INTERCELLULAR COMMUNICATION AND TISSUE GROWTH

II. Tissue Regeneration

WERNER R. LOEWENSTEIN and RICHARD D. PENN

From the Cell Physics Laboratory, Department of Physiology, College of Physicians and Surgeons, Columbia University, New York

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ABSTRACT

Intercellular communication was examined in regenerating rat liver and urodele skin, two tissues of fast but normal growth. In both, cellular communication is in general as good as in their respective normal intact state. This stands in striking contrast to the lack of cellular communication in tissues with cancerous growth. Upon wounding of the urodele skin, the normally permeable junctional membranes of cells near the wound border seal themselves off, thereby insulating the interiors of the communicated cell systems from the exterior. When the cells of two opposing borders make mechanical contact in the course of wound closure, communication between them ensues within 30 min. Within this period all cell movement also ceases ("contact inhibition"). The possible implications of these findings in the control of tissue growth are discussed.

INTRODUCTION

The finding that cancerous liver has poor intercellular communication (18) poses the question of whether this is a manifestation of uncontrolled growth or a manifestation of growth in general. To answer this question, we shall inquire into the cellular communication of normally growing tissues. Regenerating rat liver and healing urodele skin were chosen for this purpose, because two major aspects of growth, cell proliferation, and cell movement are well represented in these tissues. In regenerating liver, cell proliferation is as fast as in the fastest growing cancerous liver; and in the healing skin, cell movement is as active as in invasive cancers.

The healing urodele skin also provided the opportunity to examine the beginnings of cellular communication as two advancing cell fringes establish contact in the process of wound closure. The study of this point is our second purpose.

METHODS

LIVER: The abdominal cavity of adult white laboratory rats was opened under ether anesthesia. The median and left lobes of the liver, which constitute about 70% of the total liver mass, were ligated at their pedicles and then excised (6). The abdomen was sutured and the animal was left to recuperate unanesthetized. The animals were killed 20, 48, 72 hr, and 1 wk after partial hepatectomy Their livers were quickly isolated in Krebs' solution, and cell communication was measured electrically as described in the first paper of this series (18). Most measurements were taken on the outermost layer of cells along the liver edge, where cells could be viewed in transillumination and where distances between intracellular recording points could be accurately determined. Some measurements were also made on cells in surface areas away from the edge and on cells deep in the liver. These measurements gave essentially the same results.

SKIN: Rectangular pieces of skin, 0.2–1 mm^2, were cut out on the back or abdomen of 15–35 mm long larvae of *Ambystoma opacum* and *Triturus viridescens*. The cut through the epidermis was made with a sharp microdissecting instrument under a microscope; the spatial definition of the cut was generally better than one-fifth of an epidermal cell diameter. The wound edges were visible at all times, and individual epidermal cells could be tracked in their movement until they came to a standstill when the two opposite edges met. Some of the cells around the wound edges were marked with dyes (azure B, orange G) to facilitate their recognition. The dyes were injected into the cells by iontophoresis with the same type of micropipettes used for passing current. The skin was left to heal *in situ* (temperatures: 19–25°C). For electrical measurements, the skin region containing the wound was isolated and mounted in a holder (14), as shown in Fig 1. The skin isolation followed immediately after the killing of the animal or its anesthesia with MS 222 (Sandoz). The cell outlines were clearly visible in this isolated preparation. Measurements were made at various stages of wound healing within 5–20 min after skin isolation, a given animal providing material for one stage only. The measuring arrangement was as illustrated in Fig. 1 *a* of the preceding paper (18), except that only one current-passing electrode was used.

The results were essentially the same in the *Ambystoma* and *Triturus* materials.

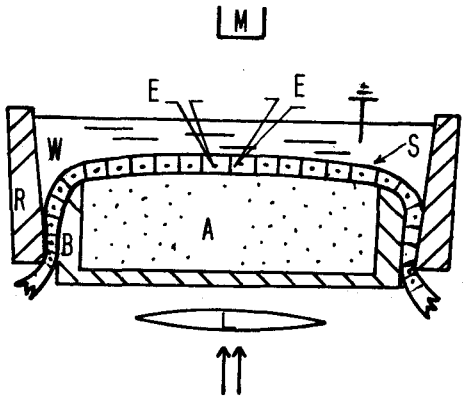

FIGURE 1 Diagram of skin set-up. *S*, skin piece mounted with its inner face on agar-Ringer's solution (*A*). The skin is fixed between the outside wall of a box (*B*) and a conic ring (*R*) of lucite which operate like an embroidery hoop (14). *W*, pond water containing 10^{-4}–10^{-3} M Ca. *L*, lens arrangement for darkfield or brightfield microscopic observations. *M*, compound microscope. *E*, microelectrodes.

RESULTS

Liver

Fig. 2 illustrates typical results of measurements of intercellular communication in the regenerating liver lobes. One microelectrode, fixed in one cell, passes current, and the other microelectrode records the resulting voltages (ordinates) from inside cells located at varying distances (*d*) from the current-passing electrode. Measurements are done 48 hr, 72 hr, and 7 days after hepatectomy. These times correspond with interesting growth phases: at 48–72 hr of regeneration, the rate of cell multiplication is maximal; the liver regenerates at the rate of 1–2 g/24 hr, and attains about 70% of its original mass at the end of this period (5, 6). By the 7th day, growth has slowed to less than 8% of the maximal rate, and the liver has regenerated to nearly its original mass (6).

As is shown by the results in Fig. 2, there is good cellular communication at all stages of liver regeneration. The resistive voltages are readily detectable over distances of more than 350 μ from the current source, i.e., over distances of more than 20 liver cells. In fact, no differences in cellular communication are detectable electrically between regenerating liver and normal liver. As in normal liver (21), the space constants of voltage decrement (to $1/e$) are 100–150 μ at all stages of liver regeneration; this is also true of the space constants measured 20 hr after hepatectomy (not shown in Fig. 2), at a time when intense changes in cellular metabolism are taking place, but relatively little cell multiplication has yet occurred (6).

Liver cells are not synchronous in their growth activities. The question thus arose whether a certain type of cell was selected by the electrical method. (This applied also to the experiments on cancerous liver described in the preceding paper.) Systematic explorations of communication were therefore made in several randomly chosen regions of regenerating livers (and cancerous livers). It is simple to implant a current-passing electrode in a given cell of the liver and to go from cell to cell with a recording electrode. In this manner, all cells in the regenerating liver parenchyma are found to be communicating. For example, in a typical exploration of 104 cells, whereof 6 were injured, as revealed by their zero resting potential and negligible input resistance, all 98 intact cells had space constants around 120 μ. A perfect contrast is provided by the results of similar explora-

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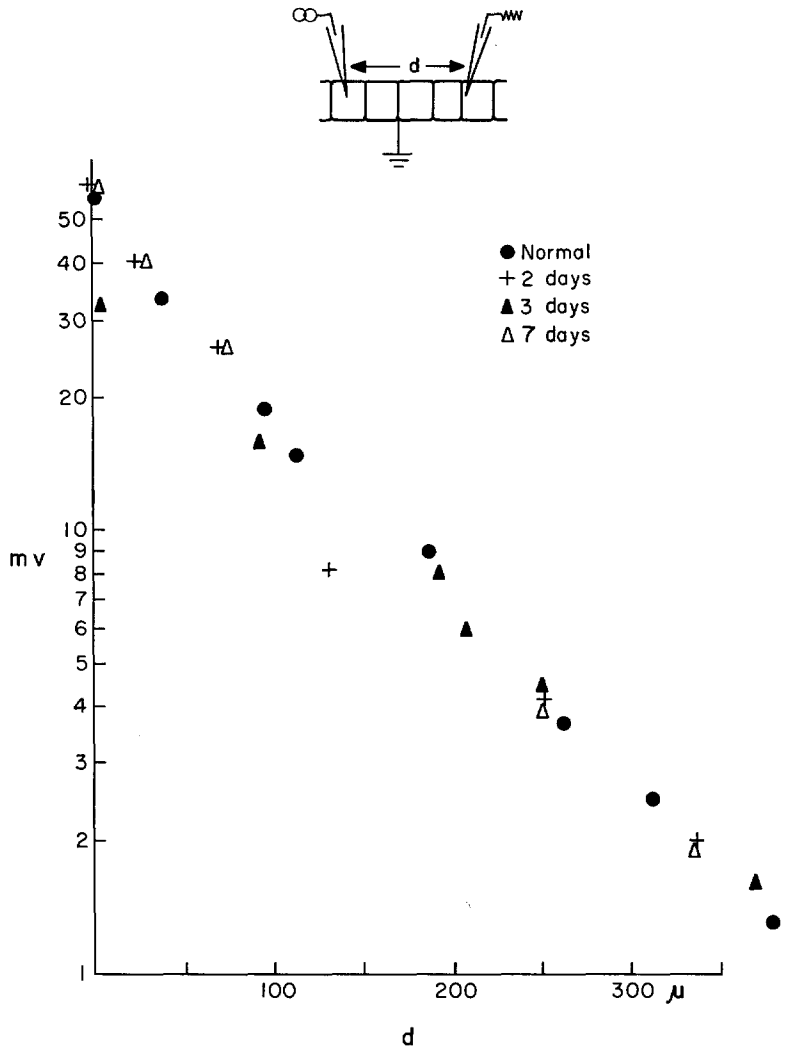

FIGURE 2 Cellular communication in regenerating liver. A current of 3×10^{-7} A is injected into a cell of the liver surface, and the resulting resistive voltages (ordinates) are recorded intracellularly at varying distances (*d*, abscissa) from the point of injection. (All measurements on cells of the liver surface). ●, normal unoperated liver; +, 48 hr; ▲, 72 hr; △, 7 days after partial hepatectomy.

tions in cancerous liver, where all intact cells show poor communication. For instance, in a nodule of Morris' cancer No. 7793, out of 32 cells examined (see Fig. 1 *b*, preceding paper), whereof 3 were clearly injured, 29 had communication ratios below detectable levels; and out of 122 cells in which input resistance was measured (single electrode, bridge method), all had resistances of 10^7 Ω. It seems thus unlikely that selection of cells could have occurred.

Skin

COMMUNICATION IN THE NORMAL SKIN: The urodele epidermis contains gland cells and so-called epidermal cells (2, 26). The epidermal cells are well intercommunicating. The electric field around an intracellular (epidermal) current source is not so uniform as in liver or in other more homogeneous epithelial cell systems (17, 20, 21), but the existence of communication be-

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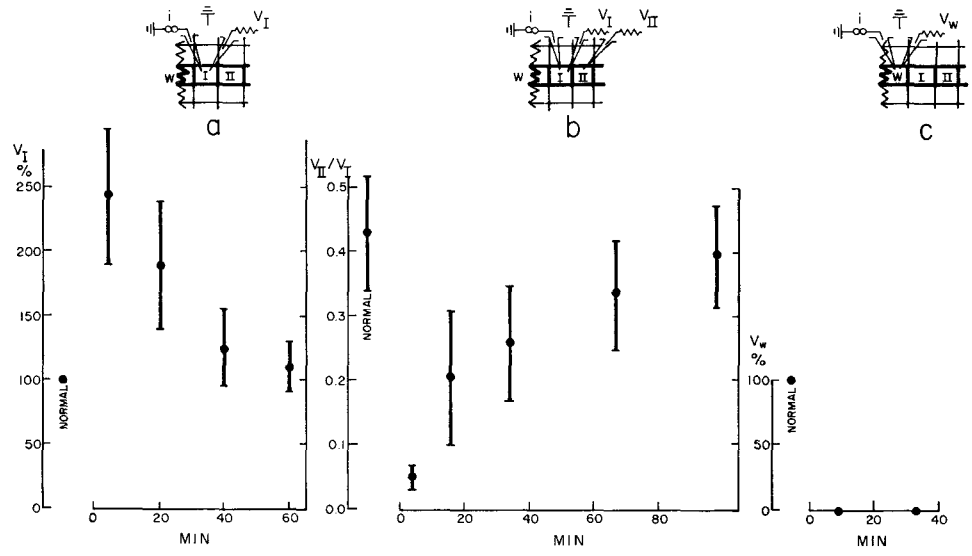

FIGURE 3 Changes in junctional communication near the wound edge. *Insets.* Diagram of cell relationships in the plane of measurement (all measurements in the outermost cell layer) and location of the current-passing (*i*) and voltage recording (*V*) intracellular microelectrodes. *W*, injured epidermal cell bordering the wound; *I* and *II*, adjacent epidermal cells uninjured. The zigzagged line represents the wound border (for spatial resolution, see Methods). Current is of the order of 10^{-7} A in all cases, and is constant in each series of measurements.

a. Junctional sealing. Ordinates, mean resistive voltage of 9 cells, all with the spatial relationship to wound border diagrammed in the inset. The voltage in each cell is normalized on the basis of the voltage value in the same cell before wounding (100%); the mean values of the normalized voltages are plotted with their standard errors (vertical bars) for four stages after wounding. Abscissa in this and other graphs of the figure give time after wounding; the measurements in each series are lumped over spans of 2–8 min. Points normal and time 5 min, and time 5 and 40 min differ at a level of significance better than 0.001; successive points on the falling phase of the curve differ at a level of 0.004, except for the last two points which are not significantly different.

b. Recovery of junctional communication near the wound border. Ordinates, mean communication ratios (ten cell pairs) with their standard errors. The value marked normal is the mean ratio before wounding. (A communication ratio of the same order was found also in measurements taken in the respective *I–W* pairs, before wounding). Points normal and time 5 min, and time 5 and 100 min differ at a level of significance better than 0.001.

c. Lack of repair in the injured cell. Ordinates, mean voltage normalized as in *a*. The first two points plotted are means from four *W*-cells; the last point, from three *W*-cells (one cell of the original four was shed). Standard errors less than size of dots.

tween pairs of adjacent epidermal cells is readily demonstrated. The communication ratio (for a definition, see first paper of this series, reference 18) averages 0.4 (Fig. 3 *b*).[1]

JUNCTIONAL SEALING UPON WOUNDING; LACK OF CELL REPAIR: Fig. 3 illustrates some of the short-term effects on cell communication of a cut made into the epidermis. Immediately striking is the fact that the interiors of the interconnected epidermal cell systems near the cut have not become leaky to the exterior. The cells which have been cut into are, of course, leaky; but the adjacent cells are not. This is clearly seen in experiments in which current is flowing between extracellular fluid and interior of an intact epidermal cell (*I*) close to the wound

[1] Evidence for intercellular ion communication in epidermis has also recently been obtained for the frog skin by B. Steinbach (personal communication). In the frog epidermis, the cells are known to have junctions of Farquhar and Palade's zonulae occludentes type (2 *a*).

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edge, and the resulting resistive voltages are measured across the surface of this cell. Not only is there a voltage recordable in *I*, but the voltage is actually much greater after wounding than it was before (Fig. 3 *a*): Cell *I*, which was well communicated with its neighbor *W* when this was still intact (communication ratio 0.5), has sealed itself off from this cell (see reference 19 for a quantitative description of this phenomenon). That this is due to sealing of the junctional membrane surfaces, and not to nonjunctional membrane repair in the damaged cell *W*, is readily verified by measurements of voltage in which both the voltage recording and current-passing electrodes are in *W*: the damaged cell *W* is leaky and stays indefinitely so until it is shed (Fig. 3 *c*).

Junctional membrane sealing upon cell injury has been found also in gland epithelia (15) and is likely to be a phenomenon of general importance in connected cell systems. Its functional role has been discussed and its mechanisms have been analyzed elsewhere (15, 19).

In addition to sealing off from the exterior, cell *I* seems also to have uncoupled to some extent from the uninjured cell neighbor *II*; the communication ratio of these cells falls right after wounding of *W*, while the input resistance of *II* rises. In general, a fringe, around the wound, several cells deep, has subnormal communication ratios when probed a few minutes after wound production. Intercellular communication in this fringe improves with time; within 2 hr after wounding, the communication ratio was generally normal again in the smaller wounds (Fig. 3 *b*).

ESTABLISHMENT OF COMMUNICATION UPON WOUND CLOSURE: Within minutes after the wound is made, the well-known phenomenon of cell movement starts which brings together eventually the opposing wound edges (references 4, 11, 12, cf. references 1, 25). In the rectangular wound here, cell movement was chiefly in the direction of the minor wound axis, and cellular velocities averaged about 120 μ/hr. Active movement seems to occur only in intact cells. Most of the injured cells formerly lining the wound border seem to be shed in the process of wound closure. By the time the borders come into contact, only intact cells are generally seen at the border. As Lash (11) has shown, the cell movement comes to a halt when the cells of the two edges meet. With the types of wound used in the present experiments, this happens 1–5 hr after wounding, depending on wound size and temperature. The establishment of mechanical contact between the opposing edge cells is generally followed by the establishment of communication between these cells.

This is shown by experiments of the kind diagrammed in Fig. 4 in which a current source was implanted in a given intact cell (*I*) on the wound edge and resistive voltages were measured inside another intact cell (*II*) on the opposite edge located at a distance (*d*) of several space constants of voltage decrement from cell *I*. Measurements were done just before the wound edges met, and at various times after their meeting. So long as the wound edges were separated, there were no voltages measurable in *II*. But within 1 hr after the edges had made mechanical contact, voltages were generally detectable in *II* (in some cases, within 30 min); and, within 2–4 hr, the communication ratio of the cells reached 0.4, the mean value in the unwounded epithelium (Table I).

DISCUSSION

GROWTH CONTROL AND COMMUNICATION: The present work provides two examples of normally growing and normally differentiated tissues which show good intercellular communication. In contrast with these are the various types

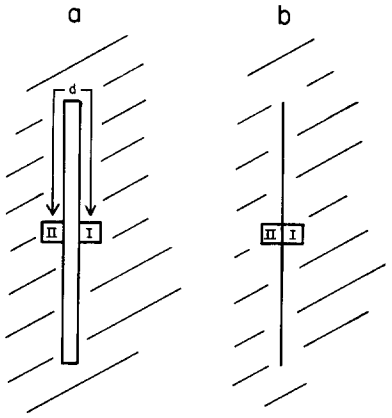

FIGURE 4 Diagram of an experiment on the establishment of cellular communication upon wound closure. Current is passed with an electrode in Cell I (intact) close to the wound border, and the resulting voltages are measured simultaneously in this cell and in cell II (intact) of the opposite wound border. $d \approx 9$ mm. Results of measurements are described in the text.

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TABLE I

Cellular Communication and Contact

Contact situation*	Communication ratio‡ (V_{II}/V_I)	No. of cases
a, Cell *I* and *II* separated by liquid or air	<0.002	32
b, *I* and *II* in direct contact	0.41 ± 0.09§	17
b, Direct contact prevented by a solid film of electrically conducting or nonconducting material	<0.002§	11

* The italicized *a* and *b* refer to diagrams of Fig. 4.
‡ Mean values, with standard errors where indicated; limit of resolution of the method = 0.002.
§ Measurements taken 2–4 hr after the establishment of the respective contact situation.

of cancerous liver tissues, which lack such communication to any appreciable degree, dealt with in the preceding paper (18). The differences in communication do not simply reflect differences in rate of cell multiplication, or in cell mobility. Cells of the normal liver multiply at the startling rate of 1 g/hr during peak regeneration, which is as fast as the fastest liver cancer studied here; and during wound healing the skin cells move with speeds comparable to the most invasive cancer we have used. The most obvious and enticing possibility is that the differences in cell communication reflect differences in growth control; or to state this more positively, *that normal tissue growth and differentiation depend on the flow of materials from one cell interior to another through the junctional cell surfaces.*

The related and more general notion that diffusion of substances between cell aggregates plays a role in their growth and differentiation is not new. This idea has been nurtured by a variety of evidence, some of which is quite compelling (cf. references 3, 7, 8, 13, 23, 24). With the present results we are simply adding an experimental argument; and our earlier work which revealed the functional organization of cell junctions, namely the high junctional membrane permeability to various substances, the continuity of surface insulation along connected cell systems, and the resulting efficient cell-to-cell diffusion path (17, 20), pointed out where and how such diffusion of substances could take place. Two further arguments may now be added. One of them comes from recent exploration of the molecular size limits for substances permeating the junctional membranes in gland cells; these limits turned out to lie as high as 10^3–10^4 molecular weight (10). This leaves ample room, indeed, for flow of possible control substances, even macromolecular ones. A second argument is provided by the work of our colleagues Ito and Hori (9) and, particularly, by that of Potter, Furshpan, and Lennox (22) which reveal extensive electric communication between embryonic cells.

One aspect of growth, the most tangible one experimentally at this time, is "contact inhibition." The present experiments on healing skin give the first example in which contact inhibition is paralleled by cellular communication. The parallel holds also in the converse experimental situation: when a thin foil of platinum or gold, or a thin strip of latex or methacrylate, is placed between the approaching wound edges of the present system, there is no contact inhibition in epidermal cells (11), and as the results summarized in Table I show, there is also no communication detectable between them.

This, of course, suggests the possibility of a causal relationship. But there are also enough elements of doubt which make this notion appear, at present, more seductive than attractive. These elements will here be emphasized so as not to run the risk of obscuring the issues we purport to clarify: (*a*) The time resolution in the present experiments is coarse. The parallelism between contact inhibition and communication means here, at best, that the onsets of the two are not more than 30 min apart. (*b*) The conditions in the experiments with separating films are not exclusive in preventing cellular communication of the kind we are concerned with here, namely diffusion of substances directly from one cell interior to another through the junctional complex. Other forms of tissue interaction may also be prevented. (*c*) In certain cultured fibroblasts "transformed" by viruses communication is at least partly present, namely for the smallest ions (22). Although some transformed fibroblast strains do present contact inhibition (Abercrombie, personal communication), those examined for electrical communication do not (Potter and Furshpan, personal communi-

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cation). This is a strong warning against oversimplification.

To sum up, while it seems permissible to infer that cellular communication and normal growth and differentiation are interrelated,[2] a decision on whether there is such an interrelationship between cellular communication and the more special aspect(s) of growth, contact inhibition, must await further analysis. (A major difficulty here may be that contact inhibition is not a single, simple process.)

JUNCTIONAL MEMBRANE SEALING UPON INJURY: An interesting phenomenon is that of junctional uncoupling in cells near the wound border. This phenomenon, which allows the communicating cell system to seal itself off from an injured cell member and, hence, from the exterior, is undoubtedly of physiological importance in an epithelium exposed to frequent injury. As analyzed elsewhere (15, 19), the uncoupling is primarily due to the influx of extracellular Ca^{++} and/or Mg^{++} into the interior of the connected cell system; upon contact with these divalent cations, the junctional membranes seal themselves off. The influx of divalent cations is self-limiting; but in a variety of tissues the kinetics of the sealing reaction are such that enough divalent cations cross at least 2 to 4 junctions in series with the open cell, before the influx is cut off (10, 15, 19). This probably accounts for the decrease in communication observed here extending initially a few junctions away from the wound border. The present results show that this decrease is reversible. It is reversible even when communication has fallen to very low levels, as in the case of cells at the edges of the intact fringe right after wounding (Fig. 3 *b*).

CELL MOVEMENT AND COMMUNICATION: In the course of wound closure, the epidermal cells move with velocities on the order of 10^2 μ/hr. In fact, closure of the epidermis is effected mainly by cell movement; cell proliferation begins only at later times (11, 12, 25). According to Lash (reference 11, see also reference 25), the cellular movement is individual rather than in mass, i.e., cells move alongside each other. If this is so, there must be continuous breaking and making of junctional communication; communication between cells (away from the wound border) is detectable at all times. Moreover, the breaking of communication seems then to be immediately associated with junctional membrane sealing, since cell resistance measurements show no leaks to the exterior at any time. To explain such sealing, the same mechanisms involving extracellular divalent cations in junctional sealing upon injury may be invoked. All elements for such a sealing reaction are built into the cell system and are critically poised: the Ca^{++} concentration profile falls off steeply across the cell membrane in the inward direction, and the junctional membranes are clearly capable of sealing when exposed to sufficiently high $[Ca^{++}]$ (19). All that is required to set the reaction into motion is a break in the surface insulation of the connected cell system; the effects are the same, whether the break occurs at the level of the cell surface membrane, as in injury, or at the perijunctional insulation, as presumably happens in cell locomotion (15).

The challenging problem right now concerns the making of junctional communication. This involves an uphill reaction, the change to a higher state of membrane permeability. The first clues on the mechanisms of this reaction have just come from work on another communicating cell system, sponges (16).

This work was aided by research grants from the National Science Foundation and the National Institutes of Health.

We thank Mr. I. Baird for unfailing technical assistance.

Received for publication 15 August 1966.

[2] The results that communication is lacking between liver cancer cells, while present in transformed cultured fibroblasts, are not conflicting here. On the contrary, they seem to bring to light interesting differences between these cells. The differences in communication may well mean that different stages in the control of growth are affected. (See 16 *a*). Moreover, it should be realized that while lack of communication, as shown by electrical measurements alone, means total lack of communication for diffusible particles small and large; a result of presence of communication obtained by such measurements provides much less information. It means that there is communication for the small ions that carry the current (K^+, Cl^-), but it says nothing about the communication for the larger and probably more relevant particles.

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