XXXVIII. COTTON SEED MEAL POISONING.

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FOR many years a condition of illness of animals attributed to the feeding of cotton seed meal has been observed in America. This has been called by some "poisoning," by others "injury," reflecting thus the somewhat obscure condition of knowledge regarding it.

It is difficult to obtain a clear conception of the disease from the literature. Friedberger and Fröhner [1910] state that only young animals are usually affected. They are said to show disorder of the digestive and urinary apparatus. The duration is variable. The autopsy reveals in the acute form haemorrhagic gastro-enteritis, opaque swelling of the liver and kidneys, oedema of the lungs, dark red urine and collection of liquid in the cavities of the body. There is no enlargement of the spleen. In chronic cases only one finds general emaciation and dropsical phenomena but at times also parenchymatous nephritis. Hutyra and Marek do not discuss the condition in their standard work on animal pathology.

Rommel and Vedder [1915] state that among the more pronounced symptoms observed in pigs suffering from the effects of cotton seed meal feeding are diarrhoea, a harsh rough curly coat, paralysis and shortness of breath. Emaciation and dropsical conditions are frequently observed. The disease manifests itself in two forms, acute and chronic. The acute form is said to be much more serious to the farmer because pigs are attacked by it with little warning before any indications of disease are noticed. The largest and best nourished pigs are often the ones attacked. The attack is sudden and sharp. The pig experiences extreme shortness of breath and suffers the most intense pain. If he recovers, recurrences of the attack are likely especially if the pig is a heavy feeder. Subsequent attacks may end fatally or the disease may assume the chronic form. In the chronic form fatal results may not occur for a considerable time. The symptoms persist if the feed is not changed and the pig appears to develop a certain degree of immunity to the effects of the disease. His condition however is continually although slowly declining. Pigs suffering from this form of disease may live for a year or more on a cotton seed meal ration.

On post mortem examination, pigs which have died from the effects of cotton seed meal feeding show large quantities of fluid in the abdominal and thoracic cavities and in the pericardial sac. The kidneys, liver, spleen, and

small intestines are usually congested. In some cases the membrane lining the stomach is eroded. The lungs are very oedematous especially in pigs which have died from sudden acute attacks. The heart is enlarged.

Wells and Ewing [1916] state that the post mortem results in their cases varied so widely as to be incapable of definite interpretation. Among the characteristics found most constantly are mentioned a rough coat, dry, harsh and scaly skin, weakness and emaciation as shown by physical appearance and entire absence of fat from kidneys and mesentery, and bones usually though not always brittle. Their experiments were performed on six weeks old pigs weighing about 6-10 kilograms at the beginning of the experiment. They state (pp. 18 and 22) that the injury from cotton seed meal in their cases was not acute. Through physical appearances and the metabolic characters it was manifested long before death. This they state is not in agreement with the observations of many other investigators. They are inclined to believe however that in the reported cases of acute cotton seed meal injury, careful periodic measurements would have disclosed the injury before death. This according to them is important: for if well-nourished animals die of the injury as often claimed, the same cannot be due to a deficient diet and inanition but must be due to a toxic effect.

Withers and Carruth [1917] in dealing with the effect of iron as an antidote to cotton seed meal poisoning, give little information as to the symptoms and post mortem appearances of their animals. On p. 256 they state that in one experiment all the pigs were in extremely poor condition at its termination. The gains were slight and the animals were found to be badly infested with internal and external parasites. Post mortem examination showed that practically all the animals were in a pathological condition, the nature of which however is not stated.

In the *Farmer's Bulletin* [1923], which we have just received, cotton seed meal is stated to produce inflammation of the digestive organs and congestion of the lungs in pigs. Fluid is found in the thoracic and the abdominal cavities and the fatty tissues have a yellow cast. We emphasise this last point because it in all probability indicates the presence of jaundice, a condition which we have found in our cases, associated with extensive changes in the liver.

It will thus be seen that the literature dealing with cotton seed meal poisoning in the pig, to which we have confined ourselves, is small in amount and somewhat indefinite in character. The symptoms etc. attributed to cotton seed meal poisoning would appear to divide the alleged cases roughly into two groups. The first group, styled the chronic group, would appear to show nothing characteristic. It is apparently differentiated by the fact that subsequent to the feeding of cotton seed meal, there developed in the pigs inanition, loss of weight and failure to grow. The second group is termed the acute group apparently from the fact that in such cases the animals die suddenly and exhibit post mortem well-defined lesions such as dropsy, oedema of the lungs, enlarged heart, congestion of the liver, etc.

From our survey of the literature it does not appear that the possibility of other diseases occurring in the experimental pigs either prior to or synchronous with the experiment have been sufficiently taken into account in considering the results obtained by feeding pigs on cotton seed meal. Again the view that sudden death in apparently well nourished pigs which have been fed on cotton seed meal is to be interpreted as a toxic action would appear not to be justifiable. It is not logically sound and as will be seen later is in all probability not correct in this particular instance. For the present it may be mentioned that this sudden death is admitted by those making this interpretation to have been associated with great enlargement of the heart and dropsy throughout the body, conditions which must have existed for some time prior to death.

On February 17, 1923, an experiment was begun with the object of reproducing if possible the injurious effects of cotton seed meal and to test the effect of iron in the form of ferric oxide in preventing them. Two lots of pigs, aged about nine weeks old, were put into concrete pens—pens 1 and 2. The pigs in pen 1 were fed on a mixture of cotton seed meal and maize in the following proportions, cotton seed meal 4 lbs., and maize, 12 lbs. Those in pen 2 were fed on the same ration with in addition 40 g. of ferric oxide to the above quantity of ration. Of these rations which were fed three times a day the pigs were allowed to eat as much as they liked. The pigs in pen 1 were numbered as follows, 654, 540, 648 and 631 and those in pen 2, 655, 548, 646 and 629.

The results of this experiment are detailed in Tables I and II. The experiment lasted about three months, from 17th February, 1923, to May 12, 1923. From the tables it will be seen that the pigs in pen 1, after an initial slight rise in weight, thereafter steadily fell off. Thus on April 3rd, after about seven weeks, the weights of all of them were much lower than their initial weights on commencement of the experiment. By this time, it should be noted, they had almost given up eating their ration. On April 6th, while the ration was continued, they were given in addition a mixture of salts, with a composition as follows: bone meal 3 ounces, chalk 1.5 ounces per ration as above. The mixture contained no iron. This effected very little improvement in their condition although for a short time thereafter they ate their ration better. The haemoglobin of the various animals in this group was estimated at frequent intervals and showed throughout an absence of any haemoglobin deficiency.

The pigs in this group were killed on the various dates indicated in the table. Post mortem nothing was found except extreme emaciation.

The pigs in pen 2 as a whole were slightly larger pigs to begin with than those in pen 1. The experiment with them lasted over the same period. In all of them the weight on April 3rd (seven weeks) exceeded that at the beginning of the experiment, although in the interval the weights had been somewhat irregular, never however falling below the initial weight. During the whole time this group showed an avidity for its ration. On April 6th the

ration being continued they were given in addition the same salt mixture as pen 1. In all of them this caused a slight fillip to the putting on of weight. The experiment was terminated on May 12th, all animals being alive in fair condition and all being considerably heavier than they were at the commencement of the experiment.

During the whole course of the experiment there was no evidence of haemoglobin deficiency.

The pigs in pen 1 therefore, fed on cotton seed meal and maize without iron, in a short time, without diminution of their haemoglobin titre, ceased to grow and eventually were reduced to a state of great emaciation. Associated with this was the fact that the pigs refused to eat the food. How far this was due to the ration being unpalatable it is difficult to say. The food mixture had as fed an undoubtedly peculiar odour. The pigs in pen 2, however, fed on the same ration with the addition of ferric oxide, ate their ration well and put on weight all the time. There was no haemoglobin deficiency. Withers and Carruth [1917] found that iron sulphate lessened the detrimental effects of cotton seed meal, a point which will be discussed later. It will be seen thus that typical cotton seed meal poisoning appeared in neither of our two groups, the non-iron or the iron group. The probable reason for this will be discussed later.

While the above experiment was in progress, three other groups of pigs in adjacent pens were on feeding experiments which eventually turned out to have a considerable bearing on the present problem as certain of them developed the symptoms and post mortem appearances of the acute form of cotton seed meal poisoning. The first group consisted of four pigs, numbered 656, 545, 645 and 627, about nine weeks old which were housed in pen 3. Their ration consisted of maize 12 lbs. and earth nut meal 4 lbs. With this they were fed three times a day and received as much as they could eat of the mixture. The results connected with this group are summarised in Table III.

The experiment commenced on February 17th, 1923, and lasted for approximately three months. In all the animals there was a fall in weight after a preliminary rise, the final weight in two of them (656 and 545) being however considerably higher than the initial weight. The haemoglobin titre remained normal in pig 656, but in the other three it fell considerably to 45 % in pig 545, 30 % in pig 645, and 40 % in pig 627. In addition these three pigs showed blueness of the ears and along the back, conditions indicative of considerable circulatory weakness. Their temperature was not raised but there was considerable thirst. All three showed spasmodic jerky breathing—"thumps." Pig 545 died suddenly on April 1st and pig 645 suddenly on April 3rd. Both pigs were in fairly good condition. Post mortem there was found in both great effusion of fluid into the serous cavities, great enlargement and marked congestion of the liver, together with the other changes in that organ already described in iron deficiency in sucklings, such as fatty change

in the centre of the lobules, etc. Pig 545 showed considerable jaundice. Great enlargement of the heart and oedema of the lungs were present in both.

Pig 627, which was badly affected, and pig 656 had ferric oxide added to their ration on April 26th. They were placed on ordinary diet with a continuation of the ferric oxide on May 8th. Subsequent to this they put on weight and were eventually marketed in good condition. The addition of the iron to the diet is reflected in the haemoglobin titre of pig 627 on April 3rd.

In this group fed on maize and earth nut meal two pigs and probably a third developed the appearances described as typical of acute cotton seed meal poisoning. Rommel and Vedder [1915] describe the production of a similar condition in pigs by feeding them on steamed polished rice and tankage. Moore [1914] and Hadwen [1915] describe like occurrences.

The other feeding experiment with pigs which has a bearing on the present condition is as follows. Two groups of four pigs each of about nine weeks old were fed on a mixture of middlings, locust bean meal, palm kernel meal, earth nut meal, and treacle. The proportions of the various constituents present is not known as the mixture was a proprietary one. One lot of pigs received in addition a mixture of salts to bring the food up approximately to the mineral composition of cow's milk, with iron in slight excess. The chemical constitution of the two rations as fed to the pigs was estimated by Mr Godden, to whom we are indebted for the analysis. It was as follows:

	CaO	P ₂ O ₅	Cl	Fe ₂ O ₃	N	Fat	Fibre	Dry matter
	%	%	%	%	%	%	%	%
Without salts	0.52	1.84	0.07	?	3.20	5.1	7.65	86.25
With salts	1.54	1.67	0.48	0.05	3.08	5.1	7.65	87.85

Table III. *Haemoglobin estimated with an instrument standardised for human blood on which 80 % = 100 % pig's blood.*

Pen 9 Pig		1923 February		March						April	
		17	27	4	9	14	19	24	29	3	8
615	Weight in lbs.	41.1	46.4	44.2	45.3	51.9	53.9	55.6	59	59	63
	Haemoglobin %	—	—	—	—	—	—	—	—	80	—
652	Weight in lbs.	34.5	36.1	37.2	40	45.1	47.7	50.8	55	57.5	63
	Haemoglobin %	—	—	—	—	—	—	—	—	70	—
636	Weight in lbs.	37.4	43.3	44.4	47.1	53.7	55	61.2	63	63	69
	Haemoglobin %	—	—	—	—	—	—	—	—	80	—
541	Weight in lbs.	42.6	47.9	48.5	52.8	59.6	60.3	66.4	69	73	80
	Haemoglobin %	—	—	—	—	—	—	—	—	70	—
Pen 10											
651	Weight in lbs.	32.1	35.8	36.5	38	40.9	41.8	42.9	41	41	40
	Haemoglobin %	—	—	—	—	—	—	—	—	70	—
613	Weight in lbs.	35.6	39.8	40.7	53.8	45.5	44.6	39.2	36	—	Dead on
	Haemoglobin %	—	—	—	—	—	—	—	—	50	4. iv. 23
638	Weight in lbs.	44	55.9	55.6	60.5	65.4	64.4	65.6	67	64	63
	Haemoglobin %	—	—	—	—	—	—	—	—	80	—
544	Weight in lbs.	43.5	48.4	50.6	52.8	56.3	55.6	54.3	57	52	Dead on
								Blue ears			5. iv. 23
	Haemoglobin %	—	—	—	—	—	—	—	—	40	—

The pigs were in two lots. Pen 9 contained pigs 615, 652, 636 and 541 and these were fed on the salt-containing food. Pen 10 contained pigs 651,

613, 638 and 544 to which was given the non-salt food. They were fed three times a day and allowed to eat as much as they wanted. The results of this experiment are detailed in Table III.

The pigs in pen 9, on the salt-containing food, grew fairly well and the growth was continuous. The increase however fell far short of what one expects with a good pig food. The haemoglobin titre in all estimated on April 3rd was normal. None of the animals in this group ever showed any signs of illness. Those in pen 10 on the non-salt-containing food on the other hand showed at first an increase of weight but thereafter a recession. The haemoglobin was estimated on April 3rd and gave the following result: pig 651, 70 %; 613, 50 %; 638, 80 %; 544, 40 %. At this time pigs 613 and 544 were obviously ill with blue ears and thumping jerky respiration. Pig 613 in addition showed jaundice. The temperatures were not raised. There was great thirst. Both died suddenly, pig 613 on April 4th and pig 544 on April 5th. Post mortem examination showed exactly similar conditions to those found in pigs 545 and 645 in pen 3. Pig 544 however did not show jaundice. Attention may also be drawn to the fact that it took practically the same time for the animals in this group to die as it did for those in pen 3. The occurrence therefore of cases showing all the symptoms of acute cotton seed meal poisoning in pen 10 on this diet should be specially noted as also its non-occurrence in pen 9 where the same food was given with the addition of salts, including a fair amount of ferric oxide.

In discussing the results obtained it may be mentioned at the outset that the symptoms and post mortem appearances here described as occurring are those we have discussed elsewhere [McGowan and Crichton, 1923, 1924] in connection with iron deficiency in suckling pigs. The only difference is that on the present occasion they are of a more advanced type, especially those found in the liver. In the condition of suckling iron deficiency we showed that the administration of ferric oxide not only restored the haemoglobin titre in a short time to normal but also that it could clear up in time the extensive organic changes present in the liver. It is known also that this disease attacks especially the fastest growing pigs and that the weaklings of a litter may escape while the faster growing litter mates are affected. The development in a pig with the disease of "runtish" characters at once stops its progress. In this connection we instance pig 15, Table I, of our previous paper [1924]. In particular it may be mentioned that this animal being killed a short time after it had become a runt, showed no signs of disease of the liver, the fatty change in the centre of the lobules, although almost certainly present before, having disappeared in the interval.

Before the introduction of the iron medication as a routine into the piggery it was found that a certain number of the pigs, which had had the disease, on being fed on an ordinary generous diet, but not one containing iron especially, lived. Some of them in the process became runts, others of them however grew well and became eventually quite good pigs. In both instances,

the livers on being examined later were found to be healthy or in the intermediate stage of returning to normality, the "fairy-ring" condition already described [1923, p. 206]. Experimental instances of this same occurrence are pigs 2 and 4, Table I, of our previous communication [1924].

It is evident therefore that suckling iron deficiency where it does not kill (leaving out of account the deficiency of haemoglobin and the after effects of the dropsy) leaves behind it on weaning more or less organic affection of the liver. This will be more particularly described in a succeeding paper on the pathology of the condition. It depends on the way the animal is fed thereafter whether this liver condition improves to become normal or progresses to become worse.

We have already emphasised the point that iron deficiency is a disease of the suckling pig. We do not think that the disease will arise for the first time in a weaned pig when fed on an ordinary mixed diet through deficiency of iron in that diet. In our opinion the nature of the diet fed at that time markedly affects the recovery or otherwise from lesions remaining from a pre-existent iron deficiency in the suckling stage.

The experimental results will now be dealt with in the light of these considerations. The pigs used in the five groups were obtained from the piggery at a time, when, although the beneficial effects of iron were recognised, the exact method of its action was not clearly understood. In particular it was thought that the iron might act by increasing the amount of this mineral in the sow's milk, whereas later experience showed that the result was obtained by the young pigs eating the iron themselves and that the aim, in relation to preventing the disease, should be to get the young pigs to eat of themselves as soon as possible. Under the circumstances therefore and considering the difficulties, which we have met with later, of preventing the occurrence of the disease unless the utmost care is taken to get the young pigs to eat the iron-rich food, it is almost certain that the batch of pigs used in this experiment were suffering more or less from slight sequelae of iron deficiency. They did not show it outwardly but in all probability their livers, judging from our other experience, were deranged in greater or lesser degree. Had they been put on to a full generous diet or one containing a large amount of ferric oxide in all probability they would have gone on all right.

In the light of these considerations, the explanation of the experimental results would appear easy. The pigs in pen 1, on the cotton seed meal and maize, ceased to eat, and passed into a state of complete inanition without any of the signs or post mortem appearances of acute cotton seed meal poisoning. Any traces of iron deficiency as sucklings would disappear in the process, as happened in the case of the runts above referred to. The pigs in pens 2 and 9, on a poor ration with abundant iron in one case and iron and salts in the other exhibited the restorative power of iron in removing traces of iron deficiency. At the same time the pigs grew moderately. The pigs of pens 3 and 10, exhibited the effect of a poor ration without iron, in allowing to progress, or possibly furthering the progress of, the sequelae of the pre-

existent iron deficiency, especially as affecting the liver. That the rations were poor ones is shown by the small increase in weight in a period of three months, even in those cases where no disease symptoms appeared.

It will be seen from the above results and from the work of Moore, Hadwen, Rommel and Vedder, that the so-called cotton seed meal poisoning symptoms and post mortem appearances are not limited to pigs which have been fed on cotton seed meal. The facts that cotton seed meal injury is said to affect principally young pigs (Friedberger and Fröhner) and that suckling iron deficiency is a very widespread disease are two additional points in favour of the view we have expressed regarding the nature of the cotton seed meal condition.

Withers and Carruth [1918] conclude from their experiments that cotton seed meal injury of swine is due not to deficient diets but to the presence of a toxic substance. In their opinion the toxic substance in cotton seed meal is the derivative of gossypol which they have called *d*-gossypol. Our experiments as just seen do not lend support to this view. These writers recognised the beneficial effect of iron in the condition but attributed the advantages derived from its use to the iron neutralising the toxic substance in the cotton seed meal.

Several writers such as Rommel and Vedder [1915], Richardson and Green [1916, 1917], Osborne and Mendel [1917] and Wells and Ewing [1916] have suggested that the condition is one of dietary deficiency. Of these Richardson and Green, and Osborne and Mendel have worked with white rats so that their results are not directly applicable. Richardson and Green suggest a mineral deficiency as in some degree responsible. Wells and Ewing working with young pigs concluded that cotton seed meal was an incomplete food. This was true even when it was fed with sugar and starch to a wide nutritive ratio. Pigs upon an absolute maintenance diet ate in addition only small quantities of cotton seed meal and were not greatly injured by it. So-called cotton seed meal injury in their opinion was due in large part to inadequate diets.

Rommel and Vedder [1915] advanced the hypothesis that cotton seed meal injury is similar to if not identical with beri-beri in man. They suggested that it was due to a deficiency in water-soluble vitamin. We ourselves suggested the resemblance between suckling iron deficiency and "wet" beri-beri in human beings. As already mentioned we believe the pig condition to be due to deficiency in iron. The fact that the pigs from sows fed largely on distillers' draff¹, which in the quantities fed must have supplied a fair amount of water-soluble vitamin, markedly succumbed to the disease, would seem to indicate, apart from the therapeutic power of iron, that the condition is not one of lack of water-soluble vitamin. The production of the disease in animals fed on peanuts also points in the same direction.

¹ Draff is malted barley after extraction with water. The material as it is fed contains a considerable amount of the extraction water.

CONCLUSIONS.

1. Cotton seed meal injury or poisoning in pigs in all probability is not due to a toxic substance in the cotton seed meal.
2. The same condition can be brought about by feeding pigs on other substances concerning which there is no suspicion of toxicity.
3. In all probability cotton seed injury is brought about by feeding young pigs, which have already suffered as sucklings to a greater or less degree from iron deficiency, on an incomplete diet.
4. The incompleteness of the diet would appear to be a general one and not one having reference to absence of vitamins.
5. Iron in the shape of ferric oxide would appear to have a specially beneficial effect in preventing symptoms from arising.

REFERENCES.

- Farmer's Bulletin (1923). *U.S. Dept. Agric.* June, No. 1244.
Friedberger and Fröhner (1910). *Veterinary Pathology*, 1, 224.
Hadwen (1915). *Canadian Dept. Agric. Rep. Vet. Director Gen.* 140.
McGowan and Crichton (1923). *Biochem. J.* 17, 204.
—— — (1924). *Biochem. J.* 18, 265.
Moore (1914). *Canadian Exp. Farm Reports*, 611.
Osborne and Mendel (1917). *J. Biol. Chem.* 29, 289.
Richardson and Green (1916). *J. Biol. Chem.* 25, 306.
—— — (1917). *J. Biol. Chem.* 30, 243; 31, 379.
Rommel and Vedder (1915). *J. Agric. Res.* 5, 489.
Wells and Ewing (1916). *J. Biol. Chem.* 27, 22.
Withers and Carruth (1917). *J. Biol. Chem.* 32, 245.
—— — (1918). *J. Agric. Res.* 14, 451.