height of the disease and in some instances in the post-febrile period.

The results when plotted on the Van Slyke acid-base diagram, so modified as to include iso-CO_2 tension lines, indicated that almost all of the points were well within the normal acid-base area. No instance of uncompensated acidosis was encountered. In three cases the points fell just outside the normal acid-base area in the compensated acidosis region. One of these patients was afebrile at the time and the other two were suffering from renal disorders. In no instance was there an acidosis of sufficient severity to indicate the advisability of bicarbonate therapy. It has been concluded from the observations thus far that the acid-base condition of patients suffering from pneumonia is usually within normal pH, CO_2 content and CO_2 tension limits.

In eight instances in which we have made repeated observations of the acid-base condition of the same patients we have found evidence that during the febrile period, the CO_2 tension has a tendency to be lower and the pH higher than after the temperature has returned to normal. These results indicate that during the febrile period there is over-stimulation of the respiratory mechanism which leads to a lower CO_2 tension and a slightly higher pH but that this disturbance does not usually remove the patient from a normal acid-base condition. No direct relation has been found between the degree of oxygen unsaturation and the low CO_2 tension of the febrile period.

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A study of the behavior of coal tar on the tissues.

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In another study Burrows has shown that growth in a tissue depends on a crowding of the cells together and a cutting down of their relative blood supply. It is the direct result of the accu-

mulation of a substance which stimulates the normal metabolism of the cell. This stimulating substance is soluble in the circulating body fluids. He failed to find any direct difference between the cancer cell and the normal cell. The independent growth seen in cancer like the shape and the arrangement of the cells may be directly related to a primary change in the normal orderly arrangement of the cells in the tissues of the body.

This growth stimulating substance is liberated in the normal metabolism of the cell. It acts directly to break down the proteins. In excess it causes a complete destruction of the cell. In less concentration it causes growth. Dense masses of cells poor in blood vessels or avenues of escape of this substance, such as cancerous tissues and the tissues of young embryos are rich in this substance. Other tissues cut off from their blood supply but supplied with oxygen accumulate this substance after a latent period which varies indirectly with the immediate cell density of the fragment of tissue being tested.

Cancer, as Burrows' studies indicate, is the result of any condition or substance which can cause the formation of a dense mass of cells relatively poor in blood vessels within the organism.

This stimulating substance as Burrows has further shown, acts to produce another substance in fixed tissue cells which is an active blood coagulant. This coagulating substance is poorly soluble in the fluids of the body but combines readily with fibrinogen to form fibrin. It flows readily over the surface of body fluids.

This coagulating substance again has strong affinities for the cell. All migration of the fixed tissue cells is the direct result of the absorption of this coagulating substance by substance or substances like fibrinogen, or the surfaces of the medium in the normal organism.

During migration this coagulating substance is taken away by the medium without. Fibrinogen becomes a stimulant for the migration of these cells in that it combines with this coagulating substance. It acts in this capacity only until it is completely saturated with this substance. In 1917 Burrows had already given evidence to show that this same substance decreases the surface tension of muscle cells in the interval between contractions and that the contractions are the result of

an explosive breakdown of some substance increasing surface tension. In growing systems this same coagulating substance is formed in excess and disappears in the growing tissue. It is apparently combined or otherwise used in the formation of the protoplasm. Any actively growing tissues must drain the organism of substances leading to the formation of this coagulating substance as well as other important constituents for protoplasmic development.

Fischer several years ago had shown that drops of olive oil containing Scharlach R induce a rapid migration of epithelial cells to them. Recent and older careful studies of blood coagulation have shown that the coagulating substance of the body is probably a phospholipin. The action of these oily substances as well as coal tar may be none other, therefore, than the result of the absorption of this coagulating substance by them.

To prove this possibility tiny and large quantities of coal tar have been introduced just beneath the epidermis, into the subcutaneous tissue and into growing embryomata. When tiny drops of coal tar are introduced just beneath the epidermis of a rat the epithelial cells migrate along the needle tract to the drops that surround them like they invade the plasma clot. This migration does not continue indefinitely but only to the apparent saturation of the tar. Many of the cells which reach the coal tar early disintegrate. Later ones form a collar about the drop of tar. This collar gradually increases in thickness as more and more cells arrive.

No mitoses are seen in the first cells to arrive. Mitoses became evident only as the mass thickens. If more tar be added after the first drop ceases to be active this migration is resumed. The cells coming in contact with the fresh tar degenerate. Later ones do not. The mass thus thickens until an active autonomously growing tissue is established.

In the subcutaneous tissue of adults the coal tar causes a similar migration of connective tissue and endothelial cells to it, an extensive hyalinization of the fibrous tissue, and a degeneration of the few cells accumulating about it. In the more cellular mesenchyme of the embryonic tissues dense masses of connective tissue cells thus develop. Growth becomes evident in these masses only when they have reached a large size or when the cells have become densely packed together. These masses be-

come larger and larger as more tar is added. They eventually became sarcomatous.

From these observations it became evident that the whole action of coal tar may be none other than the absorption of a certain blood coagulating substance which is a product of the cell's metabolism. It acts thus to accumulate cells and form an organization consistent with an autonomous growth of these cells.

It seemed evident therefore that coal tar itself must be able to produce all the symptoms of cancer. Such an active absorption of this coagulating substance must lead to an active drainage from the cells of a substance essential for the life of the organism.

In further proof for this deduction it has been found that these particles of coal tar do not remain localized in the tissue but they may migrate long distances through the tissues. From the subcutaneous tissue this migration is by way of the veins. The migrating tar metastasizes, so to speak, like a sarcomata. By this course it reaches first the lungs. Particles have also been found in distant organs.[1]

Very large doses or very frequently administered doses not only cause this migration but they also cause malaise, pronounced cachexia like that of cancer, and death of the animals.

The whole action of coal tar as we have seen it, therefore, is that of a simple absorbent of a certain coagulating substance formed by the tissue cells. As Burrows experiments have shown, the energy for activity in the body is derived from this coagulating substance. The coal tar stimulates growth in that it removes the cells from their more active blood supply and crowds them together. Whether the active removal of this coagulating substance from the cell tends also to accelerate the metabolism of the cell is yet to be solved.

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1 Since this study has been completed Mertens has noted the migration of tar from the skin of rats to internal organs, *Z. Krebsforsche*, 1923, xx, 211.