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.c.m., 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.c.m. 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.c.m. doses of the prophylactic (1 c.c.m.=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.c.m. 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.

Before discussing the interpretation of these unexpected results, the effects of scarlet fever antitoxin treatment in our wards may be recorded. Out of 960 admissions 114 of the worst cases have been given doses of scarlet fever antitoxin in amounts of 10 to 40 c.cm., according to our estimate of the severity and duration of the disease. In 96 of these the results have been extremely favourable. In this group we have observed rapid decrease in the fever, cleaning of the throat, cessation of purulent nasal discharge, and a low incidence of septic complications, such as otorrhoea (7 per cent.), in view of the fact that all the cases are severe ones. We have found antitoxin effective even so late as the fifth day of disease in septic cases. Only 3 deaths occurred out of a total of 960 cases, compared with 15 in the immediately preceding cases of the same number, none of whom received serum.

One of the fatal cases was a patient with the malignant haemorrhagic type of infection, who died a few hours following admission, after thirty-six hours' illness; 2 died of septic pneumonia. In these 3 cases the serum had no appreciable effect. In 15 others the disease was not influenced by serum. One of these was a second-day case; 6 were third-day cases; 2 were fourth-day cases; and 6 fifth-day and after.

These failures are difficult to explain, since the patients appeared no worse than others with equal duration of disease who were strikingly benefited. For many years we have used galyi with good effect in cases of scarlet fever with phagedaenic ulceration of the throat; in some of these serum failures it was used with benefit. As this drug is no longer procurable in England we have recently tried sulpharsenobenzene (three different brands), but it does not appear to be nearly so effective.

One complication that appeared in 20 per cent. of the serum-treated cases was severe secondary cervical adenitis, although only one of these cases eventually suppurated.

DISCUSSION.

In our results the most striking feature is the remarkably slight difference among the proportions of positives in the various groups: 31 per cent. in the scarlet fever convalescents, 34 per cent. in the staff group, and 41 per cent. in the diphtheria convalescents. The surprisingly high proportion of negatives in the acute stage of scarlet fever was also quite unexpected (51 per cent.). The fact that all the negative cases in the group remained negative and most of the positive cases positive on retesting strongly confirms our opinion that there was no error in observation.

Although some of the acute scarlet fever cases showed a reversal of reaction from positive to negative on retesting during convalescence more than half still remained positive. While our results on retesting in convalescence differ from those of many other observers who have retested scarlet fever cases repeatedly during convalescence, we think that others have not sufficiently recognized the powerful effect of a few repeated skin tests in producing immunity against the toxin in certain individuals.

Although four of the Dick-positive convalescents had second attacks of scarlet fever within a month clinical experience proves that the bulk of these persistently positive reactors are unlikely to contract scarlet fever again. It may be that the nose and pharynx acquire local immunity, although general antitoxic immunity is not developed.

We first thought the test material was at fault, but this cannot be the reason, because, if it had been too weak, while the number of positive reactions in convalescence would have diminished, the number of negative reactions in the acute stage would have increased. If strong enough to make all the acute cases positive it would presumably also have increased the number of positive reactions in convalescence.

Another curious fact in the etiology of scarlet fever is the rarity of attacks of scarlet fever in infancy; many observers have stated that this is indicated also by infants always being Dick (as Schick) negative. It has been too hastily assumed that this result is due to a passive immunity inherited from the mother. This view cannot be accepted in all cases, because we have frequently seen a nursing mother contract scarlet fever while her baby

escaped. Two such instances occurred in our present series of cases. In one instance the 8-day-old infant of a woman with definite scarlet fever, contracted the day after parturition, was tested and found Dick-negative. She escaped infection, although in a scarlet fever ward, while her mother was actually suffering from the disease; it is obvious that an infant cannot inherit what her mother does not possess.

Recently Dr. Fletcher¹ has stated that in the Dutch East Indies, where scarlet fever does not occur, the bulk of young children give positive Dick reactions. With increasing age the number of negatives becomes equal to that found in countries where scarlet fever is endemic; thus an immunity is obtained in spite of the absence of scarlet fever.

We would suggest that immunity to scarlet fever is partly inborn or hereditary and partly a function of age, being high in infancy, rapidly decreasing in early childhood, rising again in later childhood, and becoming comparatively high in adult life. It would appear that in any age group outside infancy reactors to the Dick test might be placed in three groups: those who are persistently strongly negative; those who fluctuate between positive and negative; and those who are strongly positive and, though convertible into the negative by artificial means, tend soon to become positive again.

We do not think the doctrine of immunity increasing in age, due to subminimal doses of infection through life, will cover all the recognized facts, especially the immunity of infants.

If it were not for the strikingly beneficial results of streptococcal antitoxin in 90 per cent. of the cases we could feel doubtful of the etiological relationship of *Streptococcus scarlatinae* to scarlet fever; but even here there are some inexplicable complete failures. Moreover, although this serum reduces the fever within forty-eight hours by several degrees in most cases, in many it does not appear to extinguish it completely, as the temperature tends to hover between 99° and 100° F. for three or four further days.

Another interesting feature is that serum does not appear to prevent secondary cervical adenitis—that is, adenitis after the throat is apparently normal. This phenomenon does not commonly occur in other streptococcal throat infections, although in scarlet fever it is certainly common even after the mildest cases. These facts, coupled with our experience of the beneficial effect of galyi (one of the arsenicals) where serum has failed, suggest the possibility that there may be another symbiotic factor, at present unknown, which might explain much that is inexplicable in the recent discoveries concerning the etiology of scarlet fever.

REFERENCE.

¹ *British Medical Journal*, March 17th, 1928, p. 448.

THE ANTIRACHITIC ACTION OF IRRADIATED ERGOSTEROL IN CHILDREN AND ADOLESCENTS.

BY

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It is now ten years since rickets was first proved by scientific experiment to be intimately related to the absence from the dietary of a specific food factor. This new conception of the etiology of the disease met with considerable opposition, but it has held its own against all previously recognized hypotheses, and to-day there are grounds for believing that the specific antirachitic food factor has actually been isolated as a pure chemical substance. The story of the experimental work that led from the original proof of the existence of the antirachitic factor to its isolation is a long but fascinating one, and the main steps in the chain of discovery may be condensed as follows.

To Mellanby¹ belongs the credit of establishing the existence of the antirachitic factor by means of his exhaustive investigations on puppies. He demonstrated that