ON THE EFFECTS OF INJECTIONS OF QUININE INTO THE TISSUES OF MAN AND ANIMALS.

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(With Plate III.)

In December 1917, Lieut.-Col. MacGilchrist of the Indian Medical Service published a paper on the necrosis produced by intra-muscular injections of strong solutions of quinine salts[1]. It might be an advantage to quote the first few lines of this communication: "Advocates of intra-muscular injections of strong solutions of quinine salts for the treatment of malaria seldom omit to state that no local ill-effects are produced." He records a case of tissue necrosis following on the intra-muscular injection of eleven grains of quinine bi-hydrochloride in thirty-four minims of water. Death supervened thirteen hours later. MacGilchrist especially noted, owing to rapid tissue necrosis, that the track of the needle remained patent. He regards as an established fact that most of the quinine injected is precipitated and probably chemically combined with serum proteins in the necrosed tissues and for this reason intra-muscular injections of concentrated solutions of quinine salts are not to be recommended for cases of emergency. Very dilute solutions of quinine salts are, in his opinion, rapidly and completely absorbed whether employed subcutaneously or by the intra-muscular route. If the views which MacGilchrist puts forward in this and other communications are to be accepted without reserve then intra-muscular injections of strong solutions of quinine should no longer be employed. It was for this reason that Major-General Sir M. P. C. Holt, K.C.B., K.C.M.G., D.M.S., B.S.F., asked me to carry out an experimental enquiry on animals as to the effects produced by intra-muscular injections of strong solutions of quinine.

Human muscle was examined from fatal cases of malaria or suspected malaria which had received an injection of quinine at periods varying from one hour to three months from the time of the inoculation, and in some instances an estimation of quinine in the affected tissues was made. For the experimental enquiry, cast mules, rabbits, guinea-pigs, and frogs were used, while the preparations of quinine employed were (*a*) bi-hydrochloride in saline,

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(*b*) acid sulphate in saline[1], (*c*) quinine alkaloid dissolved in alcohol (about the strength of hospital brandy), (*d*) and in ether (medicinal). The alkaloid shaken in blood serum and saline—a preparation which consisted of one gramme of alkaloid, one c.c. of 90 per cent. alcohol, and olive oil to 3 c.c.—and a somewhat similar preparation to the last mentioned was tested directly after it arrived in the East for trial. The quinine solutions have been injected in concentrated and dilute solutions. The preparations most commonly employed for intra-muscular injections were the bi-hydrochloride of quinine in saline, and, to a less extent, bi-hydrochloride dissolved in brandy. Human muscle was obtained in all instances from cases which had received quinine in some form in concentrated solutions as commonly employed for the treatment of malaria. Control observations were made on the action on the tissues of animals of acids and ether (quinine solvents).

Numerous cases were treated with intra-muscular injections of quinine bi-hydrochloride dissolved in brandy on the basis of three grains of the salt per 10 lb. of body weight.

Experiments have also been made on the absorption of quinine from the seat of inoculation, at periods varying from a few minutes to several weeks, and as to the question of the storage of the alkaloid in the heart-muscle, liver and kidneys.

All who have had experience of malarial patients are aware that an apparent anaemia occurs, and a true anaemia with considerable blood destruction. Further, a severe haemolytic anaemia and haemoglobinuria is associated with malaria and may occur at a period of the disease when quinine treatment is essential. For these reasons it was necessary to induce anaemia and haemoglobinuria in animals by means of immune sera so as to observe whether intra-muscular injections of quinine in concentrated and dilute solutions excited a more intense tissue reaction than in the control animals.

All the chemical estimations of residual quinine were undertaken by Captain C. E. C. Ferrey, O.B.E., R.A.M.C. (T.F.), Analytical Chemist to the Central Laboratory, B.S.F., who employed the Stas-Otto process for these investigations.

QUININE AND HAEMOLYSIS.

Although the purpose of these experiments was to observe the effects of intra-muscular injections of quinine on the tissues, yet, attention must be drawn to the haemolytic activity of quinine as estimated *in vitro*. Two solutions were prepared for the purpose: (1) 1 per cent. bi-hydrochloride of quinine in saline, (2) a solution of hydrochloric acid in saline of the same total acidity as the quinine solution—0·18 per cent. The total bulk of test solution and saline in each tube was 1 c.c. The haemolytic end point of the quinine solution, acting at 37° C. for five hours, was 0·16 c.c., while the acid solution alone induced haemolysis down to 0·1 c.c. Normal saline was employed throughout

[1] Only three experiments were made with this salt as it was found to excite more intense necrosis than the other preparations which were employed.

the experiments as the diluting agent. Further, the haemolytic action was much more rapid with the acid solution than with the bi-hydrochloride of quinine in saline. Normal human serum or citrated plasma in suitable amounts prevented haemolysis. These results briefly referred to serve to illustrate the haemolytic action of bi-hydrochloride of quinine and of the corresponding acid. It will be readily appreciated that the preparations of quinine employed for intra-muscular injections in the treatment of malaria are of considerably greater strength than in these experiments on haemolysis *in vitro*. The haemolytic activity of a 1 per cent. solution of bi-hydrochloride of quinine is extremely rapid, while strong solutions produce instantaneous haemolysis. The alkaloid when suspended in saline induces a much more gradual haemolysis than the salt in solution, although for obvious reasons a considerable error must occur in estimating the haemolytic action of varying suspensions of quinine alkaloid in saline. It has been found that the agglutination of human or other red cells, well known to be induced by free acids, is absent in the standard acid solutions of bi-hydrochloride of quinine employed in suitable strengths for such purposes. If 0·05 c.c. of the standard solution of hydrochloric acid already referred to is made up to a total volume of 1 c.c. an immediate agglutination occurs on the addition of human red cells, while with 0·15 c.c. of the 1 per cent. solution of bi-hydrochloride of quinine in 1 c.c. saline no such effect is induced. All experiments tend to show that although quinine acts as a powerful haemolytic agent the acid employed to dissolve the alkaloid is much more potent in its effect.

WHAT IS THE COMPARATIVE EFFECT OF INTRA-MUSCULAR INJECTIONS OF CONCENTRATED AND DILUTE SOLUTIONS OF QUININE?

Numerous experiments have been made to solve this question concerning which information was specially required.

The following detailed descriptions express the essential features:

(1) A rabbit received an intra-muscular injection of 0·039 gramme of bi-hydrochloride of quinine in 1 c.c. saline, and the same quantity of quinine in 3 c.c. of saline into another set of muscles.

The following day 0·078 gramme of the same preparation in 2 c.c. of saline was injected in the right side and a similar quantity in 4 c.c. of saline in the left.

The post-mortem examination took place on the following day. The results showed that no advantage was gained by injecting the quinine in twice the quantity of saline. The spreading oedema was greater owing to the increase in bulk of fluid injected, while the inflammatory process and muscle necrosis in both instances was so evident that no importance could be attached to minute differences in the affected tissues. If quinine injections are given in such dilutions that the action of quinine and free acids on the red cells and tissues is reduced to a minimum, then the bulk of fluid required would nullify, in my opinion, any advantage that might be gained. Further there is a greater

possibility of suppuration from injection of quinine in large bulk into the tissues at frequent intervals.

(2) Four rabbits were injected by the intra-muscular route as follows:

A. 0·018 gramme of bi-hydrochloride of quinine in 0·5 c.c. saline (concentrated).
B. 0·018 gramme of bi-hydrochloride of quinine in 0·5 c.c. normal rabbit serum (concentrated).
C. 0·018 gramme of bi-hydrochloride of quinine made up to 2 c.c. with auto-rabbit serum.
D. 0·7 c.c. of 1: 5000 solution of quinine alkaloid in ether.
E. 0·18 gramme of bi-hydrochloride of quinine made up to 2 c.c. with auto-rabbit serum and injected by the intra-muscular route.

In every instance obvious necrosis occurred. The interval between the time of the injection and the autopsy was six days in the case of experiments A and B, 4 days in C and E, and 3 days in D.

The most intense changes were induced when the alkaloid was injected with ether. Necrosis of muscles in all stages—wide areas of polynuclear and mononuclear inflammation especially towards the capsular area—thrombosis of vessels—red cell agglutination and haemolytic changes in the tissue blood as well as in the intra-vascular blood.

(3) A mule was injected with 1 gramme of alkaloid of quinine in alcohol and olive oil (3 c.c.). On the following day with 1 gramme of the alkaloid in 10 c.c. ether.

Although the total bulk of fluid varied considerably in each inoculation the final results were similar; further, the concentration of quinine in the solutions employed did not affect the final results. In each instance extensive necrosis—haemorrhage into the tissues—congestion of blood vessels—and foci of acute inflammation were met with. Numerous experiments have been referred to elsewhere in this communication which serve to illustrate the comparative effects of concentrated and dilute solutions when injected into the tissues of animals.

THE MICROSCOPICAL FINDINGS AS A RESULT OF INTRA-MUSCULAR INJECTIONS OF QUININE SALTS AND ALKALOID QUININE.

The first effect of an injection of a quinine preparation into the tissues is necrosis of muscle. The fibres most affected are completely necrosed leaving the empty sheaths. Oedema of the tissues accompanies the necrosis, together with agglutination of red cells and haemolysis in the vessels and in the blood which has escaped into the tissues. These changes are in evidence within ten minutes of the inoculation. At this period no leucocytic reaction has occurred, but an intense congestion of all vessels in the area has taken place. At the end of one hour the leucocytic reaction may not be a marked feature, although in preparations of quinine which include oil an intense polynuclear leucocytic reaction has been observed. The muscle fibres in the necrotic areas, as time advances, present appearances which are various as well as distinctive. In addition to the fibres which are completely necrosed others show fragmentation so that numerous "apparent droplets" are observed within the sheaths (Pl. III,

Fig. 1). Owing to a multiplication of the nuclei of the sheaths which occurs and a collapse of the sheaths themselves, the fibrous framework of the new tissue is gradually formed. Shrunken fibres with several nuclei give the well-known appearance of pseudo-giant cell formation. The large tissue cells act as phagocytes for fat droplets, red cells and free iron granules. Active destruction of the vessel walls occurs together with thrombosis which may or may not serve as a conservative process (Pl. III, Fig. 3). Polynuclear inflammation of the necrosed walls can be clearly demonstrated. Active changes occur in the vessels apart from thrombosis such as agglutination of red cells and haemolytic phenomena while similar changes are met with outside the vessel walls. In certain instances marked red cell agglutination occurs within the vessel without the evidence of inflammation (Pl. III, Fig. 2).

In course of time absorption of muscle fragments and of inflammatory products takes place so that finally we have a condition of fibrous myositis such as is met with as a result of traumatic influence or syphilis. Nerve fibres are implicated in the earliest stages. It is not uncommon to observe that haemorrhages and large vacuoles occupy the space of the original nerve fibres. Fibrous tissue formation surrounds the nerves in the muscles and also the individual fibres. Large nerve trunks may be so implicated by the oedema and spreading necrosis that complete nerve degeneration occurs.

Strands of necrosed muscle fibres may persist for ten to fourteen days after an injection of quinine, possibly owing to the diminished tissue absorption which must occur as a result of quinine inoculation. The bulk of quinine however is absorbed from the tissues with extreme rapidity—simply a question of hours.

EXPERIMENTS TO ILLUSTRATE THE EFFECTS ON THE TISSUES OF CERTAIN PREPARATIONS OF QUININE.

A cast mule was injected with the following preparations. The results were as follows:

Number of inoculation	Site of inoculation	Nature of inoculation	Naked eye appearances at autopsy	Interval between inoculation and examination
1	Back, near side	10 c.c. ether	Extensive necrosis, 6 or 7 inches long, 3–4 inches wide. Slight superficial oedema	6 days
2	Near fore leg	ditto	Extensive tissue necrosis. Slight oedema	5 days
3	Back, off side	0·25 grm. of alkaloidal quinine in 10 c.c. ether	Widespread oedema. Very extensive necrosis	4 days
4	Off fore leg	ditto	ditto	3 days
5	Near hind leg	5 c.c. of 4·3% HCl in saline	Extensive oedema spreading along muscle septa. Marked necrosis	2 days
6	Off hind leg	5 c.c. of 25% bihydrochloride of quinine in saline (same total acidity as above (5))	ditto	24 hours

This experiment gives an excellent survey of the effect produced by ether-quinine alkaloid dissolved in ether—bi-hydrochloride of quinine in saline—hydrochloric acid made to the same total acidity as the solution of quinine. In Experiment 3 of this series 0·25 gramme of alkaloidal quinine was injected in no less than 10 c.c. ether, yet the effect on the tissues was considerable. Here the quinine was given in dilute solution, but the solvent employed was largely responsible for the effect. Experiments 5 and 6 of this series show similar effects on the tissues, yet quinine was not employed in Series 5. The result must have been due therefore to the solvent. This fact must never be lost sight of in any discussion on the question of tissue necrosis induced by quinine, as will be referred to elsewhere in this communication.

Intra-muscular Injections of Alkaloidal Quinine in 60 per cent. Alcohol.

Several animals received intra-muscular injections of quinine dissolved in alcohol, either concentrated or in dilute solutions. The rabbit used in the experiment to be referred to in detail was injected daily for six days with 0·04 gramme in 1 c.c. of 60 per cent. alcohol. Blood counts were made with the object of determining whether a leucocytosis would be induced or an alteration in the red cell-haemoglobin system. The injections were made in a different muscular area on each occasion. Certain tissues were preserved at the autopsy for quinine estimation, and the entire local area was removed for a similar purpose except for a small portion reserved for microscopy. First injection: there was marked oedema and a long line of muscle necrosis. A typical fibro-myositis had been produced around the necrosed muscle in which all possible changes were recognised. Numerous new formed blood vessels were present, also blood pigment and scattered haemorrhages. Degeneration of the vessel walls was evident. The effect of the second inoculation was similar except that a well-developed interstitial neuritis was found in the nerve from the affected area. No quinine was detected in the local lesion. The third injection had produced a large haemorrhagic area superficial to a diffuse black-brown necrosis of muscle. Numerous foci of polynuclear cells were present. No quinine was obtained from the local lesion. Fourth injection made four days before death showed very considerable oedema of muscle and necrosis. Thromboses of some of the large vessels were present with necrosis of the muscular walls. The degenerated muscle fibres were fragmented and were undergoing a process of gradual absorption by which highly cellular patent sheaths remained, the walls of which ultimately coalesced and thus assisted in the formation of the fibrous scar.

Fifth injection. Diffuse haemorrhage and oedema together with a prominent area of greyish brown, dry, muscular necrosis had occurred.

Sixth injection. This was completed forty-eight hours before death. The changes noted at the autopsy were similar to those referred to as a result

of the previous inoculation. The microscopical appearances were similar, but of a more acute type. There was a very marked polynuclear inflammation, abundant haemorrhages, and active haemolytic changes. The muscle fibres were necrosed, fragmented, and broken up into coarse granules, and haemorrhages had occurred among the nerve bundles. Both kidneys and liver removed at the autopsy forty-eight hours after the last intra-muscular injection were free from quinine, although 0·24 gramme of alkaloidal quinine had been injected in eight days, and the last injection was only forty-eight hours before death. It will be readily appreciated from those experiments described in detail that alkaloidal quinine given in 60 per cent. alcohol excites intense changes in the tissues in the inoculated area.

Intra-muscular Injections of Quinine Alkaloid in Alcohol

Dates	Weights	Red cells per c.mm.	H.B.	C. I. (Colour-Index)	Leucocytes per c.mm.	Differential count of leucocytes. 1st column = %, 2nd column = no. per c.mm.							Quinine alkaloid in 60 % alcohol. Intra-muscular injections. Total bulk of fluid = 1 c.c.
						Nucleated red cells. No. to % leucocytes	Finely granular oxyphil		Lymphocytes		Large hyalines		
							1	2	1	2	1	2	
15/7/18	1000 grms.	5,400,000	83 %	0·7	8980	2	43·0	3827	55·0	4895	1·5	133	0·04 gramme
16/7/18	950 ,,	—	—	—	7900	1	48·5	3831	50·0	3950	1·0	79	0·04 ,,
17/7/18	950 ,,	5,200,000	84 %	0·8	7600	3	27·5	2190	38·0	5168	3·5	266	0·04 ,,
18/7/18	955 ,,	—	—	—	7020	1	32·5	2275	61·0	4270	5·5	385	0·04 ,,
19/7/18	1000 ,,	5,200,000	82 %	0·7	7100	3	27·5	1952	65·0	4615	6·5	461	0·04 ,,
20/7/18	1000 ,,	5,300,000	82 %	0·7	7150	—	—	—	—	—	—	—	0·04 ,,
21/7/18	950 ,,	5,000,000	80 %	0·8	6990	1	27·0	1863	63·0	4347	10·0	690	
22/7/18	923 ,,	5,200,000	84 %	0·8	7520	0	22·0	1650	68·0	5100	8·0	600	Rabbit killed

THE INJECTION OF QUININE ALKALOID WITH OLIVE OIL.

The following preparation was tried for intra-muscular injections:

Quinine alkaloid	1 gramme.
Alcohol 90 per cent. ...	1 c.c.
Olive oil (neutral)	to 3 c.c.

Injections were made of 0·2 c.c. of the above mixture into rabbits. Some animals received one injection, others as many as five on successive days. The chief features in such experiments are concentration of the alkaloid and the introduction of a fatty substance on the assumption that it would act as a tissue protector. To avoid needless repetition it will be sufficient to refer to one experiment in detail.

A rabbit received five intra-muscular injections of the alkaloid in oil commencing with 1/10 c.c. containing half a grain of quinine on five successive days. Each inoculation was made into a different area of fresh tissue. The animal was killed eleven days from the first commencement of the experiment. During the period it lost 160 grammes in weight. No advantage would be gained by recording the tissue changes met with in each muscular area. The

naked eye appearances were profound in each focus as occurs with all concentrated injections of quinine, while the oil exerted no beneficial action. On the other hand an injection of one grain of the alkaloid for a rabbit must be regarded as a full dose. The muscles were soft, showed large areas of necrosis, thrombosis of vessels and haemorrhages into the muscular tissue. The red haemorrhagic zone was sharply defined from the necrosed pale area.

Microscopically an extensive fibro-myositis had developed with diffuse muscle necrosis. A polynuclear inflammation was far more in evidence than has occurred in experiments with other preparations of quinine. Nerve fibres embedded in the muscle tissue were degenerated, while in the older lesions fibrous tissue could be recognised among the fibres and surrounding them.

The second injection amounted to 1 grain of the alkaloid in a total bulk of 1/5 c.c. It had the advantage, therefore, for this experiment of concentration. The inoculation was made in the muscles in the front of the thigh. At the autopsy 10 days later it was found that the necrosis had spread to the muscles at the back of the thigh and the great sciatic nerve was surrounded by necrosed and inflammatory tissue. The nerve was removed entire and sections were prepared in "Marchi" at various levels. An extreme degree of nerve degeneration was noted, in fact, very few of the fibres escaped (Pl. III, Fig. 4). Some were completely degenerated, others patchy, while actual haemorrhages into the nerve had taken place. Here we have an example of the destruction of the sciatic nerve following an injection of quinine. The inoculation was made distant from the nerve, directly into a muscle, and in such a manner that escape of fluid was well-nigh impossible. The necrosis, however, was so excessive that it had extended right through the thigh muscles and implicated the sciatic nerve with disastrous results for the animal. This fact, however, will be referred to later. The entire liver and both kidneys were examined for evidence of quinine storage, but no alkaloid was detected.

The Injection of Quinine Alkaloid in Creosote and Fat.

A preparation which was sent to Macedonia for trial consisting of one gramme of quinine alkaloid, 0·75 c.c. of beechwood creosote and 5 c.c. of neutral fat was not found to possess any special advantage over the other preparations referred to. Mules received intra-muscular injections of the above preparation causing extensive necrosis, and a gelatinous spreading subcutaneous oedema. A lesion some $6\frac{1}{2}$ inches long, 3 inches deep, and $2\frac{1}{2}$ inches wide was produced by the injection of 10 c.c. into the muscles of a mule. Chemical analyses of the necrosed muscle showed that the quinine had been absorbed with rapidity. Two experiments will be quoted to illustrate this point.

	Amount injected	Date	Post-mortem date	Amount of quinine recovered
Experiment 1.	5 c.c.	21st	25th	0·003 gramme
„ 2.	5 c.c.	22nd	25th	0·063 „

Similar evidence in the case of human muscle was also obtained.

A cast brown horse was inoculated intra-muscularly with bi-hydrochloride of quinine in saline as illustrated in the accompanying table:

No. of experiment	Amount of bi-hydrochloride of quinine employed	Interval between inoculation and autopsy	Naked eye appearance of the tissues at the autopsy
1	2·5 grms. in 5 c.c. saline	13 days	Marked necrosis and fibrosis.
2	1·125 grms. in 2·5 c.c. saline	8 days	Localised necrosis separated from a fibrous zone by a line of haemorrhage
3	4·5 grms. in 10 c.c. saline	3 days	Long tract of necrosis with marked oedema of muscle
4	2·25 grms. in 5 c.c. saline	2 days	Localised necrosis with oedema
5	1·125 grms. in 2·5 c.c. saline	30 hours	Very extensive gelatinous oedema with localised necrosis
6	1·125 grms. in 2·5 c.c. saline	1¼ hours	Localised necrosis with wide tracts of haemorrhage

A brief account of the microscopical appearances of the lesions referred to in the previous table will be recorded.

No. 1. Fibrous myositis with complete capsulation of the necrotic muscular tissues. Active polynuclear inflammation present.

No. 2. Fibrous myositis completely enclosing necrosed muscle—haemorrhagic foci and polynuclear inflammation.

No. 3. Extensive necrosis of muscular tissue and of the walls of blood vessels resulting in haemorrhage and active haemolytic changes in the diffused blood. Agglutination of red cells very obvious.

No. 5. Wide necrosis of muscular tissue and an intense leucocytic reaction in and around muscle fibres which are fissured, fragmented, and show all stages of degeneration. Active haemolytic changes and masses of agglutinated red cells present.

No. 6. Diffuse muscle necrosis with long tracts of oedematous tissue evident. Haemorrhagic foci and active haemolytic phenomena present. Walls of blood vessels necrosed and ruptured.

A cast grey mule was injected intra-muscularly with certain solutions of quinine with the following results:

No. of experiment	Amount of quinine injected and total bulk of fluid	Amount obtained at autopsy	Interval between the intra-muscular injections and the P.M. examination	Appearances of the muscle lesions at the autopsy
1	4·1 grms. alkaloid in 10 c.c. of 70 % alcohol	0·014 gramme	8 days	Fibrosis and extensive necrosis
2	4·5 grms. bi-hydrochloride in 10 c.c. saline	0·020 „	7 „	Central black necrosis, scattered haemorrhages. Gelatinous oedema
3	2·25 grms. bi-hydrochloride in 5 c.c. saline	0·003 „	6 „	Central necrosis with haemorrhagic zone at periphery. Gelatinous oedema
4	Ditto	0·0085* „	5 „	Ditto (Pl. III, Fig. 5)
5	1·125 grms. bi-hydrochloride in 2·5 c.c. saline	0·012 „	4 „	Changes similar, but lesions less extensive
6	4·1 grms. alkaloid in 10 c.c. of 70 % alcohol	0·074 „	3 „	Extensive gelatinous oedema surrounding a wide area of dry necrosis (7)
7	2·05 grms. alkaloid in 5 c.c. of 70 % alcohol	0·048 „	2 „	Central black necrosis with oedematous tissue around
8	2·25 grms. bi-hydrochloride in 5 c.c. saline	0·938 „	1 hour	Extensive dry necrosis about 4 inches square

* This does not represent the sum total because some of the extract was blown out of a flask.

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In each instance a different area of the animal's body was used for the injection.

The mule was killed one hour after the last inoculation. At the post-mortem examination, the affected tissues in the region of the injections and some of the surrounding healthy tissue were removed for estimation of quinine content, while a small portion was reserved for microscopy.

We can infer from the results of the chemical investigation of the muscle lesions as illustrated in the accompanying table that the bulk of the quinine is absorbed whether injected as an alkaloid in alcohol, or as the bi-hydrochloride in saline. It was also found that at the expiration of one hour from the time of the inoculation to the death of the animal only 0·938 gramme of alkaloid was recovered out of 2·25 grammes injected.

It may be an advantage while referring to the rate of quinine absorption to cite the following experiment.

0·1 gramme of bi-hydrochloride of quinine in 0·25 c.c. saline was injected into the thigh muscles of both hind legs of a guinea-pig; ten minutes later a similar quantity was inoculated into the muscles of the left fore leg, and the animal was killed immediately. The left hind leg was amputated at the hip joint and handed to Captain Ferrey entire. He obtained 0·061 gramme of alkaloid from the tissues which amounts to 0·075 gramme of the bi-hydrochloride. The tissues in the injected areas showed spreading oedema and marked necrosis of muscle. Agglutination of red cells and haemolytic changes had occurred. No tissue reaction was present.

The tissues examined *immediately* after the intra-muscular injection were oedematous and the muscles showed evidence of necrosis.

Microscopical Changes in the Affected Tissues.

Lesions Nos. 1 *and* 2. The tissue changes in the affected muscles which are of eight and seven days standing respectively were similar although quinine alkaloid was injected in the first case and quinine bi-hydrochloride in the second. Microscopically there was typical fibrous myositis with diffuse muscle degeneration. The abundance of nuclei in the muscles among the fragmented fibres was very apparent, and in some instances gave the well-known appearances of pseudo-giant cell formation. Large haemorrhages were observed more especially in relation to strands of necrosis. Mononuclear cells were numerous throughout the new-formed fibrous tissue, and foci of polynuclear phagocytes. The free iron reaction was demonstrated, and spider cells lying in the fibrous tissue were filled with these granules.

Lesions Nos. 3 *and* 4 resulted from the injection of quinine bi-hydrochloride on successive days. The fibrous tissue formation was somewhat similar to that which has been referred to in the case of the first two experiments. Large tracts of structureless walls filled with tinged serum were abundant, as also scattered haemorrhages and phagocytosis of red cells by large mononuclear cells. Necrosis of muscle and splitting up of muscle fibres were more evident than in the first two experiments.

Lesion No. 5. Extensive necrosis of muscle and "vacuolation" had occurred. Some of the larger blood vessels were thrombosed and complete necrosis of the muscular walls was evident while other vessels showed intense polynuclear inflammation. Strands of polynuclear cells were scattered all through the connective tissue stroma.

Lesion No. 6. The most striking feature in this experiment was a zone of necrosed muscle with fibrosis divided from a layer of vacuolated and distorted muscle cells by a broad line of haemorrhage, while acute oedema extended for some distance between the fibres.

Lesion No. 7. This lesion showed two distinct pathological changes:

(1) Haemorrhagic area which contained tracts of free blood and congestion of blood vessels together with areas of haemolysed blood in which were present agglutinated red cells. Intense polynuclear inflammation had occurred in the vessel walls and all stages of muscle degeneration.

(2) Necrotic area. The contrast with the vascular area was most marked. Extensive necrosis of muscle with outlying fibres swollen, vacuolated, and distorted and necrosis of the muscular walls of the large blood vessels was found. Throughout the whole tissue there was polynuclear inflammation.

Lesion No. 8. This was produced at the end of one hour by one injection of 2·25 grammes of bi-hydrochloride of quinine. Wide tracts of haemorrhage occurred along the muscle bundles with acute oedema spreading in all directions. Muscle fibres were necrosed and in all stages of degeneration. In one portion of the affected muscles wide areas of haemorrhage had occurred with direct destruction of large blood vessels. In this area intense polynuclear inflammation was present while in an adjoining area leucocytic reaction was absent. Rings of polynuclear cells were in evidence in the sheath of the muscle fibres, infiltrating the fibres, and dividing them up into large granular masses. Wide areas of lysed and partly lysed red cells were present. Phagocytosis of red blood corpuscles by large mononuclear cells was very evident, also clumps of agglutinated erythrocytes.

FIXATION OF QUININE IN THE TISSUES.

These experiments were undertaken at the suggestion of Captain J. F. Gaskell, R.A.M.C., so as to ascertain whether quinine when injected into the muscles becomes immediately fixed locally, as if so, quinine "absorption" from the tissues would be only an apparent effect.

Experiment 1. Cast Mule. 1·0 gramme of alkaloid quinine was injected as the bi-hydrochloride into the belly of a leg muscle which had been exposed for this purpose. The blood vessels were tied immediately by Captain Moir, A.V.C., and the whole muscle and tendons were removed without delay. The chemical analyses were made by Captain F. S. Hele, M.D., R.A.M.C., and the results were as follows:

Watery extract, 0·217 gramme.

In muscle, 0·595 gramme.

In cloth (used in the experiment), 0·026 gramme.

Total quantity of quinine alkaloid obtained from the muscle, 0·838 grm.

Experiment 2. Similar experiment to No. 1 except that the muscle remained in the body for twenty minutes after the blood vessels were tied by Captain Moir, A.V.C.

Chemical analysis by Captain Hele, R.A.M.C.

Watery extract, 0·307 gramme.

In muscle, 0·460 gramme.

In cloth, 0·029 gramme.

Total quantity of quinine alkaloid extracted from muscle, 0·796 gramme.

The results of these experiments do not suggest that quinine is fixed in the tissues immediately after inoculation to any appreciable extent. Captain Hele considers that the amount "lost" in the above experiments was due to technical difficulties.

The Effects of Intra-muscular Injections of Quinine in Animals rendered Anaemic.

These experiments were undertaken to ascertain whether intra-muscular injections of quinine produced more severe tissue changes in animals in which a severe haemolytic anaemia had been induced than in control animals. The anaemia and haemoglobinuria were induced by injecting rabbits with the serum of a cat which had been immunised with rabbit's cells for the purpose of these experiments. The immune serum was injected intravenously. Blood counts were made at daily intervals and the weights of the animals were carefully recorded. It was necessary to have records of these data because many patients who receive intra-muscular injections of quinine are anaemic and some are suffering from various grades of haemolytic toxaemia. The most exhaustive experiment will be referred to in detail. Intra-muscular injections of bi-hydrochloride of quinine in saline were given in varying amounts from large to excessive doses with the object of exciting more severe tissue changes in the anaemic animals than in the control. The quinine injections were made previous to and during the period of severe anaemia. There was no leucocytosis. On the contrary a definite reduction in the total white cells occurred, followed by a rise to the total previous to the inoculation as the condition of the blood improved. A full record of the three most important varieties of white cells are given, but the only noteworthy feature is the absolute increase in larger hyaline cells, as met with in malarial fever. The animal showed the effects of each injection, but no more so than normal rabbits which received similar inoculations. When the animal was killed one month from the commencement of the experiment the sites of the quinine inoculations were represented as patches of scar tissue which were most obvious in the case of the excessive dose of 0·6 gramme given thirty days before the death of the animal. The results of the microscopical examination of the scar tissue were similar in

each instance. Fibro-myositis—necrosed muscular tissue—scattered round celled inflammation, well shown as a perivascular effect—and small foci of polynuclear inflammation were the conspicuous features of the various lesions. To quote this experiment is sufficient for the purpose intended, as it is definitely shown that quinine when given by the intra-muscular route in con-

Dates	Weights	Red cells per c.mm.	H.B.	C.I. (Colour-Index)	Leuco-cytes per c.mm.	Differential count of leucocytes. 1st column = %, 2nd column = no. per c.mm. Nucleated red cells. No. % of leucocytes	Finely granular oxyphil 1	Finely granular oxyphil 2	Lympho-cytes 1	Lympho-cytes 2	Large hyalines 1	Large hyalines 2	Doses of quinine bi-hydrochloride in saline. Total bulk injected on each occasion = 1 c.c.
29/5/18	1510 grms.	6,000,000	100 %	0·8	7500	0	21·9	1642	76·0	5700	0	0	
30/5/18	1490 ,,	—	—	—	—	—	—	—	—	—	—	—	0·25 gramme
31/5/18	1490 ,,	—	—	—	—	—	—	—	—	—	—	—	0·45 ,,
1/6/18	1510 ,,	6,000,000	100 %	0·8	6400	0	32·6	2086	66·0	4224	0·6	38	0·6 ,,
2/6/18	1515 ,,	—	88 %	—	—	0	13·0	—	85·3	—	1·0	—	0·45 ,,
3/6/18	1445 ,,	4,300,000	50 %	0·5	7200	6·0	20·0	1440	79·3	5709	0	0	
4/6/18	1400 ,,	1,500,000	32 %	1·0	5000	7·0	27·0	1350	72·3	3615	0·6	30	0·09 ,,
5/6/18	1400 ,,	1,500,000	32 %	1·0	4500	2·0	34·0	1530	65·3	2938	0	0	
6/6/18	1390 ,,	2,000,000	36 %	0·9	5200	1·0	55·0	2860	44·6	2319	0	0	0·045 ,,
7/6/18	1300 ,,	2,056,250	40 %	1·0	5400	4·0	34·3	1812	56·6	3056	4·3	232	
8/6/18	1330 ,,	2,170,000	35 %	0·8	5000	16·5	60·0	3000	40·0	2000	0	0	0·15 ,,
9/6/18	1335 ,,	3,280,000	65 %	1·0	4900	10·0	30·0	1470	69·0	3381	1·0	49	
10/6/18	1365 ,,	3,290,000	65 %	0·9	6800	2·5	32·0	2176	67·5	4590	0·5	34	
11/6/18	1320 ,,	4,200,000	66 %	0·7	7260	2·0	42·0	3024	55·0	3960	2·0	144	
12/6/18	1350 ,,	4,290,000	65 %	0·7	7280	2·0	29·0	1988	66·0	4752	5·0	360	
30/6/18	1610 ,,	4,496,875	82 %	0·9	7220	0	31·0	1532	58·0	4176	9·0	648	

centrated and massive doses excites no greater reaction in the tissue of animals rendered anaemic than in the case of the normal, while no general effect occurred even when the inoculations were made on successive days. Other experiments completed on these lines led to similar conclusions. One rabbit,

in which a severe experimental anaemia had been induced, received two massive intra-muscular doses of quinine during the period of haemoglobinuria, but the effects were similar to those obtained in the control animals, while a diminution in the total leucocytes was recorded.

Human Muscle.

Muscle tissue from the region of a previous quinine inoculation has been examined from several cases in this Command. The interval between the inoculation and the examination varied from so short a period as one hour up to three months. It has been suggested that the effects of quinine on the tissues is not capable of demonstration until twenty-four hours from the time of the inoculation. This view is erroneous on experimental evidence while it is equally fallacious in the case of a human subject. A man, comatose from malarial fever, was admitted to hospital, an intra-muscular injection of twenty grains of bi-hydrochloride of quinine was given, but the patient died one hour later. At the autopsy a large area of black green necrosis about four by four inches surrounded by gelatinous oedema was discovered at the seat of inoculation. All cases which I have had the opportunity to examine have received concentrated quinine. Experimentally, quinine injections can be given and the autopsy performed immediately, but the neurotic action is quite obvious. No detailed description of the microscopical changes will be given in this section except such as refer to points of special importance. Certain cases of special interest will be briefly referred to so as to illustrate the most essential features as regards quinine inoculation. Twelve grains of bi-hydrochloride of quinine were injected into the right buttock forty-eight hours before death. At the autopsy a large area of complete necrosis of muscle was observed together with a wide tract of haemorrhage due, as was proved on microscopical examination, to complete destruction of the wall of a large artery. The entire necrosed muscular tissue together with that tissue in immediate contact was examined chemically, except for a small portion reserved for microscopy, but no quinine was detected. Two intra-muscular injections of fifteen and twenty grains respectively had been made at an interval of twenty-four hours and death occurred about twenty hours later. The resulting lesion was similar in each case—large area of necrosis, a band of haemorrhage and congestion, with a wide tract of gelatinous oedema.

In the case of a Greek labourer who had received an intra-muscular injection of fifteen grains of bi-hydrochloride of quinine twenty-two hours before death, only 0·02 gramme of the alkaloid was obtained from a large area of necrosis at the seat of the inoculation. The absorption here was rapid in spite of the fact that the patient was dying from fulminating pneumococcal septicaemia.

Certain cases of malarial fever with malarial parasites present in the circulating blood were complicated with blackwater fever, but the effects from intra-muscular injections of bi-hydrochloride of quinine were similar to those

observed in the uncomplicated cases, except that the haemorrhagic zone appeared darker in colour, almost black in some instances (Pl. III, Fig. 6).

One of the most important cases which illustrate the action of quinine occurred in the case of a man who died from blackwater fever and malaria. Four days before death he received an intra-muscular injection of twenty grains of bi-hydrochloride of quinine. The inoculation was made into the same buttock which had been injected three months previously with a similar dose for malarial fever. This man had complained of aching and cramping pains in the buttock at the site of the inoculation, especially if he sat for any length of time on a hard seat or had prolonged exercise. At the autopsy intense necrosis had occurred at the site of the recent injection which merged into the old lesion, which showed dense fibrous tissue at the centre of the focus, and a definite broad band of fibrous myositis at the periphery. Acute polynuclear inflammation from the recent injection had extended to this layer of fibrous myositis. The pain referred to could be explained by the patch of dense fibrous tissue in the centre of an important muscle surrounded by a zone of fibrous myositis, but further, owing to a fibro-neuritis which existed in this area. Some of the nerves of the muscle were surrounded by dense fibrous tissue, and similar foreign tissue had replaced many of the nerve fibres. Similar examples were met with in cases of much shorter duration, and also experimentally, a fibro-myositis, and fibro-neuritis.

A patient was admitted to hospital with malignant malaria. He received an intra-muscular injection of 1·33 grammes of bi-hydrochloride of quinine but died two hours later. The whole of the necrotic tissue, which was three inches square, surrounded by oedema, was removed for chemical investigation except for a small portion reserved for microscopy. There was extensive necrosis of muscle, necrosis of the walls of blood vessels, marked evidence of haemolysis, but no acute inflammation was present.

Although the patient was inoculated when *in extremis*, only 0·344 gramme of alkaloidal quinine was extracted from the tissues.

The fact that necrosis of the tissues always accompanies the intra-muscular or subcutaneous injections of quinine is not realised sufficiently by Medical Officers, even those who have employed these methods on a large scale. No better illustration of the correctness of this statement can be furnished, than by quoting the following instance. Owing to certain bad results which had occurred from intra-muscular injections of quinine, an Army order was issued to the effect that all Divisional Officers must report in detail to the D.M.S. any ill effects subsequent to intra-muscular injections of quinine. One Divisional Officer after fifteen months' experience of this method of treatment of malaria furnished a report to the D.M.S. to the effect that a man had died from malaria and at the post-mortem examination a wide area of necrosis of muscle was found at the seat of injection. He concluded his evidence with the statement that all Medical Officers in his unit had been warned of this unfortunate incident and that every effort would be made to prevent a

recurrence of this disaster! I have discussed the question of quinine necrosis with innumerable Medical Officers who have had wide experience of intra-muscular injections of quinine and it is by no means uncommon to learn from them that they were unaware that such effects occurred in the tissues apart from negligence. It is this lack of knowledge of the methods of quinine administration which serves to explain the cause of many of the disasters which have occurred. It is, therefore, necessary to emphasize that quinine injections should not be given in the vicinity of large nerve trunks, or main arteries, that the injections should not be repeated in the same area of muscular tissue and that this method of quinine administration should only be employed when circumstances demand it[1].

The chief complications of intra-muscular injections of quinine in the human subject during 1916–17 and '18 of which I have records were as follows: (1) Tetanus, (2) Gangrene, (3) Abscess formation, (4) Pyaemia, (5) Nerve Palsies, (6) Haemorrhage from large Arteries, (7) Sciatica, (8) Chronic muscular pain, (9) Pain and deficient movements in affected muscles, (10) Thrombosis in varicose veins.

The Results of the Estimation of Quinine Alkaloid in Human Muscle subsequent to Quinine Injections.

No. 1, Broncho-pneumonia. Intra-muscular injections of 21 grains of bihydrochloride of quinine into left buttock. Two days later 26 grains were injected on the opposite side. Death on the following day. Amount of quinine alkaloid recovered from first injection, 0·227 gramme, and from the second injection, 0·345 gramme.

No. 2, Malignant malaria. Intra-muscular injection of 15 grains of bihydrochloride of quinine. Death four days later. Amount of quinine alkaloid recovered, 0·002 gramme. This patient had received ten intra-muscular injections in fourteen days amounting to 115 grains, and six intra-venous injections which totalled 55 grains.

No. 3, Malignant malaria. Intra-muscular injection of 10 grains of bihydrochloride of quinine. Death three days later. Amount of quinine alkaloid recovered from muscle, 0·0115 gramme.

No. 4, Lobar pneumonia. Intra-muscular injection of 15 grains of bihydrochloride of quinine. Death 24 hours later. Amount of quinine alkaloid recovered from muscle, 0·048 gramme.

No. 5, Malignant malaria. Intra-muscular injection of 18 grains of sulphate of quinine. Ten days later large quantity of pus evacuated. From 50 c.c. of the pus, 0·0012 gramme of quinine alkaloid was obtained.

No. 6, Malignant malaria. Intra-muscular injection of 10 grains of bihydrochloride of quinine. Death 26 hours later. Amount of quinine alkaloid recovered from muscle, 0·041 gramme.

[1] The oral method of administration of quinine is greatly neglected by some medical officers who are placed in charge of cases of malarial fever.

No. 7, Malignant malaria. Intra-muscular injection of 20 grains of bi-hydrochloride of quinine. Death 2 hours later. Amount of quinine alkaloid recovered from muscle, 0·344 gramme.

No. 8, Lobar pneumonia, Pneumococcal meningitis. Intra-muscular injection of 15 grains of bi-hydrochloride of quinine. Death 20 hours later. Amount of quinine alkaloid recovered from muscles, 0·0215 gramme.

In every instance the quinine was injected into the muscles in concentrated solution—the total quantity of fluid injected did not amount to more than a few c.c. The results show, however, that the absorption was rapid, as only traces of quinine were recovered from the entire lesions, apart from a small focus which was reserved for microscopy, and from the surrounding muscular tissue. In No. 7, 20 grains of the bi-hydrochloride of quinine were injected into the muscles, and the patient died two hours later, but only 0·3 gramme was recovered. In each instance the area of necrosis was considerable, and the tissues showed very marked changes on microscopical examination.

AN EXAMINATION OF MUSCLE TISSUE NECROSED FROM QUININE INJECTIONS FOR THE PRESENCE OF MALARIAL PARASITES.

Certain specimens of muscular tissue which had been examined for the presence of malarial parasites subsequent to the injections of quinine showed most unexpected results. The blood cells in the necrotic vessels were completely haemolysed, yet malarial parasites were present in some instances in relatively large numbers and the bodies of the parasites were well stained. The parasites would be diminished in numbers as compared with the control muscle from another area of the body or from some visceral lesions, but perfectly staining parasites were found lying in a necrosed vessel in which there were no normal red cells. It is strong evidence that destruction of red cells and tissues generally is much more readily excited by quinine solutions than malarial parasites.

One case will be referred to in detail to emphasize this fact:

Malignant Malaria.

Blood film showed a very heavy infection of red cells with the ring form of parasites. Sporulating parasites were also numerous. Time 10.30 a.m.

20 grains of bi-hydrochloride of quinine were injected intra-muscularly at 11 a.m. and 20 grains were injected intra-venously. Death at 3.45 p.m. on same day.

Wide areas of necrosis of muscle at the seat of the quinine injection existed. There was great destruction of the walls of blood vessels and the blood cells were completely lysed, while the muscle tissue itself showed considerable necrosis. Large dot parasites with well-stained bodies and abundance of pigment were relatively numerous lying among the red cell *débris*. Parasites

however were far more numerous in the internal organs and in other muscular areas.

Intra-muscular Injection into Frogs.

Several frogs received intra-muscular injections of quinine bi-hydrochloride in saline in suitable doses for body weight, and were killed three hours later. The muscles at the sites of the quinine injections were opaque. There was marked oedema, complete necrosis of muscle fibres, other fibres vacuolated or represented as granular masses and haemolysis of red cells in the affected areas.

Four frogs with an average weight of 60 grammes were injected (I.M.) with quinine and the resulting lesions were as follows:

1. Frog injected with 0·0004 gramme of quinine bi-hydrochloride (0·1 c.c.) and killed 22 hours later. Muscles opaque and showed extensive necrosis.

2. Frog injected with 0·0004 gramme of alkaloid in 0·02 c.c. of ether and killed 22 hours later. Extensive muscular necrosis. Slight inflammatory reaction.

3. Quinine injection as in case of frog 1. Animal killed 3 days later. Extensive muscular necrosis—abundant haemorrhages—and widespread inflammation were very evident.

4. Frog injected with 0·0004 gramme of the alkaloid suspended in saline and killed 3 days later. Results similar to Experiment 3.

These results were similar to those obtained in the case of the warm-blooded animals.

CONCLUSIONS.

(1) Concentrated preparations of quinine produce more intense necrosis than dilute, but dilute preparations such as are of practical utility excite oedema and necrosis at the seat of inoculation. The difference between these two methods of quinine inoculation is not of sufficient value to justify active opposition to the method commonly employed.

Inoculation of quinine in solutions so dilute as to avoid oedema and tissue necrosis is not of practical utility in the human subject.

(2) A concentrated solution of quinine is absorbed rapidly from the tissues as shown by chemical analysis even in patients who are *in extremis*. It is not apparently stored as such in liver, kidneys, or heart muscle.

(3) It is essential to realise that tissue necrosis—spreading oedema and local blood destruction—are produced by the solvents employed for quinine administration and the effects are only slightly inferior to those excited by quinine salts and the alkaloid.

(4) No advantage was obtained by the addition of olive oil or fat or by injecting the alkaloid dissolved in alcohol, or ether, whether in concentrated or in a dilute solution.

(5) Tissue necrosis occurs immediately and persists for a considerable period. In some instances the fibro-myositis which results is associated with

a fibro-neuritis which causes various symptoms definitely related to the pathological processes.

(6) Necrosis of blood vessels in the area of inoculation is a common result. This leads to small haemorrhages into the tissues, and has caused severe haemorrhages in the human subject, and experimentally, from rupture of a large vessel. The destruction of the vessel wall is associated with an accompanying thrombosis.

(7) An extensive necrosis produced by an intra-muscular injection of quinine, in the neighbourhood of an important nerve trunk, may result in nerve palsy. Experimentally, complete degeneration of the great sciatic and other nerves has been produced apart from any direct injury to the nerve at the time of the inoculation. In the human subject this disastrous result may be due to spreading oedema and extensive tissue necrosis.

(8) Experimentally, no leucocytosis has ever occurred from quinine injections; on the other hand a leucopenia may develop while an increase of large hyaline cells has been recorded on several occasions.

(9) No essential differences in the degree of tissue necrosis from intra-muscular injections of quinine in malarial fever or malarial fever associated with blackwater fever were observed.

(10) Repeated intra-muscular injections of quinine should not be given into the same area of muscle, or tissue directly adjacent, as otherwise permanent injury of muscle[1] or nerves may occur.

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To Captain Moir, A.V.C., Bacteriologist to the A.V.C., B.S.F., I am indebted for considerable help in the investigation of the cast mules and horses which were inoculated with quinine.

Captain A. Wilkin, R.A.M.C., rendered me valuable assistance during the process of the work.

The tissue from human sources has been procured for me by various bacteriologists in the Command, to whom my thanks are due.

To Corporal P. Panichelli, M.S.M., R.A.M.C. (T.F.), I am indebted for the illustrations which serve to explain what the text is incapable of defining.

[1] The gluteal regions, obtained from a man who had daily intra-muscular injections of quinine, nine in all, were shown at the British Medical Association meeting in London, 1919. As a result of the injections wide tracts of muscle were necrosed and only fragments of healthy tissue remained.

DESCRIPTION OF PLATE III.

Fig. 1. *Quinine rabbit*, 53–(4). Section of muscle from a rabbit which had received an intra-muscular injection of 0·04 gramme of alkaloid quinine in 1 c.c. of alcohol four days before death.

Fig. 2. Agglutination of red blood corpuscles in a large vessel in the tissue of a horse which had been injected with 1·1 gramme of bi-hydrochloride of quinine 30 hours previously.

Fig. 3. Complete necrosis of large artery as a result of an intra-muscular injection of quinine alkaloid in brandy.

Fig. 4. Section of great sciatic nerve in a rabbit which had received an intra-muscular injection of 1 grain of quinine alkaloid in alcohol 11 days previously.

Fig. 5. Muscle from a mule which had received 2·25 grammes of bi-hydrochloride of quinine in 5 c.c. of saline five days before death. Natural size.

A. Oedema, necrosis, patches of haemorrhage.
B. Haemorrhagic line showing intense inflammation.
C. Oedematous muscle.

Fig. 6. Portion of human muscle from a case of Blackwater Fever and Malaria. Patient had received an intra-muscular injection of 20 grains of bi-hydrochloride of quinine 48 hours before death. Natural size.

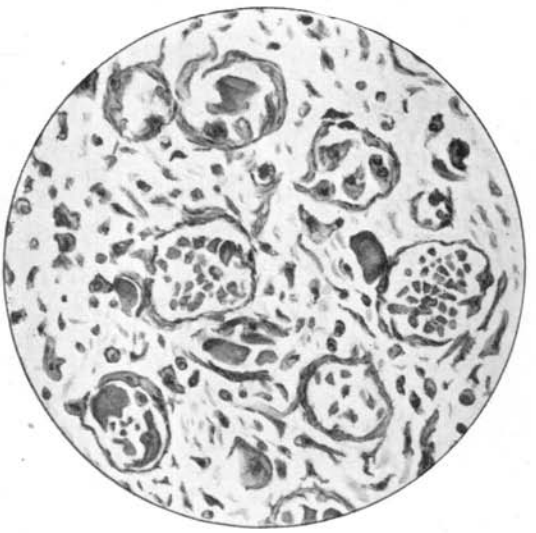

Fig. 1

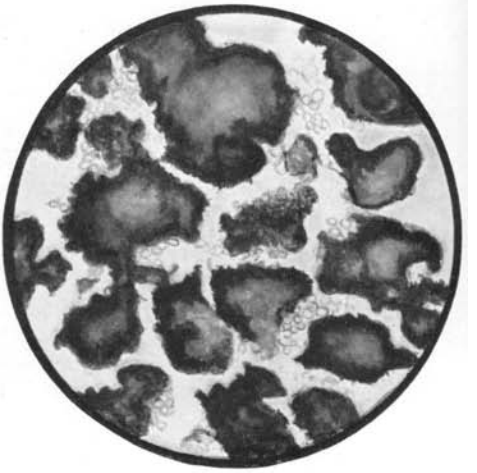

Fig. 2

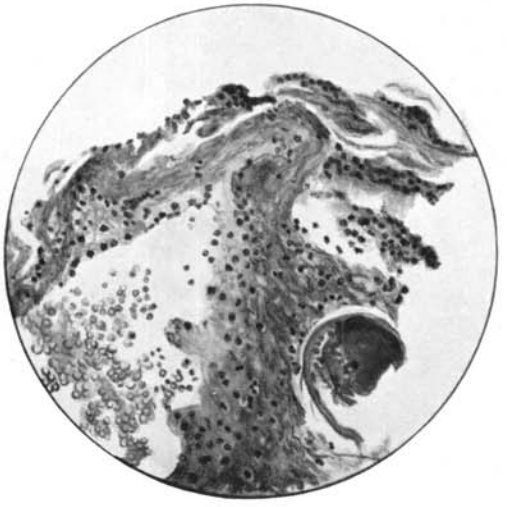

Fig. 3

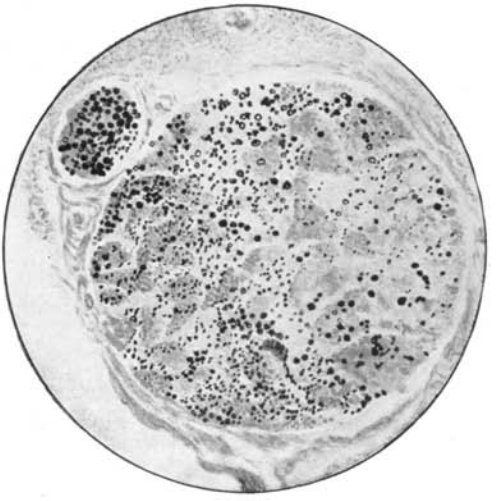

Fig. 4

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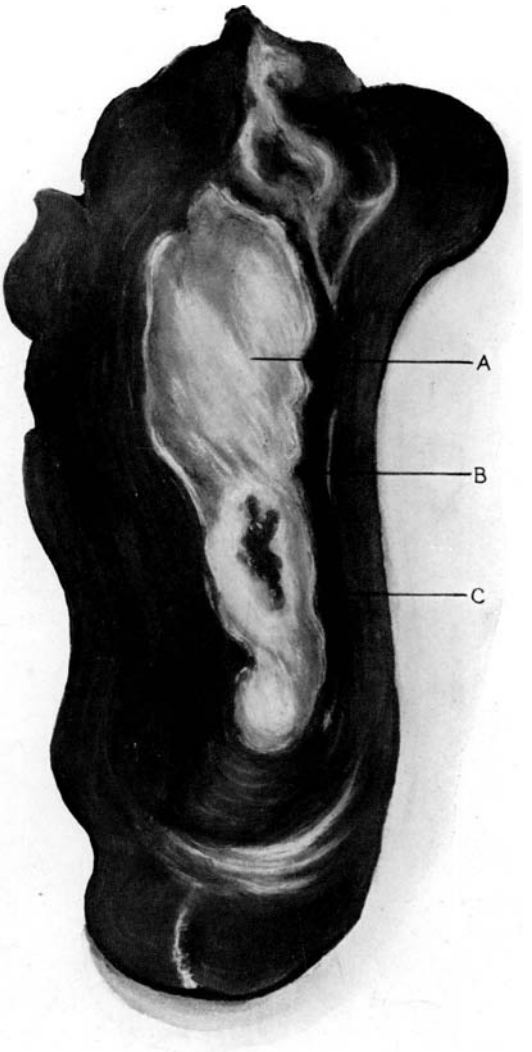

Fig. 5

Fig. 6

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