tenderness over the right lower ribs in front and over the right hypochondrium. There was no dullness, and no adventitious sounds could be heard at the right lung base. There was no abdominal hyperaesthesia. The diagnosis of diaphragmatic pleurisy was made and confirmed later by the development of dullness at the base of the right lung.

CASE III.

W. M., aged 20, on March 8th, 1921, suddenly felt a stabbing pain under the left collar-bone. The pain only lasted for half an hour, but came on again that night, and seemed to be worse on taking a deep breath. It gradually got worse, and by March 19th was fairly continuous. There was giddiness, vomiting, and also epigastric pain. When admitted to St. Mary's Hospital on March 19th the pain had become more precordial, and there was cyanosis. On March 21st a faint pericardial rub was heard just outside the sternum in the third left intercostal space. A few days after admission the patient still had a little left subclavicular pain.

CASE IV.

A man, aged 53, consulted me at the Bolingbroke Hospital (at Dr. Bradlaw's request) on account of severe gastric symptoms which proved to be due to a penetrating ulcer of the lesser curve of the stomach. I performed partial gastrectomy, and for a fortnight recovery was uneventful. The patient then complained of pain under the right clavicle, and a day or two later he had an attack of extreme pain in the right side of the abdomen, accompanied by sweating and vomiting. The pain under the right clavicle continued and was worse when he took a deep breath. When I examined him a little later there was extreme tenderness and muscular rigidity in the right hypochondrium, to such a degree that the resident officer at first thought there might have been a leakage from the stomach. But the tenderness was strictly limited to the right of the middle line, and there was not the slightest pain elicited on pressure to the left of the mid-line. This strict limitation of tenderness and rigidity, together with the presence of tenderness over the right lower chest and the complaint of subclavicular pain, made me think that the pain was one referred from the upper surface of the diaphragm. I concluded that there had been a small pulmonary infarct which had caused diaphragmatic pleurisy, and this view was borne out by the gradual clearing up of the symptoms. All during the time of the pain, except at the very onset, the patient had been able to take fluid and semi-fluid food well. I saw him a month later and he was perfectly well.

CASE V.

A man of 67 was admitted to St. Mary's Hospital in November, 1929, with symptoms of perforated gastric ulcer. At the operation I found general peritonitis due to leakage from an ulcer on the lesser curve of the stomach. The perforation had been sealed up and all that remained to be done was to oversew the ulcer. Convalescence was uneventful for two weeks, when the patient complained of pain in the left subclavicular region. I at once told the house-surgeon to be on the look out for left basal pleurisy. The pain continued and fever developed, and when I examined the chest a few days later there was decided dullness at the left base. An x-ray photograph of the chest did not show any evidence of subphrenic abscess. The dullness at the left base increased, and I explored the left chest and removed several ounces of clear fluid. Though he was better after this there was still subclavicular pain, and I was not perfectly satisfied that there was no collection of pus under the diaphragm. Therefore, under local anaesthesia, I made a small incision into the upper abdomen and explored the left subphrenic space. It was perfectly normal. I later removed more fluid from the left chest and the condition gradually improved.

These cases, and others like them, have guided me to the conclusion that in cases of doubtful diagnosis subclavicular pain almost always indicates a lesion on the upper surface of the diaphragm. In those rarer cases in which an abdominal lesion causes subclavicular pain there is always some clear lead to the diagnosis from definite signs in the lower abdomen. Thus I have known slight left subclavicular pain consequent on the perforation of an ulcer on the anterior wall of the stomach; presumably the contents impinged against the anterior part of the diaphragm. In the same manner the blood from a ruptured ectopic gestation may flood up to the diaphragm and cause pain over and below the clavicles, but here other symptoms help to the diagnosis. Once also I have known subclavicular pain caused by appendicular peritonitis in which some lymph was deposited in front of the liver and caused irritation of the lower and anterior part of the diaphragm. But in these cases the other abdominal symptoms and signs were sufficient to prevent confusion in diagnosis.

THE HEREDITARY FACTOR IN ASTHMA AND OTHER ALLERGIES.

BY

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THE material on which this communication is based consisted of 200 consecutive unselected cases of asthma attending the asthma clinic at the Hospital for Sick Children, Great Ormond Street; these have been investigated with regard to sex incidence, age at onset of asthmatic symptoms, and the presence or absence of allergy in other members of their families. The manifestations particularly inquired for were: asthma, hay fever, eczema, urticaria, and migraine. Due care was taken to exclude such "positive" cases as asthma commencing late in life or in the presence of known renal or cardiac disease; sneezing of an occasional, non-seasonal, and non-environmental nature; eczema of but short duration or of presumably occupational etiology; urticaria occurring only occasionally as a child and at extremely isolated instances in later life; or migraine that did not give more than one of the characteristic ocular, cerebral, or abdominal symptoms.

In all, 4,152 relatives were considered—an average of 20 per patient. As no patient attends the hospital after the age of 12 years, the 200 cases comprise children whose asthma had its onset during the first decade of life. The homes are distributed over most of the London districts, but principally to the east and north, and some of the cases came from provincial towns. Only about 5 per cent. of the children were of Jewish parentage, and in this one respect the series differs from that described by Peshkin of 100 consecutive cases of asthma in children on the east side of New York, where 92 per cent. were of Jewish parentage.

SUMMARY OF RESULTS.

	Males.		Females.		Total.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
Total cases	145	72.5	55	27.5	200	
Family history:						
Unilateral:						
(a) Mother's side ...	78	75.7	25	24.3	103	51.5
(b) Father's side ...	48	73.0	18	27.0	66	64.0
Bilateral	30	81.0	7	19.0	37	26.0
Nil	22	64.7	12	35.3	34	17.0
Nil	45	71.4	18	28.6	63	31.5
Total related persons:						
Affected	342	57.3	255	42.7	597	14.3
Unaffected	1,712	50.9	1,650	49.1	3,362	81.0
Transmitters	64	33.2	129	66.8	193	4.7
Grand total	2,118	51.0	2,034	49.0	4,152	
Individual diseases:						
Asthma	278	63.5	160	36.5	438	73.3
Hay fever	17	46.0	23	54.0	40	6.2
Eczema	92	63.4	53	35.6	145	24.3
Urticaria	51	68.9	23	31.1	74	12.4
Migraine	13	27.0	35	73.0	48	8.0

Inheritance:

	Father	Mother	Families	Affected	Transmitters	Unaffected	Total.
	A	A	A	T	T	U	
	A	T	U	U	A	A	T
Families	7	4	14	21	8	21	45
Affected	43	32	56	54	43	87	133
Transmitters	6	12	5	30	13	8	70
Unaffected	51	38	75	170	68	118	314

A = Affected. T = Transmitter. U = Unaffected.

* Working with a grant from the Asthma Research Council.

Age Incidence.

The age at onset of first symptoms during the first decade appears greatest during the first year of life, and declines progressively towards the tenth year (Chart 1). Analyses of the cases with regard to the presence or absence of allergic manifestations in other members of the family bear out the same fact. The small peak during the second year in cases with bilateral inheritance is negligible considering the small number of cases showing such heredity.

CHART 1.

CHART 2.

In Table I the relationship between age, sex, and family history is depicted. In Table II the age at onset in this series is compared with a series of 197 children described by Bullen, 100 by Peshkin, and 135 by Coke, the onset of whose symptoms was during the first decade. If we consider the percentage of total cases in each history group per year (as in Chart 2) we notice that the age of onset of symptoms runs practically identically in the three history

TABLE I.—Relationship between Age, Sex, and Family History.

Age at Onset.	Unilateral.			Bilateral.			Nil.			Grand Total.	
	M.	F.	Total.	M.	F.	Total.	M.	F.	Total.	M.	F.
0-1	20	3	23	4	3	7	11	3	14	35	9
1-2	12	5	17	8	2	10	5	5	10	25	12
2-3	10	6	16	3	2	5	6	1	7	19	9
3-4	11	3	14	2	2	4	7	1	8	20	6
4-5	10	2	12	3	1	4	4	4	8	17	7
5-6	5	4	9	2	1	3	5	—	5	12	5
6-7	6	1	7	—	—	—	3	1	4	9	2
7-8	3	1	4	—	1	1	1	—	1	4	2
8-9	—	—	—	—	—	—	1	2	3	1	2
9-10	1	—	1	—	—	—	1	—	1	2	—
10-11	—	—	—	—	—	—	1	1	2	1	1
Totals	78	25	103	22	12	34	45	18	63	145	55

groups. Most observers have shown, in dealing with cases at all ages, that the greater or more complete the inheritance, the earlier the age at which symptoms will have

their onset. In this series of cases with onset during the first decade about 21 per cent. develop symptoms irrespective of any hereditary influences, and during the remainder of the decade the groups continue to run fairly parallel. In other words, heredity plays no part in determining the age at onset of symptoms during the first decade.

TABLE II.—Age Incidence of Asthma during First Decade (Percentage).

	Cases.	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10
Bullen...	197	13½	10	17½	13	9½	11	5½	9½	6	3
Peshkin ...	100	10	21	18	18	9	9	4	3	7	1
Coke ...	135	29	14	7	9	17	8	7	3	2	3
Average...		17½	15	14	13½	11½	9½	5½	5½	5	2½
Author ...	200	22	18½	14	13	12	8½	5½	3	1½	1

Sex Incidence.

The sex incidence in this series was: males 72.5 per cent., females 27.5 per cent. Rackemann, in 90 children, found 73 per cent. males and 27 per cent. females. Comby, in 75 children, noted 57 per cent. males and 43 per cent. females. Coke's 135 children comprised 60 per cent. males and 40 per cent. females. Among 4,152 relatives the sexes were fairly evenly distributed—males 51 per cent., females 49 per cent.

The total affected persons in the whole group were: males 342, females 255. If we subtract the total number of patients from these figures we find that the sex incidence among the remaining affected relatives is practically identical—males 197, females 200. These figures closely approximate the 400 cases in adults described by Walker, where 198 were males and 202 were females. In adults similar figures are given by other observers: Bullen in 265 cases found 49.4 per cent. males and 50.6 per cent. females; Coke in 350 cases found 178 males and 172 females at all ages, but 71 males and 101 females from puberty to the menopause.

It is thus apparent that from birth to puberty the sex incidence of males to females is nearly 3:1, whilst from puberty onwards the incidence is less than 1:1. Puberty, therefore, is a definite decisive milestone toward which a great number of males must improve and beyond which a greater number of females develop symptoms. There is another possibility that at this point the allergic tendency manifests itself in another form. Obviously puberty must exert some beneficial effect upon the symptoms in the male and some deleterious effect upon the female. Such a fact is in full accord with the life-histories one often hears in these asthmatics. How often does the father say he suffered from asthma till he left school or commenced to work, or the mother assign the onset of her asthma to post-school years or marriage! When we consider the transmitters—sons or daughters of allergic parents who, whilst not showing any symptoms of allergy in themselves, have a child or children who manifest the allergic state—we note that the proportion of females to males is as 2:1. Also in cases with a unilateral family history we notice that transmission is twice as often through the mother's side as through the father's. Adkinson, even though she did not find asthma inherited more frequently from either parental side, did note that twice as many women as men inherit asthma from the maternal side, and that 25 per cent. more women inherit asthma directly from the parents. In addition, in tabulating the inheritance particulars, we note that there are twice as many affected with allergy where the male is unaffected and the female has or may transmit the tendency as when the male is affected or a transmitter and the female quite free.

Such figures suggest that inheritance of allergic manifestations is twice as frequent through the female as through the male, and that twice as many offspring are likely to be affected when the female transmits. Of the offspring, over twice as many males as females are likely

to be affected before puberty; the probability of a speedy recovery about puberty is much greater in the boy than in the girl; and the chance of developing allergic manifestations after the age of puberty is more probable in the female than in the male. Migraine appears to be far more common among female relatives, especially in the same family, whilst asthma, eczema, and urticaria appear to be more common in males. Four cases of ichthyosis occurred in males, whilst of a total of five cases of angioneurotic oedema four were males. Hay fever appears with about equal frequency in males and females among the relatives, but more in adults than in children.

Family History.

A positive family history of allergy was determined in 68.5 per cent. of cases. In 51.5 per cent. the history was unilateral, whilst in 17 per cent. it was bilateral. Comparable figures have been given by Rowe, who in 110 cases of asthma in patients under the age of 20 found that 51.8 per cent. gave a unilateral family history and 19.1 per cent. a bilateral one. At the same time it must be appreciated that some of the cases in which a negative family history is recorded may in reality be positive, or would have been positive had the members lived longer, or come in contact with the allergen to which they may be sensitive, or might develop a sensitivity—as, for example, a person showing no evidence of allergy in England, but who would manifest sensitivity in America in a ragweed environment.

In numerous cases members of families have gone abroad, and all trace of them has been lost, a fact that may reduce the percentage incidence. In addition, the figures given include all persons of any age, whether dead or alive; this necessitated the inclusion of a lot of infants who were under 1 year of age at the time of death, four out of five of which, even in the presence of a strong hereditary tendency, would not have developed any symptoms before the age at death.

Among presumably normal persons Balyeat determined the presence of a positive family history in 8.3 per cent. of the relatives of 1,117 students; Spain and Cooke in 7 per cent. of 115; and Cooke and Van der Veer in 14.5 per cent. of 68 families.

Hereditary Transmission.

From a consideration of the figures given it is obvious that one cannot consider the transmission of specific diseases from parent to child, as one can such an anatomical peculiarity as lobster hand, since it is only a tendency or diathesis that is transmitted. Adam aptly states: "Asthma is no more hereditary than phthisis or gout; the tendency—the soil—is inherited; whether the disease will develop depends on nurture." Nevertheless most observers are agreed that this tendency is transmitted as a Mendelian dominant factor. The main dissenters from this view are Buchanan, who says that "essential asthma in its familial appearance follows none of the known laws of heredity," and Adkinson, who, in a paper restricted to the discussion of asthma as an inherited character, states that transmission is as a Mendelian recessive, and does not attempt to probe the larger problem of inheritance of sensitization to protein in general.

The tendency to manifest allergic symptoms is definitely transmitted. Whether the person will develop any manifestations or not depends on numerous external factors other than heredity—as, for example: (1) Extent of exposure to various proteins. Peshkin's children slept on rabbit hair, to which 49 per cent. were found sensitive. Balyeat, in a similar series, found 43 per cent. sensitive to feathers and only 2 per cent. to rabbit hair. (2) Extent of previous lung damage. Children with badly damaged lungs frequently develop asthmatic symptoms independent of heredity, but in the presence of heredity such symptoms appear to develop earlier than would otherwise be the case. Many parents assign the onset of a child's asthma to a previous pneumonia, whether of a simple nature or following measles and whooping-cough. (3) The presence of focal infections—in children, especially enlarged tonsils and adenoids, and dental caries.

Among other points may be mentioned constipation, nervous or endocrine disturbance, achlorhydria or hypochlorhydria, colouring (pale skin, blonde hair, blue-eyed type).

Historical.

The hereditary factor in asthma has been recognized for many years. Sir John Floyer (1698) states: "As my asthma was not hereditary from my ancestors, so, I thank God, neither of my two sons are inclined to it, who are now past the age in which it seized me." Cullen, in his *Practice of Physic* (1784), and Ryan (1793) both suggest the possibility of hereditary transmission. American authors, as Eberle (1831) and Goode (1836), maintained that hereditary transmission was the generally accepted opinion. Andral (1839) mentions heredity as one of the prime factors predisposing to asthma. Ramadge (1847) gives an instance in which the disease appeared in four generations. Salter (1860), in a study of 35 cases, determined a positive family history in 38 per cent. Steavenson (1879) described how he inherited his asthma from his paternal grandmother. Geddings (1883) states "that this tendency is hereditary in nature is conceded by every prominent writer on asthma." Osler (1884) speaks of the hereditary tendency manifested by allergic dermatoses.

The first important contribution to this study in the present century is that of Czerny (1905), in discussing asthma and other allergies in his exudative diathesis. Drinkwater (1909) records a very impressive family history. The more recent investigators and their conclusions are tabulated in the following summary.

OBSERVATIONS ON PERCENTAGE INCIDENCE OF POSITIVE ALLERGIC FAMILY HISTORY IN VARIOUS MANIFESTATIONS OF ALLERGY.

Normals.

Balyeat: 1,117 cases; 8.3 per cent.
Spain and Cooke: 115 cases; 7 per cent.
Cooke and Van der Veer: 68 cases; 14.5 per cent.

Allergy.

Balyeat: 1,217 cases. Believes Mendel's law followed as single dominant. With bilateral history symptoms manifested in first decade in 58.6 per cent., in second 10 per cent., after 30, 0.3 per cent. With unilateral history 32.3 per cent. in first decade, 30.8 per cent. in second.

Smith: 94 relatives in five generations; 56.2 per cent. suffered from some form.

Unger: 189 cases; 19 per cent.

Food Allergy.

Rowe: 175 cases; 68 per cent.

Asthma.

Adam: 20 per cent. Only tendency or soil that is inherited.

Adkinson: 400 cases; 48 per cent. Nature of inheritance is as recessive. 191 protein sensitive, 52 per cent.; 209 negative, 41 per cent.

Berkhart: 16 per cent.

Buchanan: Follows none of known laws of heredity in appearance.

Bullen: 500 cases; 39.4 per cent.

Coke: 350 cases; 46 per cent.

Drinkwater: 20 relatives in four generations; 10 affected, 10 unaffected.

Goodhart and Spriggs: 21 per cent.

Rackemann: 150 cases; 58.7 per cent. in sensitive cases, 10.5 per cent. in non-sensitive.

Rowe: 234 cases; 53.4 per cent. 45 cases; 62.2 per cent.

Salter: 35; 38 per cent.

Van Leeuwen: 49 cases; 63.6 per cent.

In Children Only.

Bullen: 235 cases; 50.7 per cent.

Comby: 75 cases; 58 per cent. hereditary and similar; 46 per cent. and dissimilar.

Peshkin: 278 cases; 42.5 per cent. 40 per cent. in sensitive group, 45 per cent. in non-sensitive.

Rowe: 110 cases under 20; 70.9 per cent. 19.1 per cent. with bilateral history, 51.8 per cent. with unilateral history.

Schloss: 80 cases; 47 per cent.

Asthma and Hay Fever.

Spain and Cooke: 482 cases; 58.4 per cent. 7.3 per cent. with bilateral history, 51.1 per cent. with unilateral history. In 549 families with 1,889 children, where there was a bilateral family history 71.6 per cent. eventually develop symptoms, with unilateral history 51.1 per cent.

Cooke and Van der Veer: 504 cases; 48.4 per cent. Believe Mendel's law followed as single dominant, but may be multiple.

Kahn: 100 cases; 80 per cent.

Rackemann and Colmes: 25 per cent.

Allergic Dermatoses.

Piness and Miller: 345 cases; 41 per cent.

Urticaria.

Menagh: 260 cases; 32.6 per cent.
 Rackemann and Colmes: 25 per cent.
 Rowe: 20 cases; 55 per cent.

Angioneurotic Oedema.

Ensor: 33 of 80 persons in five generations; 41 per cent.
 Osler: 22 of 36 persons in five generations; 61 per cent.
 Rowe: 14 cases; 43 per cent. gave history of similar complaint.
 Whiting: 205 cases; 53 per cent. 110 in family groups comprising total of 207 individuals.

Eczema.

O'Keefe and Rackemann: 239 cases; 28 per cent.
 Rackemann: 36 per cent. children, 50 per cent. adults.
 Rowe: 16 cases; 69 per cent.

Migraine.

Bramwell: 50 per cent. cases show direct transmission, mostly through mother.

Buchanan: Transmission is expression of Mendelian phenomenon. Unilateral history in 100 families with 631 children, 22.6 per cent. had migraine. No history in seventeen families with 115 children, 26 per cent. had migraine. Bilateral history in three families with 15 children, all had migraine.

Diamond: 35 cases. Nearly all gave positive family history with transmission in main through mother.

Rowe: 30 cases; 86.6 per cent.

Tileston: 50 per cent. cases show direct heredity, even for three to four generations.

Ball: From 1,000 unselected family histories—261 cases migraine; associated with migraine in other members in 45.9 per cent. 162 cases asthma; associated with migraine in 37 per cent. 91 cases hay fever; associated with asthma in 49.4 per cent., and with migraine in 38.4 per cent. Eczema; associated with eczema in 21.3 per cent. and with migraine in 40.9 per cent.

Established Facts.

The main facts which have accrued from the vast amount of consideration that has been given to the subject of the transmission of the tendency to exhibit allergic manifestations may be summarized as follows:

1. The allergic diathesis is transmitted as a Mendelian dominant.
2. The greater the heredity the earlier are symptoms manifested.
3. The earlier in life the individual becomes sensitive the greater the tendency to multiple sensitization.
4. Asthma, hay fever, eczema, urticaria, angioneurotic oedema, and migraine appear to be intimately correlated, and to be interchangeable.
5. A child born in a family with a pure hay fever lineage is much more likely to be affected with hay fever than with asthma, and vice versa.
6. Where several members of one family are affected, sensitization is not identical as regards the specific proteins, nor are the clinical types of allergy or the symptoms displayed in each type themselves identical in different members of the same family.

The main additions deduced from this study are:

1. Puberty must exert some beneficial effect upon the symptoms in the male and/or some deleterious effect upon the female, for before puberty the incidence of males to females is over 2:1, whilst from puberty onwards it is less than 1:1.
2. Heredity plays very little part in determining the age at onset of symptoms during the first decade.
3. Transmission appears to be twice as frequent through the female as through the male, for (a) when there is a unilateral family history it is twice as frequently on the mother's side as the father's; (b) when the parents are unaffected the transmitter is twice as often the female; (c) when the male is unaffected and the female has or may transmit the tendency, twice as many are affected with allergy as when the male is affected or is a transmitter and the female is quite free.
4. A positive family history of allergy is present in about 70 per cent. of cases of asthma in children—in over 50 per cent. unilateral, in nearly 20 per cent. bilateral; 10 per cent. appears to be the maximum incidence in the families of presumably normal persons.

In conclusion, I would like to convey my thanks to the physicians at the Hospital for Sick Children for kind permission to make use of cases under their charge, as well as to the Asthma Research Council, under whose grant these investigations have been rendered possible.

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NOTES ON ADDER BITE.

BY

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SOME years ago Sir Thomas Oliver published an article on adder bite in the *British Medical Journal* (December 9th, 1922, p. 1115), and at his request I sent some notes, published on March 13th, 1923 (p. 375), on a case I had seen and on others of which I had knowledge. Since then I have seen the two cases now to be described.

CASE I.

About four years ago I examined, with Dr. Ryder Richardson of Saxmundham, Suffolk, a child, aged about 3 years, who had been bitten about two hours previously. The bite was on the dorsum of a terminal phalanx of a finger. Before our arrival the district nurse had applied silver nitrate so effectively that the punctures were invisible. The child was comatose, pallid, sweating, and almost pulseless. Dr. Richardson injected strychnine, incised the area of the punctures, and rubbed in permanganate. By that time the hand and arm were much swollen and discoloured. Later he informed me that the child had recovered, after suffering several days' severe illness, during which the arm and side of the chest became very swollen and turned all the colours of the rainbow.

CASE II.

In March, 1927, a strong and healthy man of 57 (a patient of Dr. Barber of Sandown, Isle of Wight) was out adder hunting, and while catching an adder in some rough grass he thought his finger had been pricked with a bramble. About twenty minutes later he felt pain in the hand and noticed that it was swelling. The swelling spread up the arm and over the chest, and he began to feel nausea and giddiness; he became so sleepy that he had difficulty in getting back to his farm. Forty-five minutes after he was bitten he was put in a car and taken to the doctor, who injected a stimulant. Violent diarrhoea set in, but the patient was able to walk to the car, in which he was driven home. During the journey he had hallucinations, seeing "large girders being erected for the construction of a skyscraper." When he arrived home he was unable to walk upstairs, and on getting into bed he had a rigor and his breathing was stertorous. Vomiting and diarrhoea continued for some hours; his face was swollen and purplish; the arm continued to swell for three days, and was quite lifeless. He suffered intensely from thirst and drank large quantities of barley water and lemonade, but passed no urine for seventy-five hours after he had been bitten. When, at the end of a fortnight, he was able to get up, he felt very weak and found that his right leg was slightly swollen. The swelling of the right arm persisted for some nine months; he could use it only with difficulty, and the movements were limited apparently by the oedema.

I saw the patient in August, 1928, some seventeen months after the accident. He was getting electrical treatment and massage,