The object I have in publishing the case is entirely that of showing the effect on the kidneys of a rapid intravenous infusion; I believe the result is purely mechanical—namely, a rise of blood pressure in the renal area and a consequent renewal of the process of filtration or osmosis, or whatever the precise mechanism may be, which is temporarily in abeyance. It may be that pilocarpine had some effect, but there is no doubt in my own mind, and in the minds of those who saw the case, that the patient's life was saved on three separate occasions by infusion.

After the first attack of suppression the urine was loaded with albumen (to figure 6 on Esbach's albuminometer), the specific gravity was 1010, and when he went home on February 3rd there was still almost the same amount of albumen present, and the specific gravity was 1015.

History.

Mr. D., aged 64, sent by Dr. Baker Young, Liverpool. For many years he has had some indigestion after food, but will not admit that he suffered any inconvenience, except on rare occasions. At any rate, he has always taken ordinary food. Twelve years ago he was in bed with influenza, but there was some doubt whether it was not typhoid fever, as he was in the bedroom for seven weeks; three years ago he had another attack of "influenza," less severe than the first one.

He dated the beginning of his present illness from only six weeks ago, when he had a sudden fainting attack, with a "sinking in the body," accompanied by a feeling of sickness, but no actual vomiting. It is probable that he was a little yellow after this attack. He had his first attack of real pain fourteen days ago in the right side of the chest and body, not very severe, but accompanied by vomiting, shivering, and sweating; he was markedly yellow after this attack, and the colour has shown no sign of lessening, if anything, it has rather deepened. During the last ten days or so he has rarely been free from a sense of great discomfort in the upper part of the body and a feeling of faintness, and has been unable to take ordinary food with comfort. He has been constipated, and the motions have recently been of a lighter colour than natural. He has lost weight considerably.

Examination.

He is a stoutish man who has lost some flesh, is fairly deeply jaundiced, and holds the right rectus tightly contracted. Nothing abnormal can be made out.

Operation.

On November 6th, 1909, an incision was made through the right rectus; there were no stones in the ducts, pancreas a little hard. Gall bladder was very large, tightly distended with fluid, and pointed to the left. It was a dull red colour, and had lost its peritoneal gloss; at the fundus was an area (dull grey in colour) where the wall was very thin, possibly a spot of incipient perforation. It was clearly an acutely inflamed gall bladder. Cholecystotomy was performed, and the thinned grey area at the fundus excised. A culture was taken of the bile in the gall bladder, but no growth occurred. The bile was dark brown, and extremely viscid. It was considered inadvisable to remove the gall bladder because the patient's condition under the anaesthetic became serious, and rapidity was thought necessary.

His recovery uneventful up to November 24th.

From November 6th he had a little bronchitis, and the tube from the gall bladder came away on the tenth day. The bile escaping from the sinus caused some superficial erosion of the abdominal wall for a distance of 2 in. from the wound, but he did not complain of this after the seventeenth day, and the surface quickly healed. He passed from 17 to 20 oz. of urine in the day, but on November 23rd he only passed 12 oz. in twenty-four hours. On the night of November 24th he did not feel so well, the pulse was very weak, he vomited copiously and continuously, and complained much of flatulence and headache. Bile was still coming freely from the sinus. He was very ill indeed all the next day: headache, occasional vomiting, bringing up small quantities of mucus and altered blood, complained of twitching in the legs, skin was dry and hot, respirations feeble and slow, pulse 90; he lay in a semicomatose condition, and had to be roused to drink. He was thought to have uraemia, and a catheter passed found the bladder empty. Pilocarpine was given four-hourly, with the result that sweating was profuse; calomel and Seidlitz powders were tried, and enemata. At 6 p.m. 3 pints of saline were put into the right median basilic vein; he did not feel the incision at all. There seemed to be no improvement, and at 11.15 p.m. 2 pints of saline were run in under the skin of the left thigh.

During the night of November 25th he was very bad, and on November 26th at 10.45 a.m. a catheter passed brought 3 oz. of urine away, loaded with albumen. During the morning he became more conscious, and the vomiting was less, and later on he passed a further 12 oz.

On November 27th he passed nearly 40 oz. of urine; he was very comfortable, had no vomiting, and appeared quite well again.

From this time to November 30th he was very fit, but bile was still escaping from the sinus at intervals, each complete closure of the sinus corresponding to the onset of a rigor; it was therefore decided to keep the drainage as free as possible,

and a probe was frequently passed down the track. On November 30th he vomited all day, complained of flatulence, and was retching continuously, twitching in the legs was pronounced, and again there was a state of semicomatose, from which he was roused to take food, etc. He passed this day only 5 oz. of urine, highly albuminous, with a specific gravity 1015.

On December 1st he passed no urine at all, and a catheter drew none away; the coma and other symptoms were accentuated. At 7 p.m. he was given 4 pints of saline by subcutaneous infusion into both sides of the chest; pilocarpine and the usual purgatives were given. He was extremely ill, and his condition was thought to be hopeless.

On December 2nd, in the early morning, the left median basilic vein was opened and he was given 2 pints of saline rapidly; he did not complain of any pain when the incision was made. Four hours afterwards he passed 4 oz. of urine loaded with albumen and with a specific gravity 1010. His condition again began to improve, and he became rapidly conscious, and passed 22 oz. of urine. He was vastly better. On December 4th he was comfortable, and passed 48 oz. of urine.

On December 5th much depressed; vomited once; urine 40 oz. December 6th, urine 42 oz. December 7th, urine 37 oz.

Up to the end of December he was fairly well, having occasional attacks of great depression. The bile fistula was not closed until the end of the month. All this time the urine was loaded with albumen and he was passing on the average 26 to 30 oz. a day (twenty-four hours).

On January 14th, 1910, he was not so well; passed only 16 oz. of urine in twenty-four hours; he had been up on a couch on the previous day for twenty minutes.

On January 17th and 18th he passed only 16 oz. each day; he was again much depressed and suffered from thirst and nausea. The skin was hot and dry and headache was pronounced.

On January 23rd he passed only 8 oz. of urine loaded with albumen. In the evening he had twitchings in the legs, vomiting, and presented the picture of a man dying from uraemia; he again became semiconscious. Next day he was given rectal salines three-hourly, two pints of saline subcutaneously, and he passed only 1½ oz. of urine.

On January 25th no urine at all passed; another intravenous infusion was performed and two pints of saline were rapidly run into the left median cephalic vein; pilocarpine was again given four-hourly. Again the same result followed. At 10 p.m. he passed 4 oz. of highly-albuminous urine, and although he was very ill through the night, he improved in the early morning. He ceased vomiting and all the symptoms of uraemia disappeared rapidly.

On January 26th he passed 30 oz. of urine, and on the 27th and 28th 40 oz.

When he went home, at his own urgent request, on February 3rd, his urine contained a very large amount of albumen, but he passed 40 oz. in twenty-four hours, and the specific gravity was 1015. His condition was far from satisfactory; he was pale, his tongue was dry and he had great depression at times.

My thanks are due to Mr. Moynihan, who operated on the case, for permission to publish these notes.

FURTHER STUDIES IN HAEMOLYSIS BY WEEVER VENOM.

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IN a paper published in the BRITISH MEDICAL JOURNAL, 1907, and in a recent communication to the Pathological Section of the Royal Society of Medicine,¹ I gave the results of a number of experiments with the poison of the weever fish in relation to haemolysis. I showed that with the washed red corpuscles of pigeon, guinea-pig, sheep, ox, horse, and man, haemolysis took place without the addition of, and in the presence of, normal serum, with the corpuscles alone, and without the addition of serum heated for an hour at 56° to 60° C.

This was in contradiction to the results obtained by the French school, in particular by Briot.¹ To quote Calmette² in his review of the venoms:

The poison of the weever dissolves the red corpuscles of the horse in the presence of normal serum which has been heated, but it does not dissolve them in the presence of fresh serum. The serum that has not been heated, therefore, contains a natural antihaemolysin of the same nature as that which I have shown to exist in the case of haemolysis by cobra venom.

It seemed important to investigate this matter further, as I did not feel content with the explanation of Preston Kyes³ in regard to the phenomenon of haemolysis by venoms without added serums—namely, that the toxin (in his case of cobra venom) was an amboceptor which was complemented by the endocomplements of the red cells. Preston Kyes explained the different action of the same venom on the blood of different animals by assuming that there were two groups of blood cells—(1) those that are in themselves dissolved by cobra venom; (2) those

that are only affected by venom after the addition of other substances, complements, etc. In the case of weever venom, according to my experiments, there was but one group of blood cells, belonging to Group I, and therefore we must assume, according to his amboceptor theory of the nature of venoms, that the blood of pigeon, guinea-pig, sheep, ox, horse, and man contained endocomplements to weever poison.

The difference between my results and those of Briot might depend on the method of preparation of the toxic solution or on its freshness, as weever venom seems to be of a very unstable nature. As was pointed out at the time, it seemed that my method of extracting the venom from the opercular glands with a syringe was more likely to yield a pure solution than the removal of spines and glands with scissors, maceration in glycerine, and filtering through filter paper, the method employed by Briot.

In order to throw further light on the difference between my results and those of the last-named observer, I have made a series of experiments, mixing my extracted venom with glycerine, and filtering it through filter paper or through a Berkefeld filter. In this way a toxin giving similar reactions to Briot's was obtained.

Experiment I.

In each tube 2 c.cm. 5 per cent. human red corpuscles washed with normal saline three times and centrifuged. The solution of venom was made by extracting the poison with a syringe from 100 fresh weevers, and mixing it well with 30 minims pure glycerine (4 drops of the unfiltered glycerinated venom gave immediate complete haemolysis). The mixture was then filtered through paper.

Incubated Two Hours at 37° C.

1 m. Filtered Glycerinated Weever Venom alone.	1 m. Filtered Glycerinated Weever Venom + Normal Serum.	1 m. Filtered Glycerinated Weever Venom + Serum heated Half-hour at 60° C.
Slight haemolysis	Very faint haemolysis	Almost complete haemolysis.

This experiment is in almost complete accord with Briot's results, but it is to be noticed that with venom alone there was slight haemolysis. The normal serum acted as an antihæmolytin, and the heated serum acted as a complement. Nevertheless, with the unfiltered venom there was complete and rapid haemolysis.

Experiment II.

Similar solutions were used as in Experiment I, but the first portion of the fluid to pass through the filter was collected and called the first filtrate, and the second portion was called the second filtrate.

Incubated Two Hours at 37° C.

First Filtrate only.	First Filtrate + Normal Serum.	First Filtrate + Heated Serum.
Marked haemolysis	Almost complete haemolysis.	Complete haemolysis.

This result is a grade further, so to speak, in comparison with Experiment I. There was complete haemolysis with heated serum, but still marked haemolysis with the corpuscles alone.

Incubated Two Hours at 37° C.

Second Filtrate only.	Second Filtrate + Normal Serum.	Second Filtrate + Heated Serum.
Almost complete haemolysis	Almost complete haemolysis	Complete haemolysis.

Experiment III.

November 25th, 1909. Venom extracted from sixty fish was mixed with 60 m. glycerine. The following day the mixture was filtered through filter paper. On November 27th each tube was filled up with 2 c.cm. washed human red corpuscles.

It had been ascertained that 2 drops of fresh unfiltered venom caused marked haemolysis with 2 c.cm. red cells without added serum, normal or heated.

Incubated Two Hours at 37° C.

10 Drops Only.	10 Drops + Normal Serum.	10 Drops + Heated Serum.	10 Drops + Lecithin.
Slight haemolysis	Slight haemolysis	Marked haemolysis	Marked haemolysis.

In this experiment the glycerine extract, when filtered, gave a result somewhat similar to Briot's—namely, increased haemolysis with heated serum and lecithin—but the antihæmolytic action of normal serum was not so apparent.

Experiment IV.

Experiment IV was made with the venom of 100 weevers mixed with 100 m. pure glycerine. This was put into a Berkefeld filter. The first filtrate was a clear fluid, and of this 20 m. was used in the first part of the experiment.

2 c.cm. 5 per cent. Washed Human Red Corpuscles. Incubated Two Hours at 37° C.

4 Drops alone.	4 Drops + Normal Serum.	4 Drops + Normal Serum.	4 Drops + Serum heated Half an Hour at 60° C.	4 Drops + Serum heated Half an Hour at 60° C.
No haemolysis	No haemolysis	No haemolysis	No haemolysis	No haemolysis

The further filtrate was next used:

Usual Incubation.

2 Drops alone.	2 Drops + Normal Serum.	2 Drops + Normal Serum.	2 Drops + Heated Serum.	2 Drops + Heated Serum Half an Hour at 60° C.
No haemolysis	No haemolysis	No haemolysis	Very faint haemolysis	Slight haemolysis

The further filtrate was next used in larger quantities.

Incubated Two Hours at 37° C.

5 m. Alone.	5 m. + Normal Serum.	5 m. + Serum heated Half an Hour at 60° C.	5 m. + Serum heated Half an Hour.	5 m. + Solution of Lecithin.
Slight haemolysis	No haemolysis	Marked haemolysis	Marked haemolysis	Marked haemolysis

The venom in this case acted purely as an amboceptor, and if we assume the presence of a complement in my unfiltered venom, it is quite clear that the complementary body had been lost, since, with the exception of Column 1 in the last series, the venom has acted precisely as the filtered extract of Briot. But we must still note that there is slight haemolysis, with large quantities of second filtrate and washed corpuscles only.

It was necessary to find if this complementary property was left behind in the filter, and to do so 1 c.cm. of salt solution was added to the glycerine remaining in the filter, so as to wash through the remaining glycerine extract. The salt solution carried through the filter a venom producing marked haemolysis without the addition of heated serum.

Experiment V.

Experiment V was made with venom from eighty weevers mixed with 80 m. pure glycerine, which was then filtered through a Berkefeld filter. There was obtained in the first filtrate, after exhausting the vessel, 30 m. of a clear yellowish fluid; 15 m. of this was heated for an hour at 56° C., and the remainder left unheated.

2 c.cm. Human Red Corpuscles in each Tube. Incubated.

5m. Filtered Glycerinated Weever Venom.	5 m. Glycerinated Weever Venom + Normal Serum.	5 m. Glycerinated Weever Venom + Heated Serum.
No haemolysis	No haemolysis	No haemolysis.

The same result was obtained with 5 m. of glycerinated venom heated at 56° C.

The following morning 1 drachm of salt solution was added to the glycerine extract remaining in the filter, and the receiver exhausted; 84 m. of clear fluid was obtained. Half of this was heated for forty minutes at 56° C. The other half was used for an experiment which we will call Experiment V a.

Experiment V a.—Salt Solution Washings of Glycerine Extract. Incubated as usual.

13 m. only.	13 m. + Normal Serum.	13 m. + Heated Serum.
Marked haemolysis	Marked haemolysis	Marked haemolysis

Experiment V b.—Salt Solution Washings of Glycerine Extract heated at 56° C. Incubated.

13 m. only.	13 m. + Normal Serum.	13 m. + Heated Serum.
Marked haemolysis	Marked haemolysis	Marked haemolysis

It would seem that both amboceptor and complement were carried through the filter by adding a small quantity of salt solution.

Experiment VI.

5 per cent. washed human red corpuscles, 2 c.cm. in each tube. The venom used was from ninety fish mixed with 90 m. glycerine, and filtered through a Berkefeld filter. (The original mixture gave marked haemolysis with washed red cells alone.) The second filtrate gave with heated serum and red cells slight haemolysis, and with normal serum *nil*.

One drachm of glycerine was then added to the filter.

Ten drops of this with red cells only gave faint haemolysis.

Ten drops of this with red cells + heated serum gave marked haemolysis.

Ten drops of this with red cells + normal serum gave *no* haemolysis.

We are now in a position to review the results of these experiments, and in order to make the results quite clear I have tabulated them and arranged the tables to show the results first of all with venom glycerinated and filtered through filter paper and then the results obtained by filtering through a Berkefeld filter.

SUMMARY OF RESULTS.

Washed human red cells, 2 c.cm. Incubated 2 hours at 37°C., and allowed to stand in the cold. Serum was heated from 56°C. to 60°C. for $\frac{1}{2}$ to 1 hour in different experiments.

Signs.—Faint haemolysis is denoted by f.h.; slight haemolysis by h.; marked haemolysis by H.; almost complete haemolysis by Hc.; complete haemolysis by HC.

Filtered Glycerinated Venom (Filter Paper).

Experiment.		Only.	+ Normal Serum.	+ Heated Serum.	+ Lecithin.	
I.	m. j	h.	f.h.	Hc.	—	100 weavers + 30 m. glycerine. Record lost.
II.	—	H.	Hc.	HC.	—	
III.	m. v	h.	h.	H.	H.	60 weavers + 60 m. glycerine.

Filtered Glycerinated Venom (Berkefeld Filter).

Experiment.		Only.	+ Normal Serum.	+ Heated Serum.	+ Lecithin.	
IV.	m. j	0	0	f.h.	0	100 weavers + 100 m. glycerine.
	m. j	0	0	h.	0	
	m. v	h.	0	H.	H.	
	m. v	h.	0	H.	H.	
VI.	m. ij	0	0	h.	—	90 weavers + 90 m. glycerine.
	m. v	f.h.	0	H.	H.	

An analysis of the results of these experiments shows the broad facts that the admixture of glycerine and filtration alters the character of the venom, first, as to its virulence, and secondly, as to its character.

With filtration through filter paper, we find that, contrary to what happens with unfiltered venom, heated serum increases the amount of haemolysis in Experiments I, II, and III, and that in Experiment I normal serum diminishes haemolysis, in Experiment III it remains the same, and in Experiment II it appears to have increased it. At any rate we have the uniform definite result of diminished virulence and of an increase of haemolysis by the addition of heated serum.

With filtration through a Berkefeld filter, we found diminished virulence and an *absence of haemolysis* with normal serum, that is to say, a more definite loss of haemolytic power in the presence of normal serum when filtered through a Berkefeld filter than through filter paper. On the other hand, there is a more marked increase of haemolytic power with heated serum when filtered through a Berkefeld filter, as shown in Experiments IV and VI, where we get either slight haemolysis or marked haemolysis.

It would be possible to explain these results by assuming the presence of a complement-like body in addition to an amboceptor in fresh venom. The complement appears to pass through the filter less readily than the amboceptor,

and its passage can be encouraged by adding salt solution as shown in Experiments IV and V.

It was also observed that lecithin was able to complement the venom amboceptor in the cases in which heated serum increased the haemolysis.

The results of these observations confirm my original contention concerning the action of fresh venom; they explain how the difference in Briot's results and my own may have been produced, and they also show the possibility of the existence of a hitherto unsuspected body in weaver venom—namely, a complementary body that allows haemolysis to take place without the addition of heated serum or lecithin. This complementary body is, however, not a true complement, as it is able to withstand heating for half an hour to 56° C.

If the venom extracted by a syringe be dried *in vacuo*, and, after keeping several days, be dissolved in normal saline and filtered, a solution is obtained capable of dissolving washed red corpuscles without the addition of serum, normal or heated.

In conclusion, it will have been observed that throughout this paper the terminology of Ehrlich's school has been used, and the experiments have been made in the light of the studies on venoms by Preston Kyes, Sachs, Flexner and Noguchi and others. In view, however, of the recent work on the colloidal nature of antigens and their antibodies, especially the researches on haemolysis by colloidal silicic acid by Jagic and Landsteiner,⁴ it would seem possible that my results may be readily explained according to this newer theory.

REFERENCES.

- 1 Briot: *Comptes rendus Soc. de Biologie de Paris*, 1902 and 1904.
- 2 Calmette: *Les venins*.
- 3 Preston Kyes, in Ehrlich's *Collected Studies on Immunity*.
- 4 Landsteiner and Jagic: *Wien. klin. Woch.*, vol. xvii, p. 63.
- 5 Muir Evans: *Transactions, Pathological Society of London*, vol. lviij, Part I, 1907; and *BRITISH MEDICAL JOURNAL*, 1907.

A NOTE ON COWPOX IN MAN ;

WITH A REPORT OF A RECENT CASE.

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THE first distinct description of cowpox was given by Jenner when he published *An Inquiry into the Causes and Effects of the Variolae Vaccinae, a Disease Discovered in Some of the Western Counties of England, and known by the Name of the Cow Pox* (London, 1798). The disease is described as consisting of "irregular pustules on teats, of a palish blue colour surrounded by an erysipelatous inflammation, and characterized by a tendency to degenerate into phagedaenic sores." The communication of the disease to man was no doubt fairly common for a considerable period before the above treatise was written.

The gossip among cowherds of the vague, obscure, but popular belief regarding the possible communication of this disease to the milkers, and the protection from small-pox which this conferred, was the source which first attracted Jenner's attention.

One finds that Jenner cited a number of instances of accidental inoculation occurring on the fingers, hands, wrists, arms, and on the lips. Pearson¹ also cites cases, mostly on hands and arms. One of his cases is, I think, of special interest.

Annie Francis had pustules on her hands from milking cows affected. These pustules soon became scabs, which, falling off, discovered ulcerating and painful sores, which were long in healing. Some milk from one of the diseased cows having spurted on the cheek of her sister and on the breast of her mistress, produced, on these parts of both persons, pustules and sores similar to her own on her hands.

The two latter cases seem to me to be open to the question whether the milk from the animal suffering from cowpox was the infecting source, or whether the fingers of the originally infected case were the immediate inoculating factor.

I was talking to a cowman in a large dairy farm about cowpox recently, and he informed me that some years ago he was himself infected, chiefly about his finger-nails, and that during the course of the disease (to put it in his own words) "he was acting about with his missus one day, and accidentally scratched her forehead." About a week later the disease appeared at the site of the scratch; papule, pustule, and scab followed, with con-