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An Address

ON

THE PROBLEM OF CANCER.*

BY

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MR. PRESIDENT,—Before discussing the problem of carcinoma I must emphasize the importance of isolating all forms of hyperplasia from the processes now described under the comprehensive term "inflammation." All authorities in pathology agree that so-called "chronic inflammation" is a different process from "acute inflammation." The inclusion of so many different processes under one term compels me to say that the time has come to orientate afresh the present chaotic outlook on the subject of "inflammation" and to discover how the matter can be simplified. I urge the limitation of the term "inflammation" to the circulatory disturbances which occur inside and outside injured and structurally intact blood vessels, provided the injury does not cause their death. I exclude all forms of hyperplasia from "inflammation," and by hyperplasia I mean that process where even one cell begins to divide into two cells; therefore, I would exclude from the subject of "inflammation" the formation of granulation tissue and the healing of wounds, and place them under the term "hyperplasia," of which they are very beautifully controlled and regulated forms, the laws governing which are slowly beginning to dawn upon us. If all forms of hyperplasia were included in one self-contained subject important changes in our conception of many things would necessarily follow. For example, the condition now described as "chronic mastitis" would not be regarded as an "inflammatory" process. The desquamative epithelial hyperplasia and the hyperplasia of the pericanalicular and periacinous connective tissue containing lymphocytes, which are characteristic of so-called "chronic mastitis," will be seen to have a fundamental physiological significance when they are compared with the precisely similar changes in breasts of newly born male and female children and of females at puberty and lactation. "Chronic mastitis" is really a state in which physiological activity becomes pathological by being present when the breast should be at rest. It is not an inflammatory condition at all. Again, the cellular flora evoked by the irritation of the tubercle bacillus is an example of the importance of considering the morphological effects from the point of view of hyperplasia, instead of regarding them merely as "inflammatory" in origin. The importance of the point lies in this respect: all the connective tissue cells are in contact with the irritant at the site of inoculation, yet the cells which undergo hyperplasia are only the endothelial cells which produce the epithelioid and giant cells of a tubercle. This fact shows that there is a mutual affinity, so far as hyperplasia is concerned, between the irritant and endothelial cells only.

Take another example. Gonococcal infections can induce formation of papillomata, showing that only the epithelial cells responded by hyperplasia to the irritant, although many other types of cells are in contact with it at the same time. I give this as an example of gonococcal selection for epithelium, knowing full well that certain observers—Dr. G. M. Findlay of the Imperial Cancer

Research, for example—believe that the formation of papillomata of the skin in gonorrhoeal infections is not due to the gonococcus but to the presence of an ultra-microscopical organism which is capable of inducing warts in other situations also. In any event the formation of papillomata is a decisive example of a selective action between the products of micro-organisms and one type of tissue cells only.

Before leaving the subject that concerns the relationship between direct irritation of epithelium and the formation of papillomata I must point out that formation of papillomata is of frequent occurrence in proemial epithelial hyperplasia of the large and small ducts respectively in carcinoma of the breast. Lastly, the staphylococcus, when inoculated into the subcutaneous tissue, induces the hyperplasia of fibrous tissue in two parts—(1) as a process of repair in the parts that are killed, and (2) in the strands of fibrous tissue which surround the lesion.

There is another important example of the necessity to separate hyperplasia from "inflammation." It is pretty widely held, and I believe wrongly held, that the dilatation of the blood vessels, and also increase in their number, causes hyperplasia. John Hunter appears to have maintained this thesis, and in order to demonstrate that hyperplasia occurs as the result of increased blood supply he transplanted a cock's spur into a cock's comb, expecting that in consequence the cock's spur would undergo hyperplasia. His expectation was fulfilled, and the spur underwent an enormous increase in size. I repeated Hunter's experiment and, besides transplanting one spur into a cock's comb, I transplanted at the same time the other spur under the skin of the cock's back. These transplanted spurs underwent about the same amount of hyperplasia during the time they were under observation. I had to kill these birds before I wanted to because the noise they made interfered with the classes in King's College and with the amenities of several business offices in its neighbourhood. During the operation of transplanting the spur into the cock's comb there was decided haemorrhage from the wound made by excision of the spur, and there was no haemorrhage when I incised the cock's comb, which appeared to me to consist of gelatinous, glutinous, avascular structure. The comb is vascular only when it is erect. By planting the spur into the comb it did not appear to me that I was placing it in a more vascular medium. Then what could be the explanation of Hunter's transplanted spur? The explanation seems to me to be this—that in its new situation it was not subjected to the wear and tear of life it met with in its normal position, and in consequence grew into enormous proportions. There are many other examples of continuation of growth occurring in the structures not subjected to the ordinary normal wear and tear of life—the claws of animals, for example. However, let us suppose for a moment that Hunter was right, that this cock's spur became so large because it was receiving a greater supply of blood than normal. If this were so Hunter's experiments would have raised the following much more vital problem of hyperplasia: if a comb were able, on account of its presumed enormous blood supply, to induce hyperplasia in another structure, why did the comb itself cease growing?

Beyond what I have stated I do not consider that Hunter's experiment proved anything at all. In granulation tissue there is a vast amount of new blood-vessel formation, but when it has been covered by epithelium and ends in a scar these new blood vessels all atrophy. Why should this be so? The answer is perfectly clear to me. It is the hyperplasia of granulation tissue formation that demands the increased blood supply, and when the

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demand is over the large vascularity is no longer necessary to maintain the life of the cicatrix, and consequently the blood vessels disappear. So far as I am concerned, it is a law that the demand of hyperplasia induces vascularity, and hyperplasia is not induced by an increased blood supply.

I pass on to the hyperplasia which more intimately concerns carcinoma. There are decided indications in breast pathology that an addition should be made, with all due care, to the present limited conception of the morphological appearances of carcinoma. All pathologists agree that carcinoma exists when epithelial cells can be seen invading alien country, wherein they grow and from which they are disseminated and grow in different parts of the body. My statement that an addition to the morphological status of carcinoma is essential is based upon what I consider to be a law—namely, that before epithelial cells invade the parts outside the normal boundaries of ducts and acini there has been malignant epithelial hyperplasia within them, and that the process of carcinoma really begins before invasion occurs. I can see in every early carcinoma of the breast the presence of this malignant change within the normal boundaries of ducts and acini. It can frequently be discovered in advanced carcinoma in microscopical sections that have been made in series of the whole focus of primary disease. The epithelial cells outside the normal boundaries possess the same morphological appearances as those inside. I feel sure that the epithelial hyperplasia inside the normal boundaries is malignant and that it is the source of supply to the invading cells.

I now show you a state of things which can be commonly demonstrated in breast lesions which are not now generally considered to be carcinoma. Here are terminal ducts and acini that are filled by an epithelial hyperplasia that cannot be distinguished from the invading cells of carcinoma in other specimens, but here they are all enclosed in normal boundaries. This type of lesion usually occurs in the breasts of females before the carcinoma age. This specimen I removed from a woman of 25 years. I believe the catastrophe of carcinoma here was a question of time and opportunity, and that this lesion represents the true precancerous stage, and can be regarded as malignant if not carcinomatous. I may here state that I have never seen in the earliest examples of carcinoma of the breast this malignant change occurring in the acini alone; the terminal ducts as well have always contained the malignant epithelial hyperplasia. In all instances the elastica must be stained to make sure that the cell-containing spaces are dilated ducts.

Before leaving this part of my subject I would like to state definitely that by morphological examination I can never detect any visible indication of a local attempt to arrest the process of carcinoma. Some people have suggested that the enormous hyperplasia elastica around the ducts and even the acini, which I have shown sometimes occurs in carcinoma, is an indication of an attempt to bar its progress. All I can say on this matter is that hyperplasia elastica is rare in breast carcinoma and when present has proved to be inefficient; and that hyperplasia elastica occurs frequently round ducts and acini wherein there is nothing more than a slight desquamating epithelial hyperplasia. Other people consider the accumulations of lymphocytes which are observed at some parts of a growing carcinomatous edge to be further indications of a local attempt to limit the disease. There are so many parts of the growing edge at which there are no lymphocytes that it is hardly fair to Nature to believe her capable of exerting so feeble a defence. Again, upon *post-mortem* examination of a patient who had suffered from advanced mammary carcinoma I discovered small unsuspected supraclavicular lymphatic glands, which contained vigorous-looking epithelial cells which must have been lying dormant for a considerable time. There was no local reaction of any kind round these cells, although the disease must have been growing with intense rapidity in the liver of the person at the same time. This observation demonstrates two points: (1) that where the disease was lying dormant there was no visible reaction to account for the stagnation of growth, and (2) that there was probably systemic

influence in operation to arrest the growth of the epithelial cells in the supraclavicular lymphatic glands and to allow or encourage the intensely rapid growth in the liver.

There is another factor that I consider important, although at first sight it appears to be merely academical. It is this: it seems to me important to separate in one's mind those factors which induce carcinoma from those intrinsic and extrinsic cellular operations that occur in a cell dividing into two cells. For example, there can be no doubt that tar and even x rays can induce carcinoma, that the filtrates of the Rous tumour can induce one of four varieties of sarcoma, and that the entrance of a spermatozoon into an ovum initiates a propagation of species; yet we are perfectly ignorant of the intrinsic invisible factors that are operating in the cells, nor do we yet understand how they are influenced by variations in evolution, biochemistry, internal secretions, and so forth, operating upon them from outside.

In considering the induction of carcinoma one factor remains of paramount importance—the irritant must be applied directly to the actual cells which are eventually parents of the subsequent carcinoma, and the irritant is the main factor in the localization of the future disease. There must be also a time factor in the process of carcinoma. Experimentally the length of time carcinoma takes to appear seems to depend upon the intensity of the tar application. If tar be applied only once a week the period at which the carcinoma develops in mice is within about ten to twelve months. If it be applied twice a week or oftener the time can be reduced to four to nine months or less. There is a time factor even in intensive application of tar. The time factor may have an important bearing in giving time for proemial epithelial hyperplasia in the ducts and acini of the breast, to which I have already drawn your attention. In addition to the visible effects in carcinoma there are some very cogent reasons for believing that there is a systemic invisible action or inhibition of action associated with the induction of carcinoma.

I pass on to adduce the evidence there is of a systemic influence upon the process of carcinoma.

(a) I have already indicated one, to which I do not again refer.

(b) It is perfectly well known that metastatic deposits in subcutaneous tissue in carcinoma of the breast may remain latent and show no signs either of their presence or activity for a period of thirty years after removal of the breast, then with almost dramatic suddenness a cancer *en cuirasse* develops covering the chest. Here is an indication of a systemic influence arresting carcinoma, and also of an influence which induces its subsequent intensely rapid growth. It is impossible to state whether the influences are different or whether they are due to modification of the same one.

(c) Primary carcinoma appearing in the same person at the same time in two different viscera, or on the skin and viscera, is a rare occurrence. The fact of its rarity suggests that the existence of a primary carcinoma protects a patient from the incidence of a primary carcinoma elsewhere in the body. In Great Britain most women who die of carcinoma are attacked either in their breasts or uteri. Yet it is extraordinarily rare for primary carcinoma of the breast to be complicated by a primary carcinoma of the uterus, and vice versa. It makes one wonder whether the incidence of a primary carcinoma in the breast protects a woman from a primary carcinoma in the uterus, and vice versa. In Holland carcinoma of the breast and uterus in females is not so common as in Great Britain. The females of Holland suffer more from carcinoma of the alimentary tract. Does primary carcinoma arising in these situations protect the women of Holland from primary carcinoma of the breast and uterus? Upon this point another factor must be taken into consideration.

While granting that these examples are indications of protection, there may be an explanation for the different sites of primary carcinoma of women in the two countries mentioned. It must also be granted that different sources of irritation may select different viscera for residual purposes. For instance, the nematode worm *Gongylonema neoplasticum*

Fibiger selects the stomach, another nematode worm *Trichosomoides crassicauda* Lowenstein selects the urinary bladder. The result of selection of different viscera by different agents of irritation, even though they belong to the same species, would explain the different viscera affected in the women of Great Britain and Holland respectively and collectively.

(d) There are indications that the removal of that part of an area in which carcinoma has appeared in a tar-painted area induces a later appearance of primary carcinoma in another apparently non-cancerous part in the same area (Murray). This experiment supports the assumption that the presence of one primary carcinoma may prevent or delay the appearance of another primary carcinoma.

(e) The fact that only a proportion of mice subjected to the action of tar develop carcinoma also indicates the existence of normal local or systemic protection.

(f) When carcinoma has developed and has been removed from one tar-painted area, it requires a more intense application of tar to induce a primary carcinoma in another area of the same mouse (Murray).

(g) The same difficulty in inducing carcinoma in a tar-painted area is experienced when the mouse under experiment has had a mammary carcinoma previously removed by operation (Murray).

(h) The work of Dr. Cuthbert Dukes especially conclusively proves that multiple adenomatous papillomata of the colon invariably end in carcinoma, yet only one or two, and occasionally three, among them become the site of primary carcinoma. Why is it that so few become carcinomatous unless the presence of one primary carcinoma protects from the incidence of another? When a primary carcinoma has appeared in two or three separate colonic adenomatous papillomata it may be that primary carcinoma appeared in them either at the same time or before the acquisition of immunity.

(i) Dr. Cramer excised and minced up the spleens from a number of mice and returned each to the peritoneal cavity of its own mouse. Tar carcinoma appeared much earlier in these mice compared with otherwise untreated animals.

[I pass on to another problem—namely, whether the removal of a primary benign tumour makes any difference to the rate of growth of secondary benign tumours of the same nature. I cannot verify the statement, but it is said by clinical observers that the removal of an intra-cystic papillomatous state in an ovary will induce the disappearance of secondary papillomata scattered over the peritoneal cavity. There is an observation of my own which bears upon this point. Small microscopic multiple fibro-adenomata in the breast occur more commonly than is generally supposed in the area of the breast immediately surrounding an obvious clinical fibro-adenoma. Yet it is rather rare, but by no means impossible, to discover a case in which the removal of a clinically obvious fibro-adenoma has been followed at a later period by the appearance of another fibro-adenoma in or near the same situation. All that can be said now upon this point is that either the removal of the obvious fibro-adenoma has no effect on its microscopical neighbour, or if there be one it is certainly not one that intensifies growth. I must say that at the present moment it is a hazardous speculation only, and much more investigation is required in this direction. Yet it may be that the effect of removal of benign tumours upon secondary foci of the same tumours may be different from the effect of the removal of malignant primary tumours upon secondary primary tumours.]

(j) Several years ago I drew particular attention to an influence—for want of a better term “a trophic influence”—of the nervous system upon epithelial structures, and I pointed out that in some examples where hairs become grey as the result of advancing age, grey patches appear upon the maximum points described by Sir Henry Head in his work upon herpes zoster. These are points at which nerves become cutaneous. I have seen beards becoming grey on four symmetrical points—namely, where the mental and great auricular nerves become cutaneous on the face. Moreover, I showed that the mental nerve areas described by Dr. Head were completely white when the rest of the beard was only scattered with a few grey hairs. In

continuation of this demonstration I pointed out that if a diagram were made of all patients suffering from small rodent ulcers of the back their points of instance would coincide with those points on which the posterior spinal branches of intercostal nerves become cutaneous. In this respect they resemble early patches of leucoderma and scleroderma of the back. Further, I published examples in which the areas occupied by extensive rodent ulcers are sometimes identical with the distribution of nerves. I also showed some examples in which the spread of a rodent ulcer was arrested at the edge of the areas which had lost their tactile and thermal sensations. Dr. Cramer of the Imperial Cancer Research Fund, London, in the *British Journal of Experimental Pathology* (vol. 6, p. 21) published a paper upon “Innervation as a factor in the experimental production of cancer,” in which he said his experimental observations were in agreement with my clinical observations. His conclusion was as follows:

Loss of nervous control in an area of skin does not predispose to cancer; on the contrary, the presence of a peripheral nervous mechanism is an essential factor in the process of chronic irritation which leads to the development of cancer.

I would not dwell so much on this clinical observation of mine but for the fact that it has, after twenty-five years, begun to attract attention. Cramer and Oertel, for instance, have lately drawn some attention to it. I do not want it to be understood that the distribution of rodent ulcer alone occasionally occupies definite nerve areas, because I have examples where infective processes such as erysipelas, tuberculosis, and tertiary syphilis are also occasionally delimited at the margins of nerve areas. I have no doubt that there is a mutual affinity between nerve areas and infective processes which occasionally can be demonstrated clinically as well as in rodent ulcer. The anastomosis of blood vessels and lymphatic vessels at these margins is so complete that these vessels cannot influence the limitation of which I have spoken. Moreover, microscopical sections made of these margins show no mechanical obstruction to spread of disease.

(k) Miss Maud Slye considers that heredity plays the most important part in the incidence and genesis of disease.

Finally I refer to some recent contemporary notions concerning carcinoma. (a) Gye's conception of the genesis of carcinoma is that it is induced by the combined action of an ultra-microscopic virus and a specific factor. His conception has caused a great deal of controversy, and most observers have failed to confirm beyond any possibility of doubt the presence of two agents, even when they repeat Gye's technique and experiments. Even if Gye were right in his conception, there are many points in the problem of carcinoma it would not touch, mainly those intrinsic and extrinsic cellular influences to which I have already alluded. I do not suppose for a moment that Gye would explain the evolution of an ape into a man by saying it was connected with the union of an ultra-microscopic virus and a specific factor. (b) Blumenthal associates a bacillus with the induction of malignant disease; Fibiger connects a nematode worm with rat carcinoma, and Boërl discovered a filarial worm in the breast carcinoma of mice. Other observers have associated with carcinoma bilharziasis, *Trichina spiralis*, the embedded head of a tapeworm, and hosts of other living agents.

After taking into consideration all these points it still has to be admitted that knowledge does not yet permit any definite statement to be made in answer to the question whether the incidence of carcinoma is induced by a living or lifeless agent, or both. Should a living agent be a factor, then the establishment beyond all doubt of the existence or non-existence of ultra-microscopic organisms will be more essential than ever. All the living and lifeless agents that have been described in association with carcinoma may be contaminated by the presence of these organisms. The complete establishment of their existence will upset a great deal of present bacteriological knowledge.

Do carcinoma cells differ specifically from any other cells? Warburg says that they do, and his work on the biochemistry of malignant cells enables him to state that under aerobic and anaerobic conditions they split glucose

into lactic acid and thereby differ from normal cells, except retinal cells. This is the only biochemical difference that is known between normal (except retinal cells) and malignant cells. Warburg also states that the blood of the veins leaving the malignant tumour contains more lactic acid than the blood in the arteries supplying it. The excess of lactic acid in the veins leaving the tumour disappears when the blood reaches the general circulation, therefore examinations of the blood for an excess of lactic acid is of no value for purposes of diagnosis. Since Warburg's work it has been discovered that regenerating tissues can in aerobic and anaerobic conditions break up glucose into lactic acid, but the amount of lactic acid is relatively much less than in malignant disease. On the basis of his work Warburg suggests a hypothesis accounting for tumour origin. He conceives that normal tissues are not homogeneous, but consist of a mosaic of cells growing and surviving by oxidation process of carbohydrate, interspersed with isolated cells which have a dual capacity of using either the carbohydrate oxidated process or the splitting process into lactic acid. In spite of the immense labour of Warburg and the wonderfully accurate and careful experiments he has conducted, the question still remains not very satisfactorily answered—whether normal cells can, after a time, develop the peculiar metabolism of carcinoma cells when the life of normal cells grows under conditions which impair their normal metabolism. Even if it be demonstrated that Warburg is completely right, that there are normal cells which from the moment of their existence can break up glucose into lactic acid, "it does not explain why cancer cells grow" (W. Cramer).

In carcinoma there is another outstanding morphological fact that may have a biological significance. No nerve endings can be discovered in carcinoma. Although Horst Oertel has issued a preliminary report on "Innervation and tumour growth" (*Canadian Medical Association Journal*, 1928, xviii), in which he says he has been able to stain nerve fibres among carcinoma cells, I think it would be wiser to wait to hear what Oertel says in his final communications. Great care will have to be exercised in excluding the possibility that the nerves seen in malignant tumours are due to the presence of pre-existing nerve fibres among which the invading tumours have spread.

Finally, it may be asked, Why is there so much sterility of definite statement when the attention of scientific observers throughout the world is being devoted to carcinoma? The answer to this question can be only, that the problem will never be solved completely until we know what life is.

SOME OBSERVATIONS ON THE DICK TEST.

BY

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THE investigation here recorded was primarily undertaken to determine if there was any difference in the reaction to the Dick test in the fourth week of scarlet fever between cases with septic complications such as rhinitis and uncomplicated cases. We found in 48 septic cases that 21 (44 per cent.) remained Dick-positive, and of 103 clean cases 31 were positive. The preponderance of positives was only noted in the cases with rhinitis and "spotty" faces.

The septic patients were given scarlet fever prophylactic vaccine in doses of 0.1 to 0.3 c.cm., but, except in the case of rhinitis, the effects were not favourable. In rhinitis, the administration of an anticatarrhal or even a simple staphylococcal vaccine will often bring about improvement, so that the effect is possibly not specific.

Four patients under observation, who had had definite initial attacks, showed relapses in the following circumstances. One who was convalescent had a definite relapse the day after a test dose, giving at the same time a positive test; on retesting him, fourteen days after the

acute stage of the relapse, he was still strongly positive. A second patient had a relapse nine days after giving a positive test. In another convalescent Dick-positive patient, with rhinitis, relapse followed the injection of 0.1 c.cm. prophylactic (=250 skin doses). The fourth patient, who was strongly positive during the acute stage, relapsed nineteen days later after a fourteen days' apyrexial period. A fortnight after this second attack he was still strongly positive.

Since two of these patients remained positive after two attacks of scarlet fever, and such a high proportion of convalescents were giving positive reactions, we decided to extend our investigation. We treated 194 convalescents in the fourth week of the infection, and found that 61 (31 per cent.) remained positive. As a control we tested 116 diphtheria convalescents, and found 48 positives (41 per cent.).

The next group examined was 131 patients with scarlet fever in the first three days of the disease, while still febrile and showing a rash. We found that a positive reaction could easily be read, even when a rash was present, because the scarlet fever rash affects only the papillae of the skin, giving the punctate appearance, while a positive Dick test causes a generalized erythematous patch. Many positive cases showed up brilliantly, even in a profuse rash. Here we found 64 positives and 67 negatives—that is, 49 per cent. positives. We retested 59 of these in the fourth week; all those giving an initial negative test remained negative (20 cases). Of the initial positives (39 cases) 24 remained positive and 15 became negative; 5 patients in this latter group had had antitoxic serum. We did not observe any clinical difference in the course of the disease between those giving positive or negative initial tests.

Another group reviewed was composed of newcomers to our staff during the previous twenty months; 94 were tested and 33 were found positive (36 per cent.). Eighteen of the staff tested gave a previous history of scarlet fever, and in 5 (28 per cent.) of these the result was positive. This proportion does not differ materially from that obtained among those who had no history of a former attack. Seventeen of these patients were given 0.1, 0.2, and 0.5 c.cm. doses of the prophylactic (1 c.cm.=2,500 skin test doses) and retested. Eleven of them were negative and 6 still remained positive. These became negative after two further doses of 1.0 c.cm. One of the patients who received three doses developed scarlet fever six months later, and after being tested again gave a strong positive reaction. She also gave a history of a mild attack of scarlet fever six years previously.

In recording the results of repeated test doses during scarlet fever convalescence one great fallacy has to be recognized—namely, that many persons with positive reactions may be easily converted into negative reactors by the small amount of toxin introduced into the skin by the test. To prove this point we gave repeated single skin test doses to eleven members of our staff who had given strong positive reactions on the first test. The results were as follows: one became negative after a single skin test dose; three after two doses; one after four doses; two after five doses; one after six doses; one after seven doses; while two who reacted as very strong positives to the first dose remained positive after seven doses.

Since it seemed possible that these negative results might be due to a local tissue immunity, some of those who became negative were tested on the skin of the leg. The results proved the immunity to be general, and not local.

All the staff while being immunized were employed in our sanatorium, which is a quite separate institution, so that there was no possible chance of their gaining immunity by small doses of infection apart from the injections. One nurse rendered negative by this latter method developed scarlet fever three months later; she was then found to be positive again. The attack was a very mild one, but was complicated by the onset of rheumatism and endocarditis. Tested in the third week of disease she was again negative. No nurse who was originally Dick-negative has contracted scarlet fever up to the present.*

* Since writing, one Dick-negative reactor has contracted scarlet fever. She was tested seven months ago. On testing again the first day of her illness she was still negative.