tical with, tasmanol or phenols of that type. This group is at present under investigation by this laboratory as very little is known about them.

In conclusion I have to express my thanks to Mr. J. J. Jordan of Gladstone for kindly distilling a quantity of the leaves of C. viminalis and forwarding the oil, to Dr. T. L. Bancroft of Eidsvold, Q., for the excellent supply of leaves kindly furnished at his own expense, and Mr. F. R. Morrison, A.T.C., Assistant Chemist, for his usual assistance in these investigations.

## CANCER OF THE EAR OF SHEEP:

A CONTRIBUTION TO THE KNOWLEDGE OF CHRONIC IRRITA-TION AS A SECONDARY FACTOR IN THE CAUSATION OF CANCER IN THE LOWER ANIMALS.

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Amongst the indirect causes of cancer formation in human beings, chronic irritation is accepted as being an established factor. As examples, there are the so-called occupational cancers, e.g., Chimney sweep's cancer of the scrotum, multiple epithelioma of the skin in paraffin and aniline dye workers, X Ray cancer, etc. In other instances, cancer has been observed arising from the chronic irritation and inflammation brought about by such agencies as a jagged tooth, indolent ulcers, and in smoker's cancer of the lips, pharynx and larynx, cancer of the skin in chronic eczema, etc. In veterinary pathology, however, chronic irritation is by no means universally accepted as giving rise to cancer

in the lower animals. The arguments are various but the principal one appears to be that there has been no direct evidence brought forward to prove such contention, and, furthermore, that in parts which are notoriously the subject of chronic irritation, e.g., saddle and collar galls in horses, and in dogs, in countries where they are used for haulage purposes, the parts constantly rubbed by the harness, one does not find cancer resulting. Moreover, the human breast is a common site for cancer, and it is held by some human pathologists that the step between chronic mastitis and cancer is short. It is even stated that the proportion of cases of chronic mastisis in women developing into cancer is from 10-15%. Contrasted with this state of affairs in the human being, we have the well known fact that the mammary gland of the cow is frequently the seat of injuries and that chronic mastitis from various causes is common. Yet cancer of the cow's udder is rare. from facts such as these that veterinary pathologists speaking generally, have preferred to consider as "not proven," the question of the natural production of cancer in the lower animals as a result of chronic irritation.

So far as chronic irritation as a major factor in cancer formation is concerned, veterinary pathologists have been justified in refusing to indiscriminately apply the accepted findings relating to human pathology, (although the latter may be correct as regards man), to the lower animals without further definite evidence concerning the latter, that similar mechanical causes will produce similar effects in the same anatomical situations in different species, for, as has been pointed out by a number of authorities, it is necessary to guard against false analogies when pathological processes are compared between man and the lower animals. In the case of cancer, the same cause may be in

<sup>&</sup>lt;sup>1</sup> Ewing, Neoplastic diseases, 1919. This statement is disputed.

operation but it appears evident that the reactions of similar tissues in different species may not be in the same degree. Consequently what may eventually result in a malignant growth in one, will probably remain a chronic inflammatory lesion in another. It is perhaps desirable to point out that one is not referring here to the cutaneous cancers artificially produced in some of the smaller animals by the application of tar, soot, paraffin etc. Furthermore, it is hardly necessary to state that it is realised no one maintains that chronic inflammation arising from any cause must inevitably be followed by cancer, since it is very obvious that the vast majority of cases of chronic inflammation either eventually recover if the irritant be removed, or never progress beyond that stage.

As an illustration of the different reaction of the tissues of different animals, reference is made to the experimental production of "Paraffin cancer." It has been recently shown that epitheliomata could be experimentally produced in mice by the application of coal tar to the skin, but it was unsuccessful in guinea pigs, rats and rabbits.

It is not intended here to enter into a discussion as to why any particular site should be more susceptible to neoplastic formation in one species than another, but veterinary authorities have drawn attention to the peculiar differences in the relative frequency of malignant growths, especially the carcinomata, in certain situations in man and the domesticated animals. Reference has already been made to the mammary gland and the skin. Other examples may be given, e.g., the alimentary tract is one of the common sites of cancer in man. It is uncommon in the herbivora, and much less frequent in dogs and cats than man. Again, in horses and cattle, carcinoma of the nictitating membrane and the caruncle is relatively common, much more than other species including man.

It is difficult to draw any useful comparison between man and the domesticated animals as to the actual frequency of the epithelial cancers, since they mainly occur in adult and old age, and most of the animals used for human food are killed young, or in the prime of life. Only domestic pets are as a rule kept until they reach old age.

In view of the desirability of collecting as much direct evidence as possible as to chronic inflammation in the lower animals being followed by malignant growth, this contribution is made.

The condition affecting the ears of sheep in Australia and termed by sheep men "cancer," is fairly common. Although taking into consideration the millions of sheep in this country, the actual percentage is not a high one, (actual statistics do not exist), yet every year, especially during the shearing season when the sheep are observed at close quarters, it is generally possible to obtain several cases from various localities. As a rule, in the ordinary course of events when such cases are detected by the owner, the animal, if the condition is advanced, is destroyed. The carcase is not used for food. The slight cases are either not detected, or are allowed to pass without any action being taken. It is seldom that pronouncedly affected animals are seen at the public abattoirs, as the owner would scarcely care to pay freight etc. for an animal with the almost certainty of having the carcase rejected for human consumption.

As the question of the determination of the exact nature of the condition, whether merely one of chronic inflammation, or whether the popular term "Cancer" was a scientifically correct one, was a matter of economic importance both from a meat inspection as well as a therapeutic point of view, the writer was invited by the Chief Inspector of Stock, during 1921-22, to make an examination of such

affected sheeps' ears as could be obtained, in order to ascertain the nature of the lesions. Up to the time of writing, forty-seven ears from the same number of sheep and from various localities, have been examined histologically, and it is felt that sufficient examples of the condition have been collected to justify one drawing conclusions that may have some value.

A few of the cases, nine, were evidently of fairly recent origin, but the majority, viz. thirty-two, were clinically cancerous and six were intermediate. In no instance was a history of the case sent with the specimen, merely a note saying that it was a specimen of cancered ear from a sheep. Some were obtained from sheep in the field, others at the time of shearing. It is necessary to state that no conclusions from this work can be drawn as to the relative frequency of malignancy occurring in the so-called "cancer of the ear" in sheep as a whole. Since although stock inspectors and sheep owners were requested to forward ears in all stages of the condition, the sender almost always took pains to obtain what he considered a good specimen of cancered ear. This as a rule being one in an advanced stage.

The result of the microscopical examinations revealed the fact that nearly all the cases which might be termed advanced, showed more or less evidence of malignancy and that one was dealing with squamous celled carcinomata in different stages. The nine early cases showed nothing more than a chronic inflammatory reaction. Of the remaining thirty-eight cases, six, which may be termed intermediate, showed great hyperplasia of the cutaneous epithelium, with longer or shorter papillary processes dipping down into the underlying structures, but no evidence of breaking away or unrestrained growth. Thirty-two were distinctly epitheliomatous. As the examination proceeded it became evident that the matter had assumed a more general

importance, since there appeared to be a definite answer to the question "Does chronic irritation in the case of the lower animals, ever lead to cancer formation?"

As already noted, no history was supplied with any of the specimens as to when and how the condition arose. It is only in isolated instances that it is possible to obtain a history in the case of sheep running in large paddocks, since attention is only attracted to the ear when it is exhibiting very visible changes, i.e. the condition has become well established. The early cases are as a rule only noticed when the sheep are actually being handled, as in shearing. Speaking generally however, from one's own observations in the field and the information collected from others, one can obtain a fairly complete clinical picture, and by the examination of a number of sections from each of the fortyseven cases, one is able to construct a picture of the changes undergone by an affected ear from that of ordinary local chronic inflammation to that of very obvious malignancy. Finally, as will be seen, I was able to obtain a live sheep affected with "cancer of the ear," and by keeping it under observation, was able to follow the clinical course of events of malignancy until metastasis had become well established.

## Clinical features and naked eye characters.

Most of the specimens examined have been from adult sheep, but the condition is not confined exclusively to them. I have not however seen young lambs affected. Speaking generally, it may be stated that the actual starting point of the condition is either a wound or local necrosis. Most cases apparently commencing at the tip or around the free edge of the auricula. At times the point of origin appears to be an ear mark. At others the origin appears to be necrosis of the tip of the ear, the latter condition

<sup>&</sup>lt;sup>1</sup> Portions of the ear of varying shapes are removed from the edge at different parts for the purpose of identifying sheep of any particular owner.

being commonly seen in sheep in Australia, and is due to a variety of causes.

Undoubtedly, the vast majority of wounds inflicted on the ear, no matter by what agency, never pass beyond the stage of inflammation, acute or chronic, although many of them become secondarily infected with various organisms. Sometimes this secondary infection together with the constant irritation by flies etc., induces a low grade inflammation of the part. This inflammation is constantly being stimulated by the agencies mentioned, aided by the further injuries inflicted on the ear by the animal itself in its endeavours to allay the irritation or to shake off offending insects. Thus there is presented a very varying picture according to the length of time the condition has been in existence and to what extent secondary factors have been acting.

In the case of the forty-seven ears examined, the very early lesions would naturally, in practice, be included among those that never pass beyond the ordinary stages of inflammation or necrosis and of course it is impossible to foretell what would have happened to those particular ears had their possessors been allowed to live. In the case of the ears showing simple inflammation, the lesion presented the ordinary characters of a wound healing under scab. Where necrosis was the origin, the necrosed portion of the ear varied in extent. Sometimes the necrosed portion ran along the edge of the auricula for several inches but did not extend inwardly very far, the affected part having a dried, withered up appearance.

The necrotic part and the adjacent tissues may become damaged from various causes and then the latter becomes inflamed. Secondary factors already indicated come into action and then the lesion, whether originating in a wound or from simple necrosis, becomes very much the same in

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all cases. Ears examined at a later stage show evidence of chronic inflammation. The affected area has extended. The part is covered with a thick crust of scab and on lifting this, granulation tissue may be seen underneath. There is usually a little exudate present, at times yellowish, at others purulent.

At an advanced stage, the clinical changes are very The affected ear is swollen, at times so much pronounced. that the meatus is obliterated. The swelling may extend for some distance around the base of the ear. The skin is firmly adherent to the underlying tissues. The tip of the ear is represented by a blackened mass often larger than a man's hand, with many fissures in it from which oozes an exudate often purulent and at times mixed with blood. Some of these lesions are of the cauliflower type in appearance. Not infrequently fly larvæ may be found in the If the scab, which at times appears like an fissures. ordinary blood clot and at others has a caseous crumbling character, is lifted, a granulation-like tissue is seen underneath with ulcerating edges, the latter being elevated and firm. The naked eye appearances are often complicated by injuries inflicted on the ear by the animal in its endeavour to allay irritation or to shake off offending insects. The extent and character of the lesion itself and the degree to which the adjacent tissue of the ear participates varies with each individual case and depends on the length of time the condition has existed and the injuries inflicted by the animal itself, or other agencies. In the final stages the animal becomes thin and cachectic. The wool is ragged and readily pulled out.

In the majority of advanced cases the whole of the new growth cuts very firmly on section, sometimes like tendon. These latter appear to be the cases were keratinization is very extensive, rather than to a great excess of stroma. The cut surface is of a dirty greyish-white colour except at the ulcerating edge, with small islands or strands of a lighter colour (epithelium) scattered throughout more or less abundantly. Occasionally with the scirrhous growths, after removal of the skin, portions may be flaked off, somewhat like the layers of an onion. Central softening has been observed in one case, the part having a caseous character. No tubercle or other bacilli could be demonstrated in the softened material.

# Histology.

Sections of ears examined in the early stages present merely a picture of subacute or chronic inflammation. The epithelium where present, showing little or no alteration. In the longer standing cases more pronounced changes are evident. The scab mass is thicker. Underneath this is a mass of granulated tissue, whilst deeper still is a varying amount of fibrous tissue, more or less fully formed. At the edge of the ulcer and for some distance away from it, the epithelium has undergone great hyperplasia. The layer being of considerable thickness, with finger-like processes dipping down for varying distances into the underlying There is however at this stage, no sign of malignancy, i.e. the epithelium, although greatly overgrown, shows no sign of breaking away and assuming independent growth. In the advanced cases the changes in the auricula are pronounced, the epithelium, which is of the stratifled, squamous variety, can at the extremity of the finger-like processes be seen rapidly invading the subjacent structures. In others the epithelium has broken away from the parent body and has assumed quite independent growth. auricula is greatly thickened, the conchal cartilage being normal. The tissues external to the concha are more implicated than those of the internal surface. The edge of the lesion, i.e. that corresponding to the ulcerated surface, is seen to be composed of more or less young fibrous tissue. Deeper down, the normal tissue has been replaced by epithelium and stroma. The epithelium varies very considerably. In the early stages of malignancy, the invading epithelium is not abundant, if one excepts the large down-growing papillæ from the surface. There are many signs of reaction on the part of the tissues in the form of numerous fibro-blasts around the young growing and infiltrating epithelium. More or fewer mono- and polymorpho-nuclear lecocytes are present near the ulcerated area, indicating secondary infection. The epithelial cells, which are the spinous cells from the malpighian layer are at first normal, but as the condition persists and the epithelium extends its field of growth, there is often considerable change in the cells. This being more frequently in the direction of size. Distortion of epithelial cells is rather common, especially at the edges of the young growing epithelium. This is quite apart from those cells forming epithelial pearls and undergoing hornification. Giant cells varying in size and the number of their nuclei have been seen in sections from some cases.

Keratinization appears to set in early. Even in some cases, where it was evident microscopically that malignancy had only been recently established, there was distinct evidence of pearl nest formation. In cases where the epitheliomatous condition had become the dominant one in the section, keratinization was very pronounced. At times the whole of a section has been composed of keratinized epithelium.

The stroma also varies very considerably both in age and amount. At the apices of the young, burrowing epithelial strands are fibroblasts, sometimes scanty and at others abundant. No doubt this variation in amount is due to the varying activity in growth of the epithelium.

Usually in this situation too are a number of leucocytes. In other places the stroma has the form of a spindle celled tissue. In older situations, fully formed fibrous tissue is present. The proportion of stroma to epithelium also varies very greatly. In places the former is abundant and the epithelial islands or strands scanty and small. In other situations the stroma is negligible, whilst enormous masses of stratified squamous epithelium with numerous "pearls" either discrete or confluent, dominate the picture. At times secondary changes due to bacteria tend to complicate the histological view around the ulcerating area of the primary lesion.

At the base of the ear in the cases where the burrowing epithelium has reached that locality, the picture becomes typically and purely carcinomatous. Secondary changes not having extended so deeply, the infiltration of the burrowing epithelium into the muscles of the ear, with their destruction, and the formation of the stroma of the neoplasm is striking.

# A case of "cancer of the ear" in a sheep, accompanied by metastasis.

It having been ascertained that a large proportion of advanced cases of "cancer of the ear" of sheep were epitheliomatous, it became of interest to find out whether the malignancy was a local one, or whether metastasis occurred? It was evident that the information required could not be obtained from the sheep owner, since that would imply a knowledge of what metastasis was, and also a greater degree of observation of individual sheep than is usually given in Australia. The matter therefore resolved itself into one of personal observation. Consequently, through the Chief Inspector of Stock, I obtained a live sheep affected with "cancer of the ear" and kept it under daily observation until it was killed. During this period

it was allowed to run at liberty in a small paddock with other sheep. The animal, aged about four years, was received on 10th March, 1922. The affected ear at that time showed a black looking scab mass about  $3 \times 2$  inches in area, near the apex. The condition had evidently been existing some time. Indeed, the animal had been sent as a "good specimen." The tip of the ear had disappeared. On lifting the scab a slightly purulent, granulomatous mass was exposed, with ulcerating edges. The auricula was moderately swollen and slightly thickened near the lesion. The skin was attached firmly to the underlying tissues. No treatment was attempted.

During the succeeding three months viz. March, April and May, there was very little change in the appearance of the affected ear, save that the scab mass became a little larger, the thickening of the skin around the lesion more pronounced, and there appeared to be a greater tendency for the part to bleed through the animal's own actions. Appetite and condition were maintained, and there did not appear to be any great pain.

In June (four months later) the whole of the auricula had become swollen and the granulating mass at what had been the apex, much more extensive (about  $4 \times 4$  inches), ulceration at the borders of this mass being pronounced. The edges were indurated. Bleeding from the part occurred very readily on manipulation.

In July the ulcerated area had increased. The base of the ear had also become involved in the swelling. Bleeding occurred even when the animal shook its head to obtain relief from flies. Although appetite and condition were unchanged, the animal appeared less active than usual and showed some evidence of pain in the affected ear.

August 5th (5 months later) the affected ear had now assumed a repulsive appearance, and the growth was clinic-

ally of a malignant character. There was a large cauliflower-like mass, somewhat larger than the size of a man's fist, bleeding very readily. Fissures of varying depth covered the surface of the growth, a considerable amount of exudate coming from them, at places somewhat purulent. The whole of the auricula was very swollen, the entrance to the external ear being almost occluded. The skin was firmly attached to the underlying tissues. The scab itself had assumed a more caseous or crumbling character, portions coming away very readily on manipulation. ulceration had made more rapid progress. The animal's appetite still remained good, but it was rapidly losing condition and the wool was commencing to fall out, leaving bare patches (cachexia). Flies were continually ovipositing on the ulcerated surface, and both the eggs and the larvæ were difficult to remove from the deep fissures. They added to the animal's distress.

On this date the (unnamed) cervical lymphatic gland on the same side, which lies about midway between the atlantis bone and the point of the shoulder, showed signs of enlargement, being now about the size of a small cherry; it was also very hard and painless. The thick mat of wool on the animal prevented earlier recognition of the enlargement of the gland. This gland increased in size with great rapidity. In fact one could almost see a change every day, until August 20th, it had reached the size of a golf ball. It was quite circumscribed, very hard on palpation with no evidence of softening anywhere. There were no clinical signs of inflammation either of the gland or of the surrounding tissues, if one excepts the enlargement. The skin over the gland was intact.

September 20th, the sheep was killed this day for humanitarian reasons. The distress caused by the "fly-blown" condition of the ear was great. It being impossible to keep

flies away or prevent them depositing their eggs in the fissures of the ulcerating growth. In addition to this the greatly distorted auricula, with its black cauliflower-like mass at the end, hung down the side of the animal's face, and blood and exudate were constantly dripping down the latter. Appetite had been lost and the animal stood dejectedly in the paddock making little attempt to move. The fleece had become so ragged and removed in patches, that the animal had the appearance of a scabied sheep.

## Autopsy.

Animal in very poor condition. Skin bare in patches. The wool in general very ragged and easily pulled out. affected ear was almost hidden under a mass of what looked like scab and granulation tissue. This mass was about 4×5 inches in diameter. Deep fissures ran through it in all directions. From these exuded a blood-tinged exudate. Many fly larvæ were found at the bottom of the fissures. At the edges of this mass the skin was ulcerated and indurated. The rest of the auricula was so swollen and indurated that it had more of a solid cylindrical appearance than of its characteristic shape. The external meatus was practically occluded. The skin of the ear was firmly adherent to the subjacent parts. This thickening, induration and adherence of the skin extended for an inch or so around and from the base of the ear.

The unnamed cervical lymphatic gland was enlarged to about the size of a tennis ball and very firm. The skin over the gland had ruptured in one or two places. The gland cut more like soft horn. On section the cut surface was of a greyish-white colour and had a granular appearance. Near the centre was a rather caseous area about half an inch in diameter. There was no sign of inflammation.

The prescapular gland on the same side was enlarged to about the size of a walnut and on palpation, several hard, nodular areas, about the size of a garden pea were felt. No other lesions were seen.

## Histology.

Sections taken from various parts of the ear showed a very similar histology, viz., large masses of stratified epithelium and a rather scanty fibrous stroma. sections, the whole mass had undergone hornification resulting from the fusion of large individual "pearl nests." The masses were heavily impregnated with eleidin. such sections, the fibrsus stroma was practically absent. At the base of the ear, the condition was not in such an advanced stage, the whole of the original structures having not been entirely destroyed. Sections showed numerous strands, small islands and larger masses of stratified squamous epithelium, some of the later commencing to undergo keratinization, burrowing in a rather scanty stroma. In places the latter was not fully formed and was represented by fibroblasts and spindle cells at the apices of the epithelial strands. In these situations also, a few leucocytes were present. Remains of the normal structures, such as muscle etc. could be seen here and there. There was considerable departure from the normal epithelium. A few giant cells were present.

The secondary growth (Cervical lymphatic gland). In this gland, practically the whole of the new growth had undergone hornification. Occasionally some of the keratinized masses were bordered by two or three layers of stratified squamous epithelium, with rather large cells. There was very little young, active epithelium present. The fibrous stroma was scanty. No traces of the normal gland substance could be seen, the caseous material in the

softened area contained numerous desquamated epithelial cells but no bacteria.

The tertiary growth (Prescapular lymphatic gland). Some parts of the gland were normal, but in others small islands and fine strands of stratified squamous epithelium were present, surrounded by a stroma of young fibrous connective tissue. The epithelium was apparently very active and was infiltrating and destroying the gland substance in its neighbourhood.

In the foregoing case it was impossible to say how long the condition had existed before malignancy set in. Judging from other examples, one can say that it must have been existing months if not years, purely as a chronic inflammatory lesion. It is however, probable that the growth had already assumed malignant characters when the animal was received in March. It was under observation for a period of about six months. It is of interest to note that although the primary growth increased steadily from the time it first came under observation, no metastasis was seen until August 1st, but once that was established progress was rapid. Within twenty days the secondary growth had reached the size of a golf ball. In fifty-two days it was as large as a tennis ball, and metastasis was well advanced in the next lymphatic gland, viz. the prescapular.

With regard to the condition of the secondary growth, viz. in the cervical lymphatic gland, keratinization is looked upon by some pathologists as evidence of recovery. But in this case, even if the growth in the cervical gland were no longer active, it is evident that it was too late to be of any benefit to the affected animal, since metastasis had already occurred in the next or prescapular gland.

Attempts to transfer the growth by implanting fragments about the size of a lentil from the secondary tumour

(cervical gland) failed. In two instances the graft took temporarily, gradually increasing in size to that of a large walnut, then they slowly retrogressed and finally disappeared. The transplanted growths were spherical, very firm, painless and quite circumscribed. Unfortunately, no tissue was removed from these grafts for histological examination, owing to the fear of setting up secondary inflammatory changes. No very great value can be attached to the results of this transmission experiment, since an insufficient number of sheep were used, and the histology of the secondary growth that was employed, showed subsequently that on account of extensive keratinization, the material was not suitable for grafting.

#### Remarks.

Sheep in Australia frequently receive injuries to an ear from various causes, e.g. by ear marking, or the necrosis due to a variety of factors. Undoubtedly in the great majority of cases, such injuries never result in more than a passing inflammation of the surrounding tissues. certain number, however, the part from a variety of causes becomes chronically inflamed, and in some of these, the exact proportion being unknown, the continued irritation and stimulation of the epithelium arouses unrestrained growth of the latter and a typical epithelioma results. Thus the popular term "cancer of the ear" for this condition in sheep is justified in some cases but not in all. chronically inflamed condition may and probably does exist for a relatively long period as such, but once malignancy has set in the progress is rapid. Whether the malignancy would remain local in most of the cases where it had become established, or whether all cases would become metastatic if left to themselves, is difficult to say since sheep badly affected with "cancer of the ear" are usually killed when they come under observation in the field, but the case cited in detail shows that metastasis can and does occur if the animal is allowed to live long enough.

From a therapeutic point of view, it is evident that proper treatment of injuries to the ear would result in their stopping as cases of simple inflammatiou, but such individual treatment, merely to prevent something that might or might not occur at some such later date, is not one that would appeal to the average sheep owner in Australia. It is also quite possible that early cases of malignancy could be dealt with by amputation of the affected ear, but unfortunanely, in New South Wales at least, removal of a sheep's ear is forbidden by law, since it would destroy evidence in the shape of the ear mark of ownership. It might be argued that such evidence in a case of "cancer of the ear," is already obliterated; this is true, but the statement that the ear had been removed because of cancer might be readily made use of by an individual in unlawful possession of sheep.

From a meat inspection point of view, action would depend upon whether the malignancy was local, or whether the growth had become metastatic and also on the general condition of the animal.

The work has also shown that naturally acquired cancer arising from long standing irritation can and does occur in the lower animals and that the skin of the ear of sheep is one of the vulnerable sites for epithelioma formation.



Dodd, Sydney. 1923. "Cancer of the ear of sheep: a contribution to the knowledge of chronic irritation as a secondary factor in the causation of cancer in the lower animals." *Journal and proceedings of the Royal Society of New South Wales* 57, 139–156. https://doi.org/10.5962/p.359845.

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