OBSERVATIONS ON INFECTION BY PLASMODIUM KNOWLESI (APE MALARIA) IN THE TREATMENT OF GENERAL PARALYSIS OF THE INSANE

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This investigation was directed towards overcoming certain well-known difficulties associated with the induction of benign tertian malaria for the treatment of general paralysis of the insane. The principal disadvantages of the existing method may be summarized as follows. The average clinician resident in cool climates is frequently unable to obtain a specimen of infected blood at very short notice, and much valuable time may thereby be lost in commencing the treatment of an early case. Yet again, when blood has been obtained there is a temptation to seize the opportunity of treating several other cases resident in the district by the transference of blood from one patient to another, a procedure which is only

three human volunteers in India. We have investigated the practical applicability of substituting this type of parasite for *Plasmodium vivax* in the treatment of G.P.I., and the following cases illustrate the application of this form of infection in the treatment of the disease. Clinical notes concerning the course of ape malaria occurring in man, the action of certain antimalarial remedies on this type of infection, and various experimental data are also incorporated.

The work has been carried out with a strain of parasite originally obtained from the Malaria Survey of India, and which was supplied to us by the courtesy of Sir Rickard Christophers of London, to whom we owe our thanks.

Case I

History.—The patient was a male aged 63, a coal miner. He had been physically a powerful man, whose strength had been ruined by excess. He was a noted alcoholic in his district, consuming a bottle of whisky daily during the week-ends, and had done so for years. He had become excited, very noisy, and confused, with grandiose delusions which led him to be exceedingly stubborn and resistant to any treatment. For the last twelve months he had been under the care of his own doctor as a cardiac case.

Examination.—This showed a well-built individual, with the skin clean and clear, and with marked arteriosclerosis of radial and ulnar arteries. The cardiac sounds were feeble, and there was a blowing first sound propagated into the axilla, with distinct accentuation of the second sound. The pulse was 71 and irregular in time and force. Signs of chronic bronchitis were present. As regards the alimentary system

CHART 1.—A two-hourly temperature chart of Case I, showing pyrexia of quotidian type. Inoculation with 3 c.cm. infected blood was made six days before the chart begins. Antimalarial treatment commenced at day 13. A = atebryn given. Q = quinine started. N.E. = no examination for parasites.

to be condemned. Apart from the fact that the practice of this method is liable to transmit other coexisting infections, successive passage of the parasites from one individual to another results in progressive attenuation of their virulence. Thus each subsequent patient treated has milder febrile reactions, and accordingly derives less and less benefit from this mode of therapy.

From the purely theoretical standpoint the ideal method of infecting each patient is by subjecting him to the bite of an infected *Anopheles* mosquito. Alternatively, he can be injected with blood from a case of naturally acquired malaria with a negative Wassermann reaction, both of which requirements offer a formidable obstacle to many clinicians. These two methods do, nevertheless, offer the only available means whereby malaria therapy could be instituted in disseminated sclerosis and other conditions in which the introduction of Wassermann positive sera is deemed undesirable.

In view of these considerations we have employed in the treatment of general paralysis of the insane the naturally occurring ape malaria parasite *Plasmodium knowlesi* (Sinton and Mulligan, 1932), which we have successfully transmitted to twelve human subjects. The pathogenicity of *P. knowlesi* to man has already been demonstrated by Knowles and Gupta (1932), who infected

there was nothing of note, except that the patient had a very poor appetite, and had a right-sided inguinal hernia, which was reducible. Examination of the nervous system gave the following data. Ankle- and knee-jerks exaggerated; wrist and elbow reflex strongly positive; plantar responses normal; abdominal reflex negative. There was irregularity of the pupils, and the Argyll Robertson sign was positive. Coarse tremor of the tongue and slurred speech were noticeable. The Wassermann reaction was negative. The specific gravity of the urine was 1024, with no abnormal constituents.

Treatment.—Accordingly 3 c.cm. of infected monkey blood was injected intramuscularly into the deltoid muscle on April 23rd, and two-hourly charting of temperature, pulse, and respirations was instituted. From the time of inoculation there was a sharp fall in temperature to an average of 97° F., with a rise to normal on the second day after injection. At this time blood films were made and examined, but proved to be negative.

Progress.—**Seventh day:** On the morning of this day at 2 o'clock the temperature had risen to 99.4°, but had fallen to normal by 6 a.m. There was no marked constitutional upset, and no sweating with the fall in temperature. By 10 p.m., however, the temperature had risen to 100°, when the patient was flushed and considerably excited. By midnight the temperature had dropped four points. **Eighth day:** Pyrexia progressively fell to 96° by 2 p.m., and this was

followed by a sharp rise to 98° at 4 p.m., and a further rise to 102.6° at midnight. The patient was somewhat distressed, and was very confused and excited. *Ninth day*: He was vigorously sponged, and by 2 a.m. the temperature had fallen to 99.6° , to be followed by a slight rise to 100° at 4 a.m., and a further fall to 96.8° by 8 a.m. The patient was quiet at this time, cheerful, and quite comfortable. Urine examination revealed no abnormal constituents. At midnight, however, the temperature had again reached 101.4° , when he was very noisy and excited. *Tenth day*: Vigorous sponging again resulted in a fall to 98.8° by 2 a.m., which continued to fall to 96.6° by 6 a.m., and was accompanied by profuse sweating. At midnight another rise to 102.4° occurred, and was accompanied by the same increase in mental excitement and confusion. The patient was highly resistant to anything being done for him, but after sponging again the temperature fell to 100° by 4 a.m. *Eleventh day*: The temperature continued to fall, as during the previous twenty-four hours, and was accompanied by profuse sweating. It was 97° by 4 p.m. The patient was quiet and appeared exhausted. He was submissive to treatment and quite coherent in speech. Examination of the urine again revealed no abnormalities. At midnight the temperature rose to 102.2° , when the patient was almost uncontrollable, being very excited and restless, and striking out at those around him. *Twelfth day*: Instead of falling the temperature rose to 102.8° by 2 a.m., when the patient was cold-sponged, and had 10 grains of aspirin administered. The pulse at this time was 104, and very irregular in time and force. Following the administration of aspirin the temperature again fell to 98.4° by 6 a.m., and the patient appeared very tired, quite quiet, and coherent in speech. He was afebrile for the rest of the day. *Thirteenth day*: On this occasion the temperature rose to 103.4° at 2 a.m., and despite cold-sponging and 10 grains of aspirin this level was maintained for an interval of four hours until 6 a.m., when it fell sharply to 97.6° by 8 a.m., being again accompanied by profuse sweating. The patient, seen at 9 a.m., was very exhausted, and the pulse rate was 108 per minute and exceedingly irregular in time and force. There was also marked accentuation of the cardiac murmurs. Digitalis, 10 minims, was administered three-hourly from this time onwards.

Further Progress.—Having duly considered the patient's reaction to this form of therapy it was decided, in view of the cardiac condition, that it would be necessary to discontinue further rigors. An initial dose of $1\frac{1}{2}$ grains of atebirin was therefore given at 2 p.m., which was followed by a further $1\frac{1}{2}$ grains at 8 p.m. *Fourteenth day*: Despite atebirin the temperature rose to 104.4° at 4 a.m. and was maintained until 6 a.m. The patient appeared very weak and exhausted, having a feeble and irregular pulse rate of 80 per minute: strychnine hydrochloride ($1/60$ of a grain) was next injected hypodermically and brandy administered freely. *Fifteenth day*: Although atebirin had been given at 8 p.m. on the previous evening, at 6 a.m. the temperature suddenly rose to 104.2° , and thereafter fell rapidly to 96° during the ensuing twelve hours. During this period two further atebirin tablets were given orally, and two-hourly charting discontinued in order to give the patient more sleep. *Sixteenth day*: At 10 a.m. the temperature again showed a tendency to rise abruptly, and when it had recorded 101.2° quinine dihydrochloride ($7\frac{1}{2}$ grains) was injected intramuscularly into the gluteal region and a similar quantity of the sulphate was given orally. Subsequent to the administration of quinine there was a sharp fall to 96° at 5 p.m., and at 7 p.m. a collapse reading was recorded and $1/60$ grain of strychnine was injected hypodermically. The collapse reading was recorded for the next forty-eight hours. From this time the temperature gradually returned to normal, the patient being dosed daily with 3 grains of atebirin and $1/2$ grain of plasmoquine, while at the same time he was steadily digitalized. Two doses of quinine sulphate, 10 grains, were also given orally. There was a slight tendency to relapses on the twenty-third and twenty-sixth days, both of which were easily checked by plasmoquine.

Result.—The patient's recovery could only be described as remarkable, for within ten days from the cessation of treatment he was as fit as on admission, and careful physical examination revealed that he had not suffered any aggrava-

tion of the previous cardiac condition present, or involvement of any other system as a result of the treatment. At present he is eating heartily and reading the daily newspapers with interest. He can now for the first time since admission accurately recall past incidents which occurred twenty-six years ago, his speech is much clearer, and his grandiose delusions have disappeared. He is much more amenable to treatment, and only appears a little confused on waking from a heavy sleep. His son states that his mental and physical state appear to be better than they had been for the previous twelve months.

Case II

History.—This patient was under the care of Dr. Batchelor at the Royal Infirmary, Edinburgh. He was a man aged 53 years, who had contracted syphilis in 1919. From 1930 to 1933 he had complained of tingling and weakness of his left foot, which was followed in 1934 by loss of motor power in the left arm and same side of the face. These symptoms were accompanied by mental depression with insomnia, as well as by the presence of an ataxic gait. At this stage knee-, ankle-, and triceps-jerks were absent, the abdominal reflexes active, and there was some loss of tactile sense in the left hand and foot. Blood pressure was 100/60, and during 1934 he had received a further course of anti-syphilitic remedies.

Treatment and Progress.—This individual was inoculated intravenously on June 21st, 1935, with 3 c.cm. of infected monkey's blood. After an incubation period of six days his temperature rose sharply to 101° F., and thereafter rigors occurred at twenty-four-hour intervals with great regularity, and the temperature chart of this patient (see Chart 2) closely resembled that of Case I. Attacks generally developed in the evenings, and the highest temperature recorded

CHART 2.—Showing a four-hourly temperature chart of Case II. Inoculation took place six days before the chart begins. Day 1 is actually June 27th, 1935.

attained 104.4° . After nine rigors had taken place the number of parasites seen in the patient's blood was estimated to be 205 per microscopical field, and it was accordingly decided to terminate the infection. This was carried out by administering a preliminary intramuscular dose of 10 grains of quinine dihydrochloride, followed by 10 grains of the sulphate given three times a day orally. During the next three days parasites rapidly disappeared from the blood, and the infection was successfully exterminated.

Survey of Twelve Cases of Ape Malaria Infection in Man

Ten human individuals were successfully inoculated with *P. knowlesi*, and these cases will be referred to in the subsequent text as Cases III, IV, etc., up to XII. Although the course of the disease was found to be similar in these patients to that reported in Cases I and II, minor individual variations were met with. For example, the incubation period was found to be as short as three days in two instances and as long as fourteen days in two others, but in the majority of the patients the first rise of temperature occurred after the eighth day, and parasites appeared in the peripheral blood at about the tenth day.

Marked variability was also found to exist among the patients studied with regard to the degree of susceptibility to infection with this type of parasite. Thus, whereas the majority were readily infected with monkey's blood and

parasites progressively multiplied in their blood, a few were more resistant, for the infection failed to establish itself in these subjects. The latter feature was particularly noticeable in the case of three patients who had previously received a course of *P. vivax* (benign tertian) malaria therapy a year before, and in whom ape malaria could only be reproduced with difficulty.

Patients were inoculated intramuscularly as well as intravenously with 5 c.cm. of defibrinated monkey's blood obtained by cardiac puncture from an anaesthetized monkey. Both routes of inoculation effectively conveyed the infection, but the intravenous method proved to be the most satisfactory. Temperature in these cases was generally of the quotidian type, which usually occurred at night and seldom rose to over 104° F. In a few of the cases a double rise of temperature occurred within the twenty-four hours, and the highest temperature reached was 104.5°, which was maintained for four hours. Rigors were, as a whole, less severe than those due to human malaria infection, and it is noteworthy that observations on the Arneith polymorphonuclear leucocyte count ascertained during the height of the infection showed a marked shift to the left, without the presence of a leucocytosis in the patient's blood.

Owing to the shortness of time during which we have observed the cases treated by *P. knowlesi* infection it is impossible to assess the value of this mode of therapy. Preliminary work, however, indicates that the ape parasite may ultimately prove to be an effective substitute for *P. vivax* in the treatment of G.P.I. In view of the mild nature of the infection which it produces in the human subject it appears to be eminently suitable for the treatment of elderly debilitated patients.

Clinical Effects

From observation of the foregoing cases some matters of clinical importance have been noted. Two-hourly charting is of paramount importance, for with four-hourly recording of the temperature the sudden onset and fall in temperature is liable to be missed. It should be noted that the rigors are moderately severe in nature, and cause considerable constitutional upset, and we recommend that this form of malaria therapy should be carried out in a hospital or institution where close personal contact is obtainable between the patient and the physician.

It would appear that digitalization of the patient is of great benefit, not only in cases where there is a grave cardiac lesion, but also where there is a possibility that the rigors may reveal latent circulatory damage. Ordinary standardized *B.P.* tincture has been used in these cases, but where there was any difficulty in tolerance, as in some cases, we have overcome this by using one of the trade preparations of the drug. We do not think there is any contraindication to this form of malarial treatment in cardiac cases unless the lesion is so grave—for example, auricular fibrillation—as to make treatment obviously impracticable. If signs of cardiac failure appear strychnine, hypodermically, in doses of 1/60 grain of the hydrochloride is recommended, on account both of its ease in administration and of its prolonged effect, as compared with adrenaline. We have found that brandy given in 1/2 ounce doses in hot water has proved a very useful prop to a failing pulse, and has been welcomed by the patient both for its strengthening and for its soporific effects. Diet in such cases should give no trouble. During the treatment patients were kept on ordinary light meals, such as soup, fish, a little meat, milk, eggs, etc., whilst fluids were given freely and as often as the patients demanded them. It was found that during the

severe rises of temperature dryness of the throat caused considerable distress, but this was easily relieved by the administration of a little glycerin in water. Teaspoonful doses of castor oil every second day kept the bowels free, and at no time was there the slightest hint of gastro-intestinal upset.

Antimalarial Remedies

These observations are of interest, for we have found that atebirin has little or no effect on reduction of temperature or destruction of parasites during the acute stage, but would appear to be—alone or in conjunction with plasmoquine—a satisfactory drug for prevention of relapses during the convalescent period. On the other hand, there seems to be no doubt that quinine *per se* is the ideal drug for termination of these rigors. It rapidly causes a fall in temperature, and at the same time an almost dramatic destruction of parasites. Thus by careful observation of the patient and prompt administration of quinine there should be no possibility of the rigors going beyond control of the physician in charge. In no single case have we observed the occurrence of cerebral symptoms.

We would also point out that a comparatively small dose—namely, 7½ grains of the dihydrochloride intramuscularly with an equal amount of sulphate orally—is all that is required. Convalescence was quite uneventful. To prevent relapses a daily dose of 3 grains of atebirin with 1/2 grain of plasmoquine was given over a period of ten days, and during this time 10 grains of quinine sulphate were administered orally as a precautionary measure. To supplement atebirin and plasmoquine, digitalization was carried on for fourteen days, the dose being gradually reduced, and on the sixteenth day the patient was allowed out of bed.

Finally, it should be understood that these cases were nursed in an ordinary mental hospital ward, with no elaborate seclusion, screening, or other method; and that if given careful nursing, accurate charting, and regular observation by the medical officer, any risk in therapy appears to be reduced to a minimum.

Rate of Multiplication of *Plasmodium knowlesi* In Human Blood

Blood films were made at daily intervals from cases under treatment stained by Leishman's stain, and examined for the presence of parasites. The figures referred to in the text represent the number of parasites counted per field when examined under a × 600 magnification. Thus it was observed in Case I that after a preliminary incubation period of eight days the patient developed his first rigor, parasites appearing in his blood on that day, when an average of one per field was detected among several examined. Thereafter their presence was continuously noticed in the patient's blood throughout his illness, and even persisted for two whole days after atebirin-quinine therapy had been instituted. On the twelfth day the number of parasites had increased to three per field, and a few schizonts containing merozoites were first noticed, but there was no enlargement of the erythrocytes. The ensuing two days showed a sudden rise in their rate of multiplication, for on the fourteenth day sixty-eight per field were observed, and after a transient fall in numbers to thirty-five per field they again rose no fewer than 121 per field on the fifteenth day following infection. At this stage examination of the patient's blood revealed that the red blood cells had fallen to 2,500,000 per c.mm. and a slight leucocytosis (15,000 per c.mm.) was present. No further observations were accordingly made on the blood until

after his physical condition had improved, following the administration of antimalarial remedies.

These experiences emphasize the advisability of terminating the infection by the administration of quinine after the eighth rigor, in order to eliminate any possibility of harmful effects. This point was further illustrated in Case II. The patient was permitted to undergo nine rigors, and his blood showed a parasite count of 205 per field at this stage of the condition.

Pigment in the Large Mononuclear Leucocytes

After the administration of quinine the number of parasites seen in peripheral blood steadily diminished, so that on the twenty-fifth day after infection none could be found in the patient's blood. At this time a differential white cell count revealed the following percentages of these cells: neutrophil polymorphs 48, basophils 5, eosinophils 1, large lymphocytes 8, small lymphocytes 10, and large mononuclears 28. Several of the latter contained heavy deposits of dark brown pigmented material similar to that observed in human malaria by early workers such as Guarneri and Bignami (see Marchiafava and Bignami—1894). There is no doubt that this pigment represents the remains of disintegrated parasites, for the large mononuclear cells contained ingested parasitized erythrocytes, and thus indicate the probable source of such material. Similar conclusions have been made with regard to the origin of the pigment in human malaria from the earliest of times, and Laveran (1893) alludes to "the existence of melaniferous cells which take possession of the debris of the parasitic elements and the pigment which they contain."

Transmissibility of *P. knowlesi*

In order to obtain experimental data, blood from Case III was injected into Case IV, and the disease successfully reproduced in this individual. Likewise the condition was serially propagated through three selected human subjects. It was also possible to reinfect the ape with human blood containing *P. knowlesi* after its serial passage through two human beings, and 5 c.cm. of blood from Case V proved infective to a healthy *M. rhesus* monkey (M.R. II) after ten days. It has been reported by Rowe *et alia* (1933)—also by Nauck (1934), who has investigated in great detail the susceptibility of *P. knowlesi* to chemotherapeutic agents such as atebirin, plasmoquine, and quinine—that atebirin acts as a powerful antimalarial remedy on the monkey suffering from *P. knowlesi* infection. One tablet of atebirin (0.1 gram) was accordingly given to the monkey orally, and three days later its blood contained less than one parasite per microscopical field among several examined. Eight weeks later, however, the animal relapsed, numerous parasites appeared in its blood, and despite the repeated administration of atebirin it died. It is of particular significance in this connexion that whereas atebirin appears to exert an antimalarial effect on *P. knowlesi* infection occurring in the monkey, it fails to have an analogous effect in combating similar infection of the human being. On the other hand, the powerful action of quinine dihydrochloride in the human case is of great interest, and this will be discussed in a later report. The foregoing experiments have demonstrated that *P. knowlesi* may be readily transmitted from monkey to man, man to man, or man to monkey with comparative ease.

Viability at 0° C.

On account of the practical importance of obtaining precise information regarding this aspect of the subject, it was decided to ascertain how long parasites would

remain viable in monkey blood when stored in an ice-chest. An infected *M. rhesus* monkey was accordingly deeply anaesthetized, and 12 c.cm. of blood withdrawn by cardiac puncture, placed in a sterile test tube containing glass beads, and defibrinated by gentle shaking. The blood was thereafter kept at 0° C. for eight days, after which 5 c.cm. was injected intramuscularly into Case IX, and the remaining 5 c.cm. replaced in the ice-chest for a further eight days, following which it was introduced into a healthy *rhesus* monkey (M.R. III). The results showed that the parasites retained their viability throughout his period, for they proved pathogenic to the human subject as well as to the ape, both of whom developed the characteristic disease. We have thus found that blood removed from an infected monkey and stored in an ice-chest at 0° C. retains its pathogenicity for the human individual for eight days and to the ape for sixteen days.

Advantages as a Pyrotherapeutic Remedy for G.P.I.

From the clinical standpoint four striking advances are immediately apparent. First, the inoculation period is a comparatively short one of eight to nine days, or even less. Secondly, the gentle onset of pyrexia and the gradual increase in temperature with each quotidian rigor are highly desirable features that facilitate the nursing and observation of these patients. Thirdly, pyrexia may be instantly terminated by the exhibition of quinine should any latent intercurrent infection become manifest during the course of therapy. The efficacy of quinine dihydrochloride is adequately illustrated in Cases I and II, as well as others which have not been described in detail; for as little as 7½ grains of the drug given intramuscularly is sufficient to deal with a massive infection. Fourthly, it should be remembered that blood obtained directly from the infected monkey, in contradistinction to that obtained from a case of G.P.I., is free from syphilitic infection, and is consequently available for the treatment of disseminated sclerosis and other conditions for which Wassermann-positive blood is deemed unsuitable. In conclusion, the viability of *P. knowlesi* at low temperatures renders it possible to store blood in an ice-chest and use it when required, the convenience of which will be immediately appreciated.

Summary and Conclusions

1. The naturally occurring malaria parasite of the monkey (*Plasmodium knowlesi*) has been transmitted to twelve human beings.
2. The infection has been communicated from one man to another in direct series, and three passages have been effectively carried out.
3. Ape malaria infection of man is characterized by an incubation period of three to fourteen days, followed by pyrexia of the quotidian type that usually occurs at nights. A double rise of temperature within twenty-four hours has also been observed.
4. A marked shift to the left of the Arneith polymorphonuclear leucocyte count has been noticed during the course of ape malaria in man.
5. The monkey parasite *P. knowlesi* has been successfully used for the treatment of general paralysis of the insane.
6. The data concerning the rate of multiplication of *P. knowlesi* in the human subject are recorded. Our findings indicate that it is inadvisable to continue the course of treatment after a patient has had eight rigors.
7. Although the drug atebirin acted specifically in the monkey, its administration failed to diminish the pyrexia or inhibit the multiplication of parasites in cases of human infection.

8. Quinine dihydrochloride exerts an immediate action on ape malaria infection in man, and a single intramuscular injection of $7\frac{1}{2}$ grains is sufficient to reduce fever within an hour.

9. Infected monkey's blood, when stored in an ice-chest at 0° C., retains its pathogenicity for the human subject for eight days and for the monkey for sixteen days.

Acknowledgements

We are indebted to Dr. J. H. C. Orr of Rosslynlee Asylum and to Dr. R. C. L. Batchelor of the Royal Infirmary, Edinburgh, for permission to publish the case notes referred to, and to Sir Rickard Christophers of the London School of Tropical Medicine and Hygiene for many helpful suggestions ;

also to Professor A. J. Clark of Edinburgh University and Professor E. G. Nauck of Hamburg Tropical Diseases Institute for information concerning the action of drugs.

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Clinical Memoranda

Absence of Pericardium

I am reporting this case of absence of the pericardium on account of its rarity.

CASE HISTORY

A male, aged 35 years, labourer, had been suffering from cardiac insufficiency for several years. When first seen, a few months before his death, he was suffering from heart failure. The pulse was regular and a bit rapid, and he was cyanosed and dyspnoeic. The cardiac pulsations were seen and felt all over the lower half of the left side of the chest, and the heart sounds were loud and heard practically all over the left side of the chest—from the front, back, and side. No definite murmurs were heard. There was marked expansion and retraction of the left side of the chest, and the case was diagnosed as one of adherent pericarditis. The patient was treated with digitalis, with little improvement. It was then decided to perform the operation of cardiolysis, but the patient died suddenly at the beginning of the anaesthesia.

PATHOLOGICAL FINDINGS

On post-mortem examination all the viscera were found to be the seat of marked chronic venous congestion. The heart

was found occupying nearly the lower half of the left side of the chest, compressing the lung upwards. The pericardial sac was absent, except for a small triangular piece at the emergence of the great vessels in front, and the heart was lying quite naked in the pleural cavity. There were no adhesions at all. The heart was quite smooth, and showed few small milk spots.

On removing it from the chest it was found to be nearly four times the size of a usual heart at that age. The enlargement was due to marked dilatation of all the chambers.

No valvular lesions were seen, and on the whole it did not show any abnormality except the dilatation. It weighed one kilogram.

COMMENT

As one of the functions of the pericardial sac is to prevent the dilatation of the heart during exertion, we can easily understand how this one became so markedly dilated.

Congenital absence of the pericardium occurs, but is of extreme rarity.

The photographs show the heart as seen from the front, with the small triangular piece of the pericardium seen *in situ* in Fig. 1 and reflected upwards in Fig. 2.

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