SEPSIS IN RELATION TO TUMOURS

CLINICAL IMPLICATIONS OF AN EXPERIMENTAL STUDY

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The occasional occurrence of sepsis in surgical wounds maintained under rigid aseptic conditions leads to the inference that such infection can take place by routes other than direct contact from without. Learmonth (1924) described invasion of undamaged muscle of an arm by *Clostridium welchii* following a partial gastrectomy. Okell and Elliott (1935) demonstrated the transient presence in the blood of organisms associated with oral sepsis. Buchanan and Kyles (see C. H. Browning, 1944) by repeated blood cultures showed the occurrence of bacteraemia after minor surgical intervention in a limited area where infection is present, as, for example, in the extraction of teeth. Such circulating organisms are no doubt usually disposed of rapidly by the blood, as indicated by the work of Wright and Douglas (1903), but where persistent bacteraemia exists and there are sites of lowered tissue resistance conditions will be favourable for the establishment of secondary metastatic infection.

Butler and Valentine (1943) stressed the importance of small initial staphylococcal lesions in maintaining bacteraemia—e.g., those occurring under hard skin or beneath a scar. Damage following slight trauma will supply conditions favourable for secondary localization, and degenerating tumour tissue would also appear to afford an excellent nidus in which pyogenic organisms may settle. Muir (1941) has stated that tumours have little resistance to bacterial invasion, and Boyd (1947) emphasized the part played by sepsis as a cause of death in cancer of the human subject.

Experimental Investigation

It was therefore decided to ascertain experimentally whether such abnormal tissues are in fact especially apt to harbour pyogenic organisms brought by the blood stream. The problem resolved itself into balancing the factors of tumour growth and progress of infection so that the effects of both might be assessed. A rat sarcoma originally induced by styryl-430 (P. Browning, 1941) provided a readily transplantable tumour with a regular progressive course of sufficient duration to permit observation both of the effect of the new growth and of the bacterial agent.

Following a subcutaneous injection of a coarse emulsion of about 0.05 g. of tumour tissue in saline, death takes place in six to eight weeks from pulmonary metastases, or the animal requires to be chloroformed owing to ulceration over the grafted tumour. The strain of staphylococcus was that used by Browning and Calver (1947), as it responds well to treatment with penicillin. It is noteworthy that rodents are naturally resistant to staphylococcal infection, apparently owing to their plasma being little affected by the coagulase of the organism (Hale and Smith, 1945); however, virulence may be enhanced in various ways—e.g., by addition of mucin to the inoculum. In order to reduce so far as possible the effects of toxin production *in vitro* the inoculum for a rat of approximately 200 g. consisted of 1 ml. of a 1 in 20 dilution of an eighteen-hour agar growth injected intraperitoneally.

It was necessary to control the infection by chemotherapy, three or four doses each of 1,000–2,000 units of penicillin being injected subcutaneously in the first twenty-four hours after inoculation. This treatment was the minimum necessary to

effect cure in the majority of inoculated control animals without tumours, 36 out of 43 being cured. Those which did not respond to the therapy died from septicaemia within a few days. In the survivors there were no focal lesions apart from occasional transitory suppuration in the needle-track of inoculation which appeared about a week after infection and which lasted for only a few days. Out of 52 inoculated but untreated animals 43 died within twenty-four hours from staphylococcal septicaemia; within seven days the nine survivors had to be chloroformed owing to extensive sepsis located in the inoculation track.

Tumour-bearing rats were inoculated seven to twelve days after grafting, when the growths were about 1 cm. long. Out of 62 which were inoculated and treated with penicillin as above described 52 survived; these were chloroformed before growth of the tumour led to surface ulceration (about five weeks after inoculation). Immediately after death approximately 0.1 g. of the tumour was cultured in nutrient broth; several loopfuls of spleen tissue and heart blood were also cultured and other organs examined for lesions, and it was noted that no septic focus existed at the site of inoculation. From the tumours in 19 out of the 52 animals coagulase-positive staphylococci were recovered (often in mixed culture with coliform organisms and diphtheroids). On the other hand, the tumours of all 21 uninoculated tumour-bearing control animals, which had received no penicillin, yielded no staphylococci, although coliform organisms and diphtheroids were often present. Staphylococci were not demonstrated in the spleen or heart blood of either the treated tumour series or the controls. In some of the tumours the staphylococcus was isolated where no gross central degeneration had occurred. These experiments show that localization of pyogenic organisms in a malignant tumour tends to occur as a result of bacteraemia.

Conclusions

Two conclusions of clinical importance follow from the results. First, especially in view of Butler and Valentine's work, minor sepsis should be regarded seriously in cancer patients, particularly when radiation therapy may lead to marked lowering of the local resistance. Secondly, since it has been shown that the virulence of pyogenic and other organisms is greatly enhanced by the injection of adrenaline at the site of inoculation (Evans, Miles, and Niven, 1948), where surgery is associated with the use of combined local analgesic and adrenaline the prior clearing up of septic foci which might otherwise seem of little consequence is of prime importance.

I acknowledge with thanks a grant towards the expenses of this work from the British Empire Cancer Campaign.

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The American National Multiple Sclerosis Society, which was formed two years ago to stimulate interest and finance research in disseminated sclerosis, has appointed as medical director Dr. Cornelius H. Traeger. The appointment was made possible by a grant of \$50,000 from the Milbank Memorial Fund. Dr. Traeger is a member of the Executive Committee of the New York Rheumatism Association and of the Committee of Research and Education of the American Arthritis and Rheumatism Foundation.