With the exception of Timaru a fair correlation was established, but definite conclusions could not be drawn. Many workers in different parts of the world have sought for a positive causative agent of goitre; for example, McCarrison is convinced that toxins produced in the intestinal tract by bacterial action play a definite role.

At the present time, however, a deficient intake of iodine and a resultant deficiency of the thyroid hormone (an iodine-containing compound) is the only cause established beyond doubt.

That a positive agent might tip the balance and transform a low intake into a pathological deficiency in the organs and tissues where it is required is plausible enough. Such agent might be the intestinal bacteria of McCarrison, or an unusual salt balance in the dietary producing excessive excretion either of the iodine or of the thyroid-iodine compounds. Again, Radium emanation which abounds in the artesian waters of this district, might by irritation of the thyroid render it unable to manufacture sufficient of the necessary compounds for the efficient working of the body.

In 1926 Milligan (2) reported that the administration of large amounts of emanation once a week to rabbits for the space of three months failed to produce any sign of thyroid disturbances as tested by microscopic sections of the gland. In his experiments the emanation was in some rabbits given by mouth and in others by injection into an ear vein.

Some of the observations now reported offer a criticism of the technique used in the rabbit experiments, although our conclusions agree that emanation does not appear to be a causative agent either for rabbits or for trout.

Trout were chosen for the present experiment because they are liable to contract a typical hyperplastic goitre and because they can be kept in a solution containing emanation for the whole period of the experiment.

In the grounds of North Canterbury Acclimitisation Society at Christchurch approximately one per cent. of the trout in their third year of life suffer from this goitre or so-called "gill cancer." Mr. Hope, the Curator, who has had a very long experience, states that he has never seen this condition in trout living in natural conditions.

Marine and Lenhart (3) in 1910 reported that the so-called "gill cancer" in the brook-trout of Pennyslvania (*Salvelinus fontinalis*)

was curable by the administration of iodine, and was not a true cancer of the thyroid but an epithelial overgrowth of the gland with none of the characteristic features of malignancy.

In Christchurch, the trout that have this condition are markedly undersized, thin, and sluggish in movements, but curiously, the goitrous brook-trout observed by Marine and Lenhart are stated to be larger than usual, and though excessively fat are "weak and lumbersome."

In Christchurch, as in Pennyslvania, the affected fish may live for a considerable time after the swelling has become prominent.

Marine and Lenhart speak of cases of spontaneous cure of goitre in brook-trout, but this does not appear to occur in the Christchurch ponds, at least after the goitre has become externally obvious.

The difference in behaviour of the goitrous fish is possibly accounted for by the fact that all the trout goitres seen here are hyperplastic and contain very little stainable colloid, whereas the illustrations given by Marine and Lenhart (3) show far more colloid than our specimens, and presumably they are typical sections.

Iodine Content.

Marine and Lenhart give no analysis of the glands.

The analyses of fish thryoids (normal) known to us, are given by Cameron in *The Biochemical Journal*, vol. 7, 1913.

The iodine in different species and genera of sea-fish is there stated to range from 0.2 gms. per cent. of dry gland to 1.10 gms. per cent. Eight of our own trout goitres, with an average dry weight of 1.4 gms. contained on the average 0.003 gms. per cent. It is noteworthy that this amount of iodine is much less than we have found in human goitres (0.01 to 0.10 gm.%) and in normal human thyroids (0.04 to 0.05).

The iodine-content of even such a small number of trout goitres is probably typical.

In the absence of figures for normal trout thyroids our assumption may not be correct that the trout goitres contain approximately the same total amount of iodine as the normal thyroid, although this is true for human thyroids. Making these assumptions, however, rainbow trout would store about 0.040 mgms. of iodine per kilo as against 0.15 mgms. per kilo for man, i.e. approximately one-fourth of the latter.

Comparisons of this sort which lead to physiological considerations such as the relationship of thyroid-iodine to metabolic activity are well worth making, and it is to be regretted that our own data and other available records are so scanty and possibly, misleading.

Observations on Rainbow Trout.

These were begun on 27th October, 1926, at the local hatchery, indoors, using twenty-four one year old rainbow-trout. The hatching races permitted the same conditions to the controls and to the experimental fish. The entering water was well aerated by spraying, and the lower part of the race was ensured of aeration by means of a waterfall between the two sections.

A dozen trout of suitable age, i.e. two years old, were put in each of two parallel races. The rate of flow was 80 gallons per hour through troughs one foot wide and six inches deep. The fish were fed by the Curator on raw beef liver and lung—the usual diet.

Although this question of a suitable dietary is of importance (for example a deficient supply of vitamines might be involved or an unusual salt balance) our attention was solely directed to investigating the effect of emanation on the trout.

Approximately 20 millicuries of emanation were added each day to the water at the top of the race by dissolving the emanation in a large vessel of water from which a tube delivered the dissolved emanation drop by drop directly into the race without contact with the air. Care was taken to reduce loss of emanation to a minimum but as the tube delivered the emanation during the whole of the time the quantity added fell off towards the end of the period, partly through decay and partly through loss into the air of the vessel.

This method of giving the emanation was followed in all the experiments with trout.

While emanation was freshly added each day as a rule, on Sundays this was not done.

Even over the week-ends, however, emanation was being delivered from the vessel.

The trout were all rainbow-trout, as these, according to the Curator, are more liable to goitre than the brown trout. Whether this is due to the fact that brown trout stay closer to the bottom than the rainbow and so get some dietary constituent that the surface fish do not get, or whether the reason depends on the genetic constitution of the fish, we have no means of deciding.

No goitre appeared, but several deaths occurred, due to the trout being very restless and biting at each other's tails.

The tail-fins in some instances entirely disappeared and because of this at the end of two months only twelve of the original trout remained.

Whenever a death occurred another fish was added to the race.

Tail-biting was as prevalent in the control race as in the one to which emanation was being added.

The water of the two races was tested for emanation on several occasions.

The following figures are typical:—

30th October, 1926	120×10^{-12} mc.
11th November, 1926	126×10^{-12} mc.

Control tests of the water in the other races showed a quantity of 1.5×10^{-12} so that the test trout were getting about eighty times as much as the controls.

On 3rd December, 1926, because of the tail-biting, the trout were removed to an outside race which appeared to be particularly suitable. This race was flask-shaped. In the bulbed end, which was really a hole formed in the earth and shingle by the artesian inflow, and which was without flooring, about twenty trout had been kept for some years. In one of these a fish of about three pounds weight had a large goitre.

The neck of the flask was the part where we placed the trout which were to get the emanation. This was a wooden race 35 feet by 3 feet, and the water was 10 inches deep. The inflow was 30 litres per minute from the artesian bore. Between the neck and the bulb a grating was placed and the vessel discharging the emanation was was placed here.

The number of trout receiving the emanation was made up to thirty.

From this time on, no tail-biting occurred and no deaths.

They were fed exactly as before and thrived well.

On 19th March, 1927, a sample of water from the middle of the race gave 50×10^{-12} mc. per cc.

From time to time other tests were made, and they never showed quantities less than this.

On 11th/5/27 the trout were all removed and carefully examined. No trace of goitre was observed. The Curator remarked that they were as healthy a lot as he had ever seen.

We decided to terminate the experiment, believing that we had given sufficient time—six and a half months—for the development of goitre if radium emanation were a potent cause.

We were also of the opinion that the number of trout used was sufficient and that a large number would only have confused the issue by introducing such factors as over-crowding, faecal contamination, shortage of food, and so on.

It seems clear that when such large amounts of emanation produced no visible effect in this time, the change of the small amounts occurring normally being a casual factor appears to be negligible.

A sideline on this experiment is that in a separate race we placed three trout suffering from goitre, and added crystals of Potassum Iodide, at frequent intervals.

After three months, however, all three were dead, the goitres apparently being as big as ever.

Diffusion of Emanation.

In Milligan's previous experiments emanation was given by the ear-vein route. It is desirable to know how much of the emanation is retained. To avoid loss of emanation a rabbit was anaesthetized with paraldehyde and placed in a large jar whose mouth was covered with a rubber sheet which was pierced by a hole through which the ear could be drawn.

The injection was made into an ear-vein and the jar immediately closed so that no escape of emanation could occur, either during the injection or afterwards.

The rabbit was kept in the vessel for 2½ minutes and a sample of the air was then taken in a gas sampler.

Compression of a rubber bulb maintained a constant circulation of air through the sampler and ensured the accuracy of the sample.

At 2½ minutes the sample was taken and the rabbit removed from the vessel. The vessel was filled with water and emptied several times.

At the end of of the next 2½ minutes the rabbit was returned to the vessel and after a further 2½ minutes a second sample was obtained. This was repeated several times.

Results of first 2½-minutes—the gold leaf fell 1/10.5 divs. per cc. per second.

Second 2½ minutes—gold leaf fell 1/276 divs. per cc. per second.

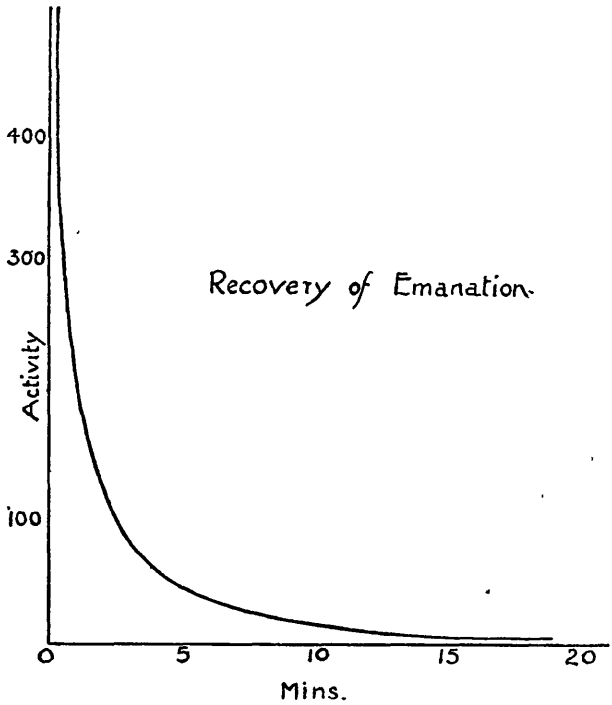
Third 2½-minutes—gold leaf fell 1/720 divs per cc. per second.

Fourth 2½ minutes—gold leaf fell 1/1800 divs. per cc. per second.

Fifth 2½-minutes—gold leaf fell 1/4800 divs. per cc. per second.

It was calculated that approximately 95% of the emanation injected had been recovered in the first five minutes, and it was felt that the amount actually expired was even greater than this. The fact that the rabbit re-breathed some of the expired emanation and that in addition some emanation would be dissolved in the water held in the fur would tend to make the apparent excretion less that would be the case if the animal were in the open air.

The graph summarizes these facts.



These analyses are of interest as we have been unable to find any similar tests in the literature available.

Medical uses of radium emanation, both by injection and by the mouth-route, are fairly common, yet it does not appear to be recognized that any introduction of emanation into the venous side of the circulation must be almost without effect on the arterial side, or that

only a small fraction of the total effect will be produced, since the emanation is very rapidly given off at the lung-surface.

By a mouth-route, however, the liver would receive more, although the emanation will still go on by the blood and lymphatic streams to the lungs. This may have been a factor in the production of the fatty liver mentioned by Milligan as occurring in one of his experimental animals.

The volume of 20 mc. of emanation is only 0.012 cmm. This minute quantity should diffuse through the pulmonary epithelium in about 0.00008 seconds if it diffuses in a manner proportional to carbon dioxide, i.e., supposing there is no injurious effect on the living membrane.

It is obvious therefore that, with the evacuation of alveolar contents occurring with each expiration, only minute quantities of emanation can be expected to cross to the arterial side. Consequently it would be unreasonable to expect effects on the thyroid gland of animals from emanation taken in with food or water. Inhalation in a closed chamber is the most effective way of studying the effects of emanation on the thyroid gland.

The exceedingly delicate method of the electroscope, however, discloses that an appreciable quantity can pass through to the arterial side since in one test, thirty minutes after giving 20 mc. of emanation to a rabbit by ear-vein, the urine gave a fairly rapid fall of the gold leaf, although this indicated only an exceedingly small fraction of the total quantity injected.

While these observations offer a criticism of the venous route in mammals, the experiments on trout were free from this difficulty.

Not only did the trout inevitably take the emanation into their branchial arteries at the same time as the other gases but in addition the water containing the dissolved emanation was always close to the exterior of the gland as it flowed over the floor of the mouth.

Our thanks are due to the Curator, Mr. Hope, for placing facilities at our disposal.

REFERENCES.

(1) Rogers "Radon and Iodine content of waters." *Trans. N.Z. Institute*, vol. 57, pp. 893-99.

(*Note*: A line was dropped in setting this paper, and the present opportunity is taken of rectifying this. On p. 899, delete line 11 of the text, and substitute for it the words "contains iodine is a surprising result, but in view of the.")

(2) Milligan "Radium Emanation and Goitre." *Trans. N.Z. Institute*, vol. 58, pp. 283-85.

(3) Marine and Lenhart "The so-called Thyroid Carcinoma of Brook Trout." *J. Expt. Med.*, vol. 12, No. 3.