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.

The experimental work referred to above has been supported by a grant from the National Health and Medical Research Council of Australia and was carried out in part during the tenure by one of us (D.S.N.) of a British Medical Association Ordinary Research Scholarship. We thank Mrs. I. M. Stephens for technical assistance.

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RIGHT HEMIHEPATECTOMY FOR PRIMARY HEPATOMA

WITH SPECIAL REFERENCE TO DIAGNOSIS AND BIOCHEMICAL CHANGES

BY

A. OTAKI, M.B., M.R.C.P.

Lecturer in Chemical Pathology, St. George's Hospital,
London

A. E. READ, M.D., M.R.C.P.

Senior Registrar and Tutor in Medicine, Department of
Medicine, Postgraduate Medical School of London,
Hammersmith

J. STUBBS, M.B., B.S., Ph.D.

Surgical First Assistant, St. George's Hospital, London

AND

H. SCULTHORPE, F.I.M.L.T.

Senior Technician, Department of Clinical Pathology,
St. George's Hospital, London

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

referred to Hammersmith Hospital for further investigation under the care of Dr. Sheila Sherlock.

Physical examination revealed a wasted, ill-looking girl with ascites and anaemia (Fig. 1). The enlarged liver was firm, with a smooth surface 5 in. (12.5 cm.) below the right costal margin, and the spleen extended 4 in. (10 cm.) below the left costal margin. There were no cutaneous stigmata of chronic liver disease and no enlarged lymph nodes. Rectal examination was normal.

Investigations (January, 1959).—Weight 6 st. 6 lb. (40.8 kg.). Haemoglobin, 8.8 g. (60%); M.C.H.C., 31.5%; W.B.C., 7,000/c.mm. (normal differential count); platelets

FIG. 1.—Patient before operation, showing abdominal distension due to hepatosplenomegaly and ascites and the marked degree of muscle-wasting.

right pleural effusion; barium meal examination revealed no abnormality in the stomach and there were no oesophageal varices; and bone films were normal.

At this stage, the condition still undiagnosed, repeat liver biopsy and a portal splenogram were performed under general anaesthesia. The portal splenogram showed normal splenic and portal-vein filling (Fig. 2) and normal filling of the left lobe of a greatly enlarged liver. On the right side, vessels were absent and neighbouring portal radicles were displaced medially. These appearances were suggestive of a large tumour in the right lobe of the liver. Needle biopsy of the liver obtained by the intercostal route, from the area corresponding to the filling defect, yielded a white and friable tissue whose neoplastic character was confirmed by microscopy. This revealed an anaplastic tumour suggestive of a primary hepatoma.

The patient was referred to Mr. Rodney Smith at St. George's Hospital for surgical removal of the tumour, a procedure which, though formidable, was considered to be a worth-while risk.

Operation.—This was performed on February 23, 1959. The approach was essentially that of Pack and Baker (1953). A long right paramedian abdominal incision was made. The right lobe of the liver was found to be greatly enlarged and splenomegaly was present. An adhesion joining the liver

normal. Urine, protein present (84 mg./100 ml.). Tests for occult blood in stools negative; serum electrolyte levels normal; blood urea, 34 mg./100 ml.; W.R. and Kahn test negative. Liver-function tests: bilirubin, 0.2 mg./100 ml.; cholesterol, 166 mg./100 ml.; alkaline phosphatase, 15 K.-A. units; thymol turbidity, 1 unit; zinc sulphate, 0 unit; prothrombin time, 15 sec. (control time, 12 sec.); transaminases—G.O.T. 19 units/ml., G.P.T. 9 units/ml.; total protein, 6.6 g./100 ml. (albumin 3.4 g. (later falling to 1.9 g.), globulin, 3.2 g.). Electrophoresis showed an increase of α_2 - and beta-globulins (see Fig. 5). Serum iron, 38 mg./100 ml. Examination of the sternal marrow showed a hypercellular marrow with evidence of iron deficiency. Coombs test negative; L.E. cells not seen. There was moderate generalized aminoaciduria. The serum copper oxidase was normal. The ascitic fluid was clear and straw-coloured. No cancer cells or tubercle bacilli were found in it.

X-ray examination: the chest film showed no abnormality apart from a small

FIG. 2.—Pre-operative splenogram, showing absence of vascular filling in right lobe of liver, compression of vessels in left lobe, and widening of portal-vein bifurcation.

to the diaphragm at one point was resected later with the right lobe. Since the thoraco-abdominal approach allows the liver to be herniated into the thorax and permits a good view of the porta hepatis, the ninth costal cartilage was divided, the abdominal incision extended into the intercostal space, and the diaphragm split towards the inferior vena cava. After identification of the structures of the porta hepatis, a formal right hemihepatectomy was performed, using the technique described by Rodney Smith (1958). The diaphragm was reconstituted and the wound closed, leaving two corrugated drains from the liver and a water-seal drain from the chest.

The specimen weighed 1,860 g. and contained a solitary tumour 15 cm. in diameter, surrounded by a false capsule of liver tissue (Fig. 3).

The line of section was beyond the tumour margin. The microscopical appearance was that of a malignant hepatoma. The low mitotic rate and the degree of differentiation indicated a slowly growing tumour.

Post-operative Management.—The chest drain was removed after 24 hours. Intravenous therapy with 4.3% dextrose in 0.18 N saline was continued for four days. In addition, three albumin infusions

FIG. 3.—Specimen removed at operation, consisting of right lobe of liver and the tumour (about 15 cm. in diameter), which is surrounded by a false capsule of normal liver tissue.

were given (total 75 g.). Vitamin K, 10 mg. intramuscularly, was given daily for seven days. Two days after operation the patient became pyrexial, and eight days later a right subphrenic abscess was opened and drained. The abscess persisted, but after being reopened three weeks later her further recovery was uneventful.

Follow-up.—The patient was readmitted to hospital six months after operation for reassessment. On examination she showed a vast improvement in physical status. There was some clinical enlargement of the left lobe of the liver, and the spleen, though just palpable, was much reduced in size. She weighed 6 st. 12 lb. (43.5 kg.) and was about to return to school.

Investigations (July, 1959).—Haemoglobin 12 g. (81%); M.C.H.C., 31.5%; W.B.C., 6,000 Liver-function tests: bilirubin, 0.3 mg./100 ml.; cholesterol, 165 mg./100 ml.; alkaline phosphatase, 18 K.-A. units; total protein 7.2 g./100 ml. Electrophoresis of serum protein was normal. Transaminases: G.O.T. 16 units, G.P.T. 10 units. A repeat portal venogram showed that the portal-vein radicles were no longer displaced medially and the left branch of the portal vein and the left lobe of the liver, now greatly hypertrophied, filled normally. The intrasplenic pressure had risen to a level of 15 mm. Hg post-operatively (just above the upper limit of normal) from the pre-operative level of 6 mm. Hg.

Diagnosis of Primary Hepatic Neoplasms

Primary hepatic neoplasms more commonly occur in cirrhotic livers (Greene, 1939) and therefore deterioration of the clinical condition of a cirrhotic patient may indicate the presence of a neoplastic change. When primary liver cancer occurs in the non-cirrhotic liver, its early recognition is valuable because the patient is usually young, because the tumour may be slow to metastasize, and because, with modern technique, the surgical risk in itself is not too great.

Some diagnostic points of possible importance arising from a comparison of this case with other cases are: the serum electrophoretic pattern; the serum alkaline phosphatase; splenic portal venography and liver biopsy; and ascites.

Serum Electrophoretic Pattern.—Six patients with primary hepatic neoplasms seen at Hammersmith Hospital in the past three years have shown the same serum protein abnormality on electrophoresis. The α_2 - and beta-globulins were increased, in contrast to the usual gamma-globulin increase seen in hepatic cirrhosis. It seems, therefore, that in a young person with unexplained hepatomegaly this alteration in serum protein justifies a vigorous attempt to exclude a primary liver neoplasm, including the use of splenic portal venography.

Serum Alkaline Phosphatase.—That malignant hepatoma need not be accompanied by abnormal liver-function tests, and in particular abnormal alkaline phosphatase and transaminase levels, is proved by the findings possible in this case. Nevertheless, helpful collateral evidence of an intrahepatic space-occupying lesion is provided by a raised serum alkaline phosphatase, provided bone disease and obstructive jaundice are absent. In four of the six cases the alkaline phosphatase was raised (22–102 K.-A. units), but in the present case and one other the levels were normal for the patient's age.

Splenic Venography and Liver Biopsy.—Bergstrand and Elkman (1955) have shown that splenic portal venography can be used to demonstrate primary and secondary tumours of the liver. Venography in our patient defined the extent of the lesion, but also indicated that as the left lobe was unaffected the condition was suitable for surgery. Early venography may produce the evidence of a deep-seated space-occupying lesion which biopsy may be unable to supply. Thus nine months after a negative operative biopsy, needle biopsy yielded pathological tissue from a tumour which must have enlarged in the interim.

Ascites.—Since ascites was present for some time before the patient's admission to Hammersmith Hospital, despite normal total serum proteins, it was logical to consider the possibility of peritoneal involvement by the tumour. It is therefore important to recognize that in such a case ascites is not necessarily a sign of inoperability. The cause of the splenomegaly is unknown, for it was not due to portal hypertension or involvement by tumour.

Biochemical Changes

Serum Bilirubin and Alkaline Phosphatase

Frequent liver-function tests and serum bilirubin, cholesterol, and transaminase estimations were made

FIG. 4.—Biochemical changes before and after operation. Top: The serum alkaline phosphatase and bilirubin values. Middle: The serum glutamic oxalacetic transaminase (S.G.O.T.) and serum glutamic pyruvic transaminase (S.G.P.T.) values. Bottom: The total, esterified, and free cholesterol values.

after the operation. Fig. 4 (top graph) relates serum bilirubin to alkaline phosphatase. Both show a rapid post-operative rise, with curves of the same general character. The bilirubin did not exceed 1.9 mg./100 ml. despite blood transfusion, but the alkaline phosphatase rose to 75 units (K.-A.). The bilirubin returned to normal (0.6 mg./100 ml.) by the twenty-fourth day, whereas the alkaline phosphatase remained above normal (18–20 K.-A. units at 14 years) until the forty-first post-operative day.

Figures published by Califuno *et al.* (1958), after partial hepatectomy in rabbits, show that the alkaline phosphatase rose from three to nine times the pre-operative level in two days and regained initial levels by the eighteenth day. After partial hepatectomy in rats the regenerating cells are reported to be rich in alkaline phosphatase, at a time when the blood levels are also high (Rosenthal *et al.*, 1952). However, incomplete biliary obstruction is also associated with high alkaline phosphatase values, out of proportion to the serum bilirubin (Sherlock, 1958), and congestive hepatic changes due to increased portal blood-flow through the remaining lobe of the liver may account for serum bilirubin and phosphatase findings in this case. Evidence for the presence of these changes after partial hepatectomy has been shown in dogs (Mazzec *et al.*, 1957). Six and eight months after surgery the serum alkaline phosphatase and bilirubin were 18 and 22 units and 0.3 mg. and 0.5 mg./100 ml. respectively.

Serum Transaminase

Serum transaminase levels (Fig. 4, middle graph), which were normal pre-operatively, rose steeply immediately afterwards to 420 S.G.P.T. units and 240 S.G.O.T. units respectively, and fell precipitously to the normal region (below 40 units) within 10 days. They represent extensive but finite tissue damage and cannot be related to liver-cell regeneration.

Slight elevations above the normal upper limit occurred later but without correlating with the clinical and surgical events connected with a subphrenic abscess present at the same time.

In July, 1959, the results were 10 S.G.P.T. units and 14 S.G.O.T. units respectively.

Serum Cholesterol

Fig. 4 (bottom graph) illustrates the changes in serum cholesterol after surgery. Pre-operative values of 161 mg. and 166 mg./100 ml. were obtained by Zak's ferric chloride method (Zak, 1957), which gives consistently higher results than Sperry's digitonin method (Schoenheimer and Sperry, 1934), used to derive the values for the graph shown.

Initial post-operative readings, even allowing for the expected difference, were unaccountably low. Total cholesterol on the first and sixth post-operative days were 72 mg. and 65 mg./100 ml. respectively. Such low values are associated usually with severe wasting disease, anaemia, hyperthyroidism, and acute infection. Prolonged malnutrition certainly characterized this case, but as pre-operative cholesterol values were normal, and as malnutrition is associated with a reduction in plasma volume (Denz, 1947; Walters *et al.*, 1947), it is more likely that the decrease was due to re-expansion of the plasma volume in response to parenteral therapy. During the operation 5 pints (2,840 ml.) of blood was transfused, and in the next three days the patient received 75 g. of albumin. A week after operation the

total cholesterol rose steeply from 65 mg. to 110 mg./100 ml., and during the next 17 days subsided to 77 mg./100 ml. This increase did not begin until the transient bilirubin elevation had passed its peak. These changes could be due to intrahepatic biliary obstruction associated with hepatic congestion (Mazzec *et al.*, 1957), but why there was a lag between the cholesterol and bilirubin peaks is difficult to explain.

The percentage of esterified cholesterol, at first subnormal (53% of total; normal 60–80%), began to increase despite the presumed obstructive process. By the twenty-second day after operation, though the total was still low (90 mg./100 ml.), the percentage of esterified cholesterol had become normal (63%). It seems, then, that in regard to cholesterol a moderate degree of intrahepatic obstruction has a mechanical effect upon the serum cholesterol level but not a functional effect upon liver cholesterol metabolism.

The general rise in cholesterol level continued. At discharge in May, 1959, the total was 128 mg./100 ml., and five months later it was 125 mg./100 ml., with 69% as esterified cholesterol. The total cholesterol by an alternative method was 165 mg./100 ml. These results are within the normal range for the methods used.

Serum Proteins

The patient suffered progressive anorexia, and her nutrition had been poor for many months, as the pre-operative photograph clearly shows. In the month before operation the serum albumin fell from 3.4 g. to 1.9 g./100 ml., reducing the total protein to 4.7 g./100 ml.

It is widely agreed that tissues in general undergo severe protein depletion before the plasma protein is reduced to any great extent. In our patient, undernourished for so long, tissue depletion is assumed to have reached a critical degree. Continued tumour growth, ascites formation, and decreasing protein intake may have tipped the negative nitrogen balance to the point at which the serum albumin would be greatly reduced.

During the operation 5 pints (2,840 ml.) of blood was transfused, followed over the next three days by 75 g. of purified human albumin. At the end of this time the total protein was 7.1 g./100 ml. (albumin 3.5 g.). But thereafter the albumin fell continuously until the twelfth day to 1.8 g./100 ml., a fall largely masked in the total protein levels by a simultaneous increase in the globulins to 4.5 g. from 2.8 g./100 ml.

The albumin then rose slowly, and by the fortieth day the total protein was 7.6 g. and the albumin 3.5 g./100 ml.

The electrophoretic analyses (Fig. 5) indicate some of the changes discussed above. They show, too, the α_2 - and beta-globulin increase referred to in discussing diagnosis. These changes commonly occur in nephrosis, therefore it is not surprising that their occurrence in six cases of primary hepatic tumour should raise the question of their diagnostic value. The α_2 - and beta-globulin together form about 17% of the total serum proteins and are largely concerned with the carriage of various substances about the body. Kekwick (1956) related the raised beta-globulin in nephrosis to the high cholesterol levels found in that condition. In our case, since both serum cholesterol and serum bilirubin were normal pre-operatively, it was not possible to account for the globulin changes in the same way.

The increase in α_2 - and beta-globulin may, of course, be a specific response to a hepatic neoplasm or even the product of the tumour's own metabolism, but the possible effects of hypoalbuminaemia and malnutrition must be taken into account before seriously considering that this is the case. Thus Gutman (1948) states that an alpha-globulin increase occurs almost constantly when albumin levels are lowered, except in many cases of multiple myeloma. Chow *et al.* (1945), examining the effects of starvation in dogs, found that despite a marked loss of albumin and a slight decrease in gamma-globulin alpha-globulin tended to rise. Kekwick (1951) noted increased serum globulin in human malnutrition, unassociated with a particular constituent. Certainly, however, an alpha- and beta-globulin increase may help to distinguish hepatic neoplasm from hepatic cirrhosis and other causes of hepatomegaly, and in appropriate cases their occurrence will warrant the inclusion of a hepatic neoplasm in the differential diagnosis.

After operation serum electrophoresis showed a peak of alpha-globulin (Fig. 5), and Schiff's reaction on a series of strips (McGuckin and McKenzie, 1958) showed

that the increase was in the glycoprotein fraction. The alpha peak then subsided, but alpha₂-globulin did not predominate again until the twenty-fourth day after operation. Califano *et al.* (1956) has also noted a moderate increase in alpha₁- and beta-globulins after partial hepatectomy in animals.

When the patient was discharged in May, 1959, serum electrophoresis was normal except for a moderate increase in gamma-globulin (total protein, 7.2 g./100 ml. (albumin 3.3 g.)).

Summary

The clinical features produced by a primary hepatic neoplasm (hepatoma) in a patient aged 13 years are described, together with an account of the diagnostic problems it presented. The value of portal splenography in the diagnosis of hepatic tumours is stressed and evidence is presented to suggest that consideration of the electrophoretic pattern (which may show an α_2 - β peak in each case) may be of value.

The biochemical changes resulting from removal of the right lobe of the liver in this patient are described. The noticeable features were a marked rise in the serum alkaline phosphatase and transaminases, accompanied by a slow rise in the serum cholesterol and its esterified fraction. The significance of these changes is discussed.

To Professor Sheila Sherlock, Mr. Rodney Smith, and Professor N. Martin we wish to express our thanks for their help and advice, and permission to publish. To Professor Sherlock and Dr. D. N. S. Kerr we are indebted for the collection of information on patients with primary hepatic tumours seen at Hammersmith Hospital.

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FIG. 5.—Changes in serum electrophoretic pattern. Top: Before operation, showing an α_2 - β -globulin increase. Middle: Three days after operation, showing a predominant increase in α_1 -globulins. (Excessive background altered the globulin baseline.) Bottom: Seven months after operation. The pattern is normal.

After the fourth teratology conference, which was held recently at the Memorial Sloan-Kettering Cancer Centre in New York City and attended by 76 scientists from Canada, England, France, Germany, and the U.S.A., the Teratology Society was formed with the aim of holding regular meetings in which investigations concerned with the aetiology and morphogenesis of congenital malformations could be presented and discussed. Inquiries about the Society should be sent to Dr. Marjorie M. Nelson, Department of Anatomy, School of Medicine, University of California, San Francisco, 22, California, U.S.A.