"Why not dilate strictures?" you ask. "The operation is safe in competent hands; the immediate results are gratifying; the risks of alternative operations are considerable; and histological preparations have shown that, even in patients who have had a long clinical history of dysphagia, muscle may predominate over scar in the 'tumour.' Moreover, many patients have been jockeyed along from year to year by repeated endoscopies."

The case against dilatation is this. Immediate relief of dysphagia is no criterion of cure. By stretching a stricture of this sort nature's barrier against reflux is broken down, and the inexorable complications of oesophagitis are rekindled to flame again. With each exacerbation the scar, that remains for ever, penetrates the muscle of the gullet more deeply and rises upwards in the mediastinum. The end is worse than the beginning.

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The number of emergency calls received by the London Ambulance Service continues to increase. In a report to the Health Committee Dr. J. A. SCOTT, the medical officer of health, says that 104,983 calls were received in 1959; in 1958 the number was 99,188 and in 1957 97,535. Calls to street accidents in 1959 numbered 21,701, 2,519 more than the previous year. Despite the extra journeys the average time taken by ambulances to reach the scene of accidents was only a fraction of a minute longer than 1958—6.6 minutes instead of 6.5. On average, patients were admitted to hospital 20.9 minutes after the calls for help were received. There were the usual peak hours for the different kinds of call—maternity cases between 3 and 4 o'clock in the morning, home accidents at midday, street accidents in the late afternoon and early evening, and cases of assault towards midnight. Maternity cases, however (27,429 of them), continued to outnumber all others.

ON VIRUS METABOLISM AND
NEOPLASIA

BY

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The term "virus" covers a range of organisms varying widely in physical and biological properties. One common feature is that all are obligate intracellular parasites. No valid evidence has been produced that any virus—bacterial, plant, or animal—possesses any equipment which would allow it metabolic activity in its own right, and it is generally assumed that virus multiplication is dependent on the metabolism of the host cell. The study of "virus metabolism" therefore resolves itself into the search for modifications of the metabolism of the host cell in the course of viral infections. With phage-infected bacteria this has been most profitable, but with infected animal tissues has so far only scantily illuminated the problem of virus multiplication.

Several limitations must be imposed on the interpretation of biochemical changes in virus-infected tissues. When only a small proportion of cells in the tissue are infected compensatory changes may occur in adjoining cells, so that a composite picture is presented of cells under the influence of two stimuli. This applies not only to complex tissues *in vivo* but also to tissue cultures containing only one cell type. The effects of infiltration with inflammatory cells can usually be excluded, either by adequate histological control or by the nature of the host tissue—that is, in tissue culture. Alterations in the overall metabolic activity of a tissue may occur owing to necrosis of some cells. It is important not to confuse the changes secondary to cell death with those causing cell death. For this reason, studies on tissues late in the course of viral infection (and damage) must be interpreted with great reserve. In general, the earlier a change is observed the more likely is it to be primarily induced by the virus.

Substances other than virus contained in the inoculum may also produce metabolic alterations, and this possibility must be excluded by inoculation of controls with material of similar origin not containing virus. Finally, where single enzyme activities are measured, alterations may be due not only to an absolute increase or decrease in the quantity or activity of apoenzyme or coenzyme, but also to a "diluted" or "concentration" effect of an increase or decrease in the amount of fat or water in the individual cell, or the amount of extracellular fluid in the tissue. Estimation of water and lipid in the tissue and calculations of activities per unit dry or lipid-free dry weight deals satisfactorily with this potential course of error.

Ectromelia virus multiplying in mouse liver forms a virus-host system for which these objections and limitations are not serious.

The activities of various enzymes in this system have been estimated and in part reported (de Burgh, 1957; Nelson and de Burgh, 1958, 1959). These have been compared with similar estimations in regenerating mouse liver. In this case new normal liver is rapidly reproduced and cell division occurs; this may be taken

as an example of normal or balanced growth. The cytoplasm of ectromelia-infected liver increases in the absence of cell division, while in neoplastic liver cell division predominated over cytoplasmic growth. Both are in effect examples of different types of unbalanced growth. The fact that growth is "unbalanced," rather than any similarity in the type of imbalance, has prompted this discussion.

Though the virus theory of neoplasia may not be valid as a general proposition there is considerable interest in the idea that both the virus-infected cell and the cancer cell are subject to a disorder in the "replication of specific pattern" (Burnet, 1956). The neoplastic change ultimately induced by chemical carcinogens is thought to be due possibly to the gain and subsequent loss of an antigenic marker (Green, 1954), while the virus-infected cell may suffer damage directly or indirectly as a result of the production of "foreign" nucleic acids and protein. Disordered growth and macromolecular change seem to be associated. In each case metabolic alterations accompany these changes. It seems profitable to compare our observations on ectromelia-virus-infected and regenerating livers with those made by others on spontaneous, induced, and transplanted liver tumours of mice and rats; on the livers of mice and rats carrying tumours at other sites; and on the changes induced by viruses multiplying in other tissues, so far as these can be interpreted. It has been suggested (Bauer, 1953) that the diversion of basic precursors (amino-acids, purines, pyrimidines, etc.) may be the cause of alterations in enzyme activities in virus-infected tissues. Therefore the comparison includes enzyme changes occurring in nutritional deficiencies. Finally, foetal liver is included, as neoplastic tissue is sometimes said to be metabolically more primitive than its parent tissue.

It is apparent even from this limited survey that there is no consistent pattern of enzyme changes in virus-infected tissues or in various hepatic neoplasms. In neither case has any completely characteristic biochemical change yet been described. The lack of specificity suggests the possibility that some changes might be quite incidental to the process of virus multiplication or neoplasia.

The remainder of this discussion is concerned with the following three factors. (a) *A possible mechanism of production of these changes in virus-infected cells, based on competition between nucleic acids of virus and host cell.*—It is suggested that metabolic changes occur partly as a result of inhibitions of replication or turnover of a host component for the synthesis of which a particular type of nucleic acid (N.A.) is the template, and partly as a compensation by the host cell for these changes. It is not thought necessary for these changes to be purposeful.

(b) *The applications of such a mechanism in explaining the host specificity of viruses and the occurrence or otherwise of a cytopathic effect.*—Host specificity could be explained on the basis of structural similarity between virus and host cell N.A. Cytopathogenicity may be determined by the inhibition of particular N.A. templates by a virus N.A. leading to disturbance of a key metabolic pathway or to loss of an essential structural component of the cell.

(c) *The relation between the virus-induced metabolic changes and carcinogenesis.*—Virus infection can produce changes in cells which are analogous to those which appear to occur in neoplastic cells—namely, metabolic

change and unbalanced growth. The possible role in carcinogenesis of a process similar to the competition between N.A.s suggested for virus infection is discussed.

Virus Metabolism and Virus Multiplication

When a cell is infected by a virus the virus appears to break partly or wholly into non-infectious particles which are thought to be the actual multiplying units. The fact that purified (protein-free) N.A. from some viruses is infective suggests that these units are N.A. and that virus-specific protein is not essential to multiplication. Some form of competition between virus and host N.A. must occur (Gottschalk, 1957). They may compete for either N.A. or protein precursors or for the energy to incorporate these precursors. The success of the virus components may be due to lowered entropy. When the virus components succeed there are two results (Fig. 1).

FIG. 1.—N.A.-H.: Host nucleic acid (R.N.A. or D.N.A.). N.A.-V.: Virus nucleic acid (R.N.A. or D.N.A.). —: Competition. ----: Inhibition.

1. *Replication of virus components, usually followed by the appearance of new infectious virus.*—In ectromelia-infected mouse liver this is reflected in a 10^2 – 10^6 -fold increase over the original titre.

2. *Inhibition of the replication or turnover of the host component.*—On current views of protein synthesis this would be reflected in a decreased synthesis of the specific protein of which that N.A. unit (or its derivative) was the template. This would occur whether the competition were for N.A. or for protein precursors. Decreased activities of some enzymes would be one reflection of this. There seems to be no need to ascribe purpose to the decreases in some enzyme activities, as they could occur as a result of a chance similarity between virus and host template. The effects on cell metabolism of purified N.A. from viruses (or other sources) and the association of different metabolic changes with different fractions of nucleic acids from the same source would obviously be of interest.

Any hypothesis of the metabolic effects of virus multiplication must also explain why there are increases in certain enzyme activities. On the hypothesis outlined above it is necessary to consider these as a compensatory response to the inhibition of some metabolic pathways as a result of virus infection. This involves the concept of a feed-back mechanism. This could conceivably occur at any of three levels (Fig. 2). (1) In the case of a rapidly turning-over enzyme, inhibition of its synthesis would soon result in a decrease in its level of activity and an accumulation of one or more metabolites. This accumulation could be the stimulus to increased production of the enzyme(s) of an alternative pathway. The metabolite might be an intermediate in the synthesis or breakdown of any cell component including coenzymes. (2) The decrease in enzyme 1 might be the information according to which enzyme 2 is produced in increasing

amounts. (3) The decrease in $N.A._1$ may directly or indirectly stimulate the synthesis or turnover of $N.A._2$.

Xanthine dehydrogenase activity of mouse liver is found to be increased very early in the course of ectromelia-virus infection, before the appearance of either new virus or complement-fixing antigen (Nelson and de Burgh, 1959). If, as appears likely, this is a compensatory response it is certainly a very rapid one.

FIG. 2.—Possible mechanisms of stimulation of enzyme activity in virus-infected cells. (Key as for Fig. 1.)

and suggests either a high turnover rate of the enzyme or a very rapid transfer of information via level No. 3 above. The possible functions of this enzyme in alternative metabolic pathways are not understood, though a part in 2-carbon metabolism is suggested. Its elevation in mouse brain infected with a wide variety of neurotropic viruses as well as in ectromelia-infected mouse liver suggests a fundamental role in the process of virus multiplication.

This hypothesis has certain corollaries.

Host Specificity of Viruses.—This could be explained on the basis of structural similarity between the virus N.A. and the host cell N.A. A cell may be resistant to a virus either because of structural dissimilarity, so that competition does not occur; or because the host cell N.A. succeeds in the competition (possibly because of lower entropy).

Virus Ecology

For the purpose of this discussion the effect of host immunity due to antibody or other factors outside the potential host cell is ignored. There are several possible types of relationship between a virus and its host cell.

1. **Virus multiplication with cytopathic effect.**—This will be observed when key metabolic pathways are disturbed as a result of the virus succeeding in competition with the host. This may occur entirely because of a chance similarity between virus and host N.A. templates. The virulence of a virus could be due to the extent of the damage thus inflicted in terms of (a) numbers of key pathways involved; (b) the degree of damage to each particular pathway. Cytopathogenicity may also result from physical disorganization of a cell. This may in turn be the result of inhibition of synthesis of a structural protein either directly as a result of virus-host N.A. competition or indirectly as a result of metabolic damage.

2. **Virus multiplication without cell destruction** (for example, mumps virus in the amniotic cavity of the chick embryo).—This might be explained on the basis of competition between virus N.A. and host N.A. governing non-essential metabolic processes in the host.

3. **Persistence of virus in the host cell without multiplication and without damage to the cell.**—This possibility has been explored mainly in connexion with rabbit papillomatosis, and considerable doubt has been cast on its validity (Beard, 1956); it is not considered further here.

4. **Multiplication without cell destruction and with protection against other virus.**—This is one form of interference.

The conditions governing its occurrence or the opposite phenomenon of dual infection are obscure. Henle *et al.* (1958) have described persistent infection of two lines of human cells with Newcastle disease, mumps, or 6-6 viruses without cytopathic effect and with protection against cytopathogenic influenza A (PR8), herpes simplex, and especially vesicular stomatitis viruses. Metabolic change occurred in the persistently infected tissue cultures in the form of increased aerobic glycolysis. Phenomena such as this represent a form of acquired cellular immunity. They might be explained as being due to the exclusion of a second virus N.A. by the first virus N.A., which has competed successfully with host N.A., the loss of which is non-lethal. Evidence for the involvement of N.A. in this type of interference is that 2,5-dimethylbenzimidazole, which inhibits N.A. synthesis and the multiplication of influenza virus, also prevents interference among various strains of the virus (Tyrrell and Tamm, 1955).

It is clearly not in the best interests of a virus to destroy its host. In the absence of a permanent supply of fresh susceptible hosts, changes in the character of a virus in the direction of decreased cytopathogenicity are likely to have considerable survival value. On the basis of the hypothesis above, these are likely to be changes in virus N.A. which allow it to replicate in competition with host N.A. without complete suppression of essential functions. Comparative studies of the effects of cytopathogenic and non-cytopathogenic viruses on the metabolism of similar host cells would obviously be of considerable interest in this respect.

Site of Damage in Ectromelia-Virus-Infected Mouse Liver

The accompanying Table shows alterations in levels of enzyme activity in all cell fractions except microsomes. Changes occur in the nucleus despite the apparent absence of viral material. In addition to the later biochemical changes, virus infection inhibits mitosis in regenerating liver as early as 10 hours after infection—that is, early in the eclipse phase (Miller and de Burgh, 1957). Ectromelia virus has not been analysed completely, but it is most likely that, as with the closely related vaccinia virus, its nucleic acid is deoxyribonucleic acid (D.N.A.). In the host cell, D.N.A. is overwhelmingly a nuclear component and is synthesized in the nucleus. However, the terminal stages of virus synthesis seem to occur in the cytoplasm, and metabolic changes occur in the cytoplasm. There is clearly a need to attempt to detect viral D.N.A. in the nucleus in the earliest stages of infection. This is likely to present considerable technical difficulties, as even with a high virus:cell ratio the amount of virus entering the cell is only 0.0004 of the total cell volume.

"Virus Metabolism" and Carcinogenesis

The ability of some viruses to cause neoplastic growth is undoubted. Of much less certainty are the following questions: Is this a direct result of virus infection? if so, What is the mechanism of production of the neoplastic change? and What is the relation of the process of virus multiplication in general to the process of neoplasia? In a review of tumour-virus problems Furth and Metcalf (1958) discuss three theories of the action of viruses in causing neoplasms: conditioning, mutation, and transduction. By conditioning is meant some correctable disturbance in the forces regulating or influencing the growth of a cell; it is suggested that a tumour virus may interfere with the production of a growth-regulating substance and that such cells might then multiply unrestrained, or that the virus prevents the cell from responding to normal extrinsic control. It is

also suggested that tumour viruses cause a "somatic mutation" or are genic material derived from neoplastic or potentially neoplastic cells and act in a manner analogous to the transduction of bacteria.

It is convenient to view neoplastic transformation of a cell as involving both a metabolic change—possibly a depletion of some enzymes (Potter, 1958)—and a change in its surface character. The former would release the cell from general growth-restriction and the latter would release it from local controls of the type visualized by Weiss (1947). In considering the relation between viruses and neoplasia there are two fundamental questions: (1) Do these changes occur in cases of infection by known tumour viruses? and (2) Can analogous changes be induced in other cells by other viruses which do not cause tumours? There appears at the moment to be a presumptive "yes" to the first question. The changes observed in ectromelia-infected mouse liver appear highly relevant to the second.

In ectromelia-infected mouse liver there occur both an abnormal form of growth and metabolic changes which are in some respects similar to those observed in hepatic neoplasms. Though abnormal growth is cytoplasmic and not nuclear, and though these changes are acute and followed by cell-death, there are obvious parallels. Whether one calls the process conditioning, mutation, or transduction, there is a possibility that at least some of the metabolic changes underlying neoplasia result from competition between host cell and foreign ("virus") N.A.

Tumour viruses with a short latent period, such as the Friend agent (Metcalf *et al.*, 1959), would produce all the necessary changes. Tumour viruses with a long

latent period would require additional processes for the production of some changes, made possible by the initial viral competition. The retention of such changes in daughter cells requires comment. If the virus remains present at an unaltered concentration in each cell the direct competition theory is relevant. If the amount of virus decreases, as it apparently does in, for example, the Rous sarcoma (Groupé and Rauscher, 1957) or Shope papilloma (Greene, 1953) virus tumours, then additional mechanisms must be invoked. Virus N.A. may persist and be passed on from cell to daughter cell, though in a form or in quantities not demonstrable by current techniques.

In other "spontaneous" neoplasms some at least of the changes involved may be due to several more or less chance competitions of this type, no single one of which is adequate to produce either neoplasia or other recognized defect. Non-viral tumours would appear compatible with this thesis. Direct damage to cell N.A. by—for example, ionizing radiation or alteration of cell N.A. synthesis by chronic inflammation, could institute stepwise alterations of metabolism leading to neoplastic transformation.

Somewhat similar views on virus multiplication (Gottschalk, 1957) and carcinogenesis (Potter, 1958) have been expressed by other writers. There has, however, always been a gap between observed facts in regard to either virus multiplication or cancer metabolism and the mechanisms proposed to explain them. The observations of an association between virus multiplication, metabolic changes, and abnormal or unbalanced growth in ectromelia-infected mouse liver may help to fill this gap.

Enzyme Levels in Virus-infected, Neoplastic, and Other Tissues

Tissue	Enzyme								
	Nuclear		Mitochondrial	Lysosomal				Microsomal	Soluble
	D.P.N. Synthesis	Adenosine Deaminase	Succinic Dehydrogenase and Mitochondria	Uricase	Acid Phosphatase	Cathepsin	Catalase	Glucose-6-phosphatase	Xanthine Oxidase or Dehydrogenase
Ectromelia-infected mouse liver	— ¹⁰	— ¹²	+ ¹⁹	± ¹⁹	— ¹⁹	— ¹¹	± ¹¹	± ¹¹	+ ¹⁹
Other virus-infected tissues		+ (Neurotropes in mouse brain) ⁸	Variable ^{4, 8, 14}		— (Polio-virus in monkey kidney) ¹⁸ ± (Bunyamwera in Ehrlich ascites. Carcinoma) ⁸ ± ¹⁹	— (Coxsackie in HeLa) ⁹			+ (Neurotropes in mouse brain) ⁸ — (Bunyamwera in Ehrlich ascites)
Regenerating liver	— ¹⁰	— (late) ¹²	— ^{1, 20, 25}	— ¹⁹	— ³			± ¹⁶	+ ^{15, 18}
Precancerous liver (azo-dye)			— (Mitochondria) ³	± ²¹	— ³			— ²⁷	— ²⁰
Azo-hepatoma	— ¹⁰	± ²⁰ + ¹³	— (Mitochondria and enzyme) ^{3, 22} — (Mitochondria) ³ — ²²	± ²¹	— ³			— ²⁷	— ²⁰
Spontaneous hepatoma	— ¹⁰			— ¹³	± ³	± ³			— ²⁷
Transplanted hepatoma					— ³	— ³		Nil ²⁷	
Livers of tumour-bearing animals	— (Leukaemia) ± (Solid tumour) ²³ — ⁷			— ²⁴			— ³	— ²⁷	
Foetal liver								— ²⁶	— ²⁷
Livers of starved animals			— (Proportional to loss of cytoplasm) ²	— (Proportional to loss of cytoplasm) ²	+ ³	— (Proportional to loss of cytoplasm) ³			— (Not proportional to loss of cytoplasm) ³

+ Increase. ± No change. — Decrease.

¹ Allard *et al.* (1952).

² Allard *et al.* (1957a).

³ Allard *et al.* (1957b).

⁴ Bauer (1947).

⁵ Bauer (1951).

⁶ Bauer and Bradley (1956).

⁷ Brinster and Morton (1956).

⁸ Colter *et al.* (1957).

⁹ Crowell and Syverton (1958).

¹⁰ d' Burgh (1957).

¹¹ d' Burgh (unpublished results).

¹² d' Burgh and Nelson (unpublished results).

¹³ d' Burgh and Nelson (unpublished results).

¹⁴ de Ritis *et al.* (1957).

¹⁵ Feigelson *et al.* (1957).

¹⁶ Glock and McLean (1957).

¹⁷ Greenstein (1954).

¹⁸ Kovacs (1956).

¹⁹ Nelson and de Burgh (1959).

²⁰ Reid and Lewin (1957).

²¹ Schneider *et al.* (1953).

²² Schneider and Potter (1943).

²³ Shuster *et al.* (1958).

²⁴ Thomson and Klipfel (1958).

²⁵ Tsuboi *et al.* (1951).

²⁶ Weber and Cantero (1955a).

²⁷ Weber and Cantero (1955b).

Summary

Ectromelia (mouse-pox) virus multiplying in mouse liver provides an excellent model for the study of the effect of a virus on the metabolism of its natural mammalian-host cell. In this host-virus system metabolic changes are accompanied by "unbalanced" (purely cytoplasmic) growth of the cell. Some metabolic changes occurring in this system are compared with those occurring (a) in other virus-infected tissues; (b) in regenerating liver showing "balanced" (nuclear and cytoplasmic) growth; (c) in precancerous and cancerous livers showing abnormal growth; (d) in the livers of tumour-bearing animals; and (e) in the livers of embryonic and starved animals. No consistent pattern of changes of enzyme activities is observed in either virus-infected or neoplastic tissues, nor are the changes similar to those in the livers of embryonic or starved animals.

A possible mechanism is suggested for the production of metabolic changes in virus-infected tissues. It is proposed that such changes occur as the result of more or less chance competition between virus nucleic acids and structurally similar host-cell nucleic acids which control, or form templates for, the synthesis of host enzymes. Some implications of this explanation are discussed with regard to various host-virus relationships.

Since virus infection, metabolic change, and unbalanced cell growth may be associated, the hypothesis of nucleic-acid competition is considered in relation to neoplasia. Neoplastic transformation may involve a metabolic change and a change in surface character: both these changes clearly could be the result of a process similar to that occurring in virus infection. The lack of pattern in enzyme changes in various hepatic neoplasms may be the outcome of chance competitions between foreign nucleic acid and host-cell nucleic acid, some of which may be quite incidental to the underlying primary changes characteristic of neoplasia. This hypothesis is discussed in relation to the causation of tumours by known tumour-viruses and to "spontaneous" neoplasms, in which at least some of the alterations involved may be due to nucleic-acid competitions.

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RIGHT HEMIHEPATECTOMY FOR PRIMARY HEPATOMA

WITH SPECIAL REFERENCE TO DIAGNOSIS AND BIOCHEMICAL CHANGES

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The surgical removal of the right lobe of the liver is a rare event. It has been performed for cysts and primary tumours confined to the right lobe, for carcinoma of the gall-bladder, for hepatic abscess, and for injuries to the liver; and may sometimes be indicated when the right lobe is the site of secondary neoplasm.

The following report describes some of the diagnostic, surgical, and biochemical features of a case in which the operation was performed for a primary malignant tumour of the liver.

Case Report

A schoolgirl now aged 14, with no previous medical history, began to have attacks of vomiting in 1957. On admission to hospital after a minor abdominal injury she was found to have gross hepatosplenomegaly. Investigation was unrewarding, and in March, 1958, laparotomy was performed. The hepatosplenomegaly was confirmed; the liver, though enlarged, looked normal; and liver biopsy showed normal liver tissue only.

Subsequently ascites and ankle oedema developed and the patient's condition deteriorated. In January, 1959, she was