Papers and Originals

The Story of Kidney Transplantation *

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Pioneers of Transplantation

When John Hunter (1771), the father of British scientific surgery, "took a sound tooth from a person's head, then made a pretty deep wound with a lancet into the thick part of a cock's comb and pressed the fang of the tooth into this wound, fastening it with threads passed through other parts of the comb" he was anticipating by a century and a half one of the most important lines of biological inquiry. But the shrewd John Hunter added a pertinent footnote to his account of the experiment, which says that he succeeded but once out of a great number of trials.

Reading his works, it is not clear if Hunter recognized the biological difference between heterotransplantation (that is, transplantation between two different species), homotransplantation (that is, transplantation between different individuals of a single species), and autotransplantation, which is transplantation of tissue or an organ in a single individual, or, what amounts to the same thing, transplantation between identical monozygotic twins. But, by the strange temporal chance, heterotransplantation, exemplified by Hunter's cock's comb experiment, is now one of the focal points on the line of biological inquiry today: at least two groups (Reemtsma *et al.*, 1964; Starzl *et al.*, 1964b) in the U.S.A. have already, with limited success, transplanted kidneys from chimpanzees and baboons into human recipients suffering from irreversible pre-terminal chronic renal failure, and one of my colleagues at Hammersmith has recently undertaken to work on this particular problem in Egypt, where suitable apes are readily available from near-by African countries and where the climate is favourable for their maintenance. At the moment it would seem that the success rate of kidney heterotransplantation between higher apes and man is far from good, but the potential reward of success in my opinion fully justifies this application of the Hunterian outlook and method of approach. It is not enough to think: there is a time when the experiment should be tried.

Another desirable source of kidneys for human transplantation is the cadaver, and few would question the ethics of this. Indeed, several successful cadaveric human kidney transplantations have been carried out and some have functioned for more than a year. The use of human cadaveric material for homotransplantation was recommended by Hunter, who transplanted cadaveric teeth in man and claimed that they sometimes persisted for years. His advice that the donor teeth should be sound and taken from the mouth of a "sound and healthy person" has a somewhat familiar ring today, for similar prerequisites are required when cadaver-kidney transplantation is under consideration: the urine of the donor should be sterile and free from protein.

Hunter's pioneer contributions to the problem of transplantation evoked strong condemnation by Thomas Bell, lecturer in anatomy at Guy's, and in his notes in *The Works of John Hunter, F.R.S.*, edited by Palmer (1855), Bell wrote that "nothing but sanguine expectations created in an ardent mind could account for a man of sound judgement continuing the practice." I fear there are even today still some faint-hearted disciples of Bell: they hold similar views about kidney homotransplantation and first require a high success rate before they are ready to join the ranks of the qualified enthusiasts. While it has to be admitted that, with some exceptions, kidney homotransplantation still cannot be claimed to be an unqualified success, there are, nevertheless, several grateful patients who have had significant prolongation of their lives by submitting to this method of treatment; and, perhaps of equal importance, much has been learned about the many problems which will have to be resolved before the technique can be reasonably advocated as sound treatment for the many thousands of young adults who die each year from irreversible renal failure.

Alexis Carrel

The operative technical problems of kidney transplantation, not to be underestimated, are now well understood, and surgical techniques used in man do not vary significantly in the several centres throughout the world where the operation is practised. Indeed, the principles and many of the details were evolved more than 50 years ago, in the main, by Alexis Carrel (1902, 1908, 1911, 1914), working first in France at Lyons and later at the Rockefeller Institute in New York. It was Carrel (1902) who introduced fine round-body suture needles threaded either with oiled thin linen used by the lace-makers of Valenciennes, or similar Alsatian cotton, for constructing end-to-end or end-to-side arterial and venous anastomoses. Then, having perfected his vascular operative technique, he was able successfully to autotransplant a dog's kidney to its neck. Carrel (1908, 1911, 1914) subsequently carried out many kidney autotransplantations and homotransplantations in laboratory animals and emphasized the difference between the fate of the autotransplanted and the homotransplanted organ. Carrel did not of course comprehend the mechanism underlying the fundamental difference between an autotransplant and a homotransplant: he did, however, suggest that the serum of the host might be injurious to the homotransplanted organ, and, in retrospect, his hypothesis may be said to have been not too far from the truth.

Apart from his valuable contributions to the technical problems of kidney transplantation, Carrel (1908) learned that the blood supply of the transplanted kidney could be occluded for 50 to 60 minutes without interference with its subsequent function and that it could with advantage be perfused with Locke's solution or serum before transplantation, and he

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suggested that cooling might have value. He also assessed subsequent function of the transplanted kidney by determination of the urine volume, reaction, specific gravity, and urinary urea concentration, and recorded the development of pre-terminal proteinuria in homotransplanted kidneys. Equally pertinent were his observations on the histological changes to be seen in the rejecting homotransplanted kidney in the unmodified recipient animal. He recorded the interstitial oedema and infiltration by plasma cells and cells of the lymphoid series, tubule dilatation with epithelial flattening and some cast formation, and excessive intrarenal and perirenal fibrosis—observations which have been confirmed, although added to, in the 50 years that have followed.

At the time that Carrel was working on organ transplantation one of his contemporaries at the Rockefeller Institute, Murphy, noted that tumour transplants to chick embryos developed normally and could be transplanted from egg to egg. But when eggs were allowed to develop into chickens such transplants disappeared within a few days. Carrel (1914) postulated that this was evidence that at a certain period of life a new function developed which gave the organism the power of eliminating a foreign tissue: an important concept which was to be explored and extended many years later by Burnett and Fenner (1949), Billingham *et al.* (1951, 1953), Gibson and Medawar (1943), and Medawar (1944, 1945). Murphy had also observed that after splenectomy in recipient rats there was prolongation of survival of mice-tumour transplants and that similar prolongation of survival of mice-tumour transplants could be achieved by diminishing the activity of of the recipient's white blood cells by injecting the recipient rats with benzol.

From these observations of Murphy, Carrel (1914) concluded that when the action of the spleen and bone-marrow was decreased transplanted tissue could develop rapidly. Moreover, he thought that one day it might be possible to apply Murphy's—or similar—principles to the problem of organ transplantation. How close he was to prophesying the present, admittedly imperfect, methods that are used to modify the immune response evoked by kidney homotransplantation in man: in my opinion Carrel is entitled to a great deal of credit for his pioneer work and observations on organ transplantation, and it is not easy to understand the apparently unfavourable comment he evoked from Professor Fulton (1946) in his book on the life of Harvey Cushing, particularly as Cushing and his equally discriminating contemporary Welch had both sponsored and recommended Carrel to Simon Flexner, who was the Director of the Rockefeller Institute at the time.

Williamson and Ibuka

The impetus given by Carrel and the Rockefeller Institute to the study of organ transplantation passed to the Mayo Foundation at Rochester, where Williamson (1926) and Ibuka (1926) developed the operative technique that is used for human-kidney transplantation today. These workers not only confirmed Carrel's observations but went on to postulate that the length of survival of a homotransplanted kidney depended upon the degree of biological compatibility between donor and host, and that if it was ever possible to match animals by some form of tissue-grouping, corresponding to blood-grouping, prolonged survival of a homotransplant might be achieved in closely related animals. Williamson (1926) even suggested that kidney homotransplantation might be justified in the human if a cadaver kidney was obtainable, if the transplantation could be effected within two hours of the death of the donor, and if the blood groups matched. There is no evidence, however, to suggest that he ever practised what he preached. Neither Williamson (1926) nor Ibuka (1926) understood the biological principles they evoked, and, not surpris-

ingly therefore, they were not able to suggest any means to influence them. For, although Little (1924) had previously established that the homograft rejection reflected genetic differences between graft and host, the foundations of transplantation biology had to await the introduction of the "self-marker" concept (Burnet and Fenner, 1949) and its practical proof by the elegant animal experiments of Billingham *et al.* (1953).

Modern Concepts

The "self-marker" concept postulated that the embryo recognizes antigenic material only as "self" and therefore does not react against it: the foetus is immunologically inert. In contrast, any foreign tissue encountered after birth is recognized as "non-self" and provokes immunological rejection. Tissue which will provoke an immune response in an adult will be accepted as self if introduced into the embryo; and if such an embryo is allowed to mature and is born and becomes immunologically competent it will not develop an immune response when tissue from the same donor is introduced again. In other words, an acquired specific immunological tolerance is developed, not necessarily due to antigenic adaptation or to destruction of host immune cells (Burnet and Fenner, 1949), but more probably to enzymatic adaptation of the host immune-cell system (Richards, 1963).

Validity of the self-marker concept was provided by Billingham *et al.* (1953), who injected intrauterine embryonic mice with adult minced tissue and then showed that subsequent skin grafts from the same donors applied to the same recipients six to eight weeks after birth were not rejected. Such acquired immunological tolerance, however, is not fully understood even today, and, equally important, its induction by such means is clearly of little or no practical value in regard to kidney transplantation in the human. To anticipate that a newborn child might subsequently develop irreversible renal failure, and to pre-arrange availability of a suitable potential donor, seems too remote a concept for serious consideration. Nevertheless, the fact that immunological tolerance can be acquired, even by impractical means, proffers an indelible hope that the problem will one day be resolved by simpler and more practical methods.

In contradistinction to the production of tolerance when foreign tissue is presented to the foetus, Gibson and Medawar (1943), Medawar (1944, 1945), and Billingham *et al.* (1954) had shown conclusively that in the adult a homograft acts as a foreign antigen and provokes an actively acquired immunity by stimulating the production of cell-bound antibodies in the recipient. A skin homograft to an unmodified animal recipient is destroyed within a few days, and, moreover, a subsequent graft from the same donor to the same recipient is rejected even more rapidly. Active immunity has been produced by the primary graft. Furthermore, when a suspension of lymphoid cells from the lymph nodes draining the site of a rejected primary skin graft is injected intraperitoneally, passive or, more accurately, adoptive immunity can be achieved and is manifest by an expedited rejection of a subsequent skin graft from the same donor: in other words, the antibodies in the lymphoid cells produce the same reaction as the primary skin homograft. Immunity produced in this way is dependent upon continued survival of the actively immunized cells of the lymph nodes: killed lymph nodes have no power to transfer this immunity.

Little is known about the biochemical nature of transplantation antibodies, but they are thought to be cell-bound to lymphocytes, plasma cells, and possibly mast cells. It is generally assumed, so far as skin homotransplants are concerned, that the transplantation antigens are transferred to the regional lymph nodes draining the site of the graft, that the

lymphoid cells in these lymph nodes then become sensitized and immunologically competent, and that these lymphoid cells then gain entrance to the blood-stream and are carried around in the circulation eventually to reach the graft and destroy it. There is no apparent structural change in the lymphoid cells when they become sensitized: they seem merely to act as carriers of antibody. When foreign tissue is enclosed in a semi-permeable membrane and implanted into the peritoneal cavity of an animal it survives because the "rejection" cells of the host cannot gain access to it: when the pores of the membrane are large enough to allow the passage of lymphoid cells the foreign tissue is infiltrated with them and is destroyed (Weaver *et al.*, 1955). In the transplanted kidney it is probable that the lymphoid cells of the host are sensitized while passing through the organ (Gowans *et al.*, 1963), and electronmicroscopy studies (Kountz *et al.*, 1963) suggest that the host lymphoid cells become attached to the donor vascular endothelium first of the peritubular capillaries and then subsequently to the endothelium of the afferent glomerular, interlobular, arcuate, and, on occasion, interlobar arteries and cause interstitial haemorrhage, tubule damage, vascular necrosis, and thrombosis (Dempster *et al.*, 1964).

Genetic Factors

Many genes are concerned in the total picture of an individual, and several are concerned in determining tissue antigenicity. Erythrocyte antigens have been recognized since the beginning of this century (Landsteiner, 1900), and are potent in respect of compatibility. Histocompatibility antigens other than these have yet to be identified in man. At one time it was thought that they were to be found in the amino-acid polysaccharide constituents of cells, but now it is believed that they are part of the lipoprotein of the cells (Mann *et al.*, 1960; Herzenberg and Herzenberg, 1961).

Little (1924) was the first to establish that the homograft reaction was caused by genetic differences between donor and recipient, and Snell (1948, 1953, 1957), who studied histocompatibility genes in mice, concluded that there were several different gene loci on the chromosome which had to do with transplantation antigens and there could be many different allelomorphs at each gene locus, any one of which might be responsible for a complex of antigens. Some histocompatibility factors may be shared between individuals but there are always many more which differ, so that the chance of success in unmodified random homotransplantation is virtually negligible. On the other hand, it has been known for a long time that successful grafting may be effected between individuals of a highly inbred (sister-brother mating) strain of animals and in human monozygotic twins (Bauer, 1927). In both cases there is identical, or virtually identical, genetic constitution. And, since genes control cell and tissue differentiation, structure, and function, the fact that homografts are successful in such circumstances should evoke little surprise: indeed, they behave as autografts in these special conditions.

Homotransplantation may be successful in another set of circumstances. On occasion, each of a pair of non-identical dizygotic twins may have in its blood-stream cells which are characteristically specific for the other twin (Woodruff *et al.*, 1962): they have shared, to varying degrees, a common placenta, and intrauterine interchange of blood has taken place. Thus, for example, one twin may have 80% group A and 20% group O red cells, while the other has 10% group A and 90% group O: when the twins are of different sexes, the male twin may be shown to possess leucocytes which contain Barr bodies characteristic of the female. Such twins may not be genetically identical, yet they will accept homografts from each other, presumably because there has been an antenatal transference of primitive bone-marrow cells.

Abrogation of the Homograft Rejection

There is now adequate evidence that the homograft-rejection process may be abrogated and that it does not necessarily obey an "all or none" rule. Homografts are accepted when the recipient possesses a significant proportion of the transplantation specificities of the donor, when the graft remains avascular, and when the immunological responses of the recipient are impaired. Impairment of the immunological response has been recorded in patients with hypogammaglobulinaemia (Good and Varco, 1955), Hodgkin's disease (Green and Corso, 1959), and chronic uraemia (Dammin *et al.*, 1957); and prolonged survival of kidney homotransplants in humans with chronic uraemia has been reported by Hume *et al.* (1955). There is no reason to think that the antigenicity of the foreign tissues is impaired in these instances and is therefore incapable of evoking an immune response: rather, it is to be assumed that there has been spontaneous modification of the recipient's immunological responses, perhaps due to lymphoid and plasma cell deficiency in the case of hypogammaglobulinaemia, but to reasons which remain obscure in the case of Hodgkin's disease and uraemia.

The first practical attempts to abrogate the rejection process in human kidney homotransplantation were made by Hamburger *et al.* (1959), Merrill *et al.* (1960), Kuss *et al.* (1960), and Shackman *et al.* (1963). On the basis of the earlier observations of Craddock and Lawrence (1948) that total body irradiation diminished antibody formation against foreign antigens, provided the irradiation preceded the antigenic stimulus, it seemed reasonable to employ pre-operative sublethal doses of total body irradiation, despite the fact that it had not proved effective in preventing rejection in dogs. Some success was achieved when high doses were given, but the complications of the irradiation—thrombocytopenia and leucopenia—so militated against success that the method has now been abandoned by all except Hamburger *et al.* (1965) for the alternative radiomimetic drugs (Calne, 1961, 1963), which are equally effective and somewhat easier to control.

At the present time azathioprine (Imuran) appears to be the best drug available for allaying rejection, but its limitations and imperfections are recognized and accepted only because there is, as yet, no significantly better alternative. Corticosteroids are also used extensively, but it is doubtful if they have much preventive effect (Hume *et al.*, 1955), and their main use seems to be for abating or reversing early rejection (Goodwin *et al.*, 1963; Marchioro *et al.*, 1964). Large doses of prednisone (200–300 mg./day) are required for this purpose, and such therapy entails the risk of gastro-intestinal ulceration and haemorrhage and impaired wound-healing, unless the dosage is reduced within a few days. And, moreover, when corticosteroids are given again for subsequent episodes of rejection their efficacy seems to decrease.

Like the corticosteroids, actinomycin C, a cytostatic antibiotic, is best used for reversing early rejection. Begemann (1960) deduced that it might be an effective inhibitor of antibody formation, and Murray *et al.* (1963) used it and thought it was responsible for reversing the rejection process in two or three of the 15 patients with kidney transplants. Starzl *et al.* (1964a, 1964c) have claimed much greater success, but, since large doses of prednisone were given concomitantly, the issue has been clouded. Like azathioprine, actinomycin C may induce severe bone-marrow and lymphoid depletion, encourage infection, and impair wound-healing if large and repeated dosage is used: and, moreover, these effects are strikingly exaggerated when infection is present at the time the drug is administered.

Rationale of Anti-rejection Therapy

It has been suggested that the continued well-being of a homograft represents a process of "adaptation"—a broad

biological concept applicable to evolutionary processes (Darwin, 1859) rather than to immunology. Adaptation has been held to account for the fact that it is not necessary to continue anti-rejection therapy indefinitely. Some experimental evidence supports the contention. First-set homografts may continue to survive despite rejection of second-set skin homografts, back-grafting skin homografts to the original donor animals not infrequently fails (Richards, 1963), and kidney homografts in dogs may continue to function long after immuno-suppressive drug therapy has been stopped (Pierce and Varco, 1963). The relatively long-term successes in human kidney transplants are presumed to depend, to a degree at least, on adaptation on the part of the grafted organ and on partial immunological tolerance on the part of the host. As total inhibition of the immune response is not required, it is possible, fortunately, for the recipient to respond favourably to bacterial invasion and there is no risk of a graft-versus-host reaction (Simonsen *et al.*, 1953).

There is no real evidence to suggest that total body irradiation or anti-rejection drug therapy influences the antigenicity of donor tissue: irradiation of donor dogs before kidney transplantation has been shown to be ineffective (Hume *et al.*, 1960). And it is generally believed that the success of these physico-chemical anti-rejection methods depends on their propensity to interfere with those host lymphocytes which proliferate before differentiating into antibody-producing cells. It is not known whether all or only a limited number of lymphoid cells respond to the antigenic stimulus, but if those which can do so are prevented from reacting for a sufficient length of time, their descendants, since they develop asexually to form clones or pure lines (Burnet, 1959), will similarly be unable to react to the continued antigenic stimulus. This postulate could account for the fact that some kidney homografts in humans have continued to function for long periods after total body irradiation of the recipients and after immuno-suppressive drug therapy. Several cases, however, have developed one or more episodes of rejection which have been controlled in some instances but not in all.

It is a matter for speculation whether this phenomenon of delayed rejection is related to the long survival—up to 200 days or more—of the majority of lymphocytes (Gowans, 1959). If anti-rejection therapy is effected only through differentiating lymphoid cells, it is conceivable that a "build-up" of antibody could occur during the interval and that a temporary increased drug dosage and subsequent prolongation of the anti-rejection therapy would be required to deal with the previously ineffective lymphoid population. Alternatively, the phenomenon of delayed rejection could represent the development of a sufficient number of mutants in the lymphoid cells. Whatever the explanation, it is recognized that total lymphoid depletion is not necessarily a prerequisite for inhibition of the homograft reaction.

Lack of consistency of anti-rejection therapy is just as hard to rationalize. But if in fact strong histocompatible genetic factors in the human are only few in number and happen to be shared by donor and recipient, and if it is assumed that anti-rejection therapy influences mainly the many weaker histocompatible genetic differences, it would be rational to conclude that success would be more likely when transplantation is carried out between subjects in whom the strong antigens have close affinities (Simonsen, 1965). The recognition of such favourable subjects would be rewarding; we are using preliminary skin grafts for this purpose, but it is too early yet to assess the results of this study (Shackman, 1965).

Present Position and the Future

It is now known that more than 600 human kidney transplantations have been carried out. But the majority, more than 500, have been done only since March 1963. The largest published individual experiences are those of Starzl *et al.* (1965)

from Denver, Colorado; of Hume (1965) from Richmond, Virginia; and of Hamburger *et al.* (1965) from Paris. In Starzl's series 37 patients (58%) were living 12 or more months after transplantation, in Hume's series there were 10 (17%), and in Hamburger's series there were 7 (16%) living with functioning transplants 10 or more months after transplantation. But there may be significance in the fact that there were several other apparently successful cases three or more months after transplantation in all three series, since it seems that the incidence of severe rejection and death is maximal in the first three months. However, it would probably be more rational to wait two to three years before committing ourselves in regard to the validity of claims of success in respect of individual patients, for it is known that progressive obliterative vascular lesions in the homotransplanted kidney may remain undetected for many months (Starzl *et al.*, 1965).

The dilemma of having to remove a healthy kidney from a live donor when there is still uncertainty about its ultimate fate after it has been transplanted would be resolved if it could be shown that comparable degrees of success follow the use of cadaver organs. But, although the most recently published series of cadaveric transplants (Mowbray *et al.*, 1965) certainly suggests that cadaveric kidney transplantations are as successful as those in which random unrelated live donors are used, the results, in my opinion, do not justify exclusion of living closely related donors. And, moreover, it is reasonable to assume that even better results will follow the use of living closely related donors when practical methods of tissue-typing become available.

Whether heterotransplantation will circumvent the problem is another matter and one for speculation. Indeed, the success reported by Reemtsma *et al.* (1964), limited though it was, could be interpreted to mean that there may be a closer affinity between some chimpanzees and some humans than there is between some humans and other humans, and further biological studies are clearly needed to elucidate this possibility. But, apart from all doubts, one thing is certain. Kidney transplantation should not be regarded simply as an exercise in surgical technique. It requires cooperation between surgeon, physician, geneticist, immunologist, and biochemist, who may be working primarily in what have been regarded as different disciplines but in fact share the problems evoked by a single common objective: effective organ transplantation in the human.

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Treatment of Acute Leukaemia in Adults: Comparison of Steroid and Mercaptopurine Therapy, Alone and in Conjunction

Second Report to the Medical Research Council of the Working Party* on the Evaluation of Different Methods of Therapy in Leukaemia

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In its first report to the Medical Research Council (1963) the Working Party found that the administration of prednisone at a daily dose of 250 mg., in conjunction with mercaptopurine at a daily dose of 2.5 mg./kg. of body weight, was harmful. This "high-dose" steroid schedule was therefore discontinued. The other two schedules (mercaptopurine at a daily dose of 2.5 mg./kg. of body weight and mercaptopurine at the same dose in combination with prednisone at a daily dose of 40 mg.) were retained, and a further schedule was instituted in which prednisone alone was administered at a daily dose of 40 mg. to allow the comparison of mercaptopurine and steroids, alone and in combination.

The procedure for the admission of patients to the second trial and that for the dispatch of bone-marrow films to Dr. F. G. J. Hayhoe were the same as in the first trial. One hundred and fifty patients were admitted to the trial between 15 September 1961 and 3 September 1963; 47 were allocated to the "prednisone alone" schedule, 51 to the "mercaptopurine alone" schedule, and 52 to the "combined drugs" schedule. A preliminary analysis showed that the survival curves of the groups of patients who were allocated to the corresponding treatment schedules in the first and second

trials were almost identical, and for this report the cases in the two trials have been considered together. Thus there were four groups of cases representing 258 patients allocated to four treatment schedules as follows: (1) prednisone alone (at 40 mg. daily)—47 patients (second trial only); (2) mercaptopurine alone (at 2.5 mg./kg. of body weight daily)—86 patients (first and second trials); (3) mercaptopurine (at 2.5 mg./kg. of body weight daily) and prednisone (at 40 mg. daily)—88 patients (first and second trials); (4) mercaptopurine (at 2.5 mg./kg. of body weight daily) and prednisone (at 250 mg. daily)—37 patients (first trial only).

These schedules were to apply essentially to the first eight weeks of treatment, after which time treatment was to be at the discretion of the consulting physician. The mercaptopurine therapy was to be administered for the whole eight-week period or until a remission was obtained. The steroid therapy at the 250-mg. level was to be administered for two weeks; the dosage was then to be progressively reduced and the administration discontinued. In the first trial the steroid therapy at the 40-mg. level was to be continued for three weeks before being progressively reduced and stopped; in the second trial, however, the physicians were asked to maintain the steroid therapy at the 40-mg. level for at least four weeks, and if possible for eight weeks. The 88 patients in the treatment schedule of 40 mg. of prednisone plus mercaptopurine are therefore a "mixed" group; nevertheless, the survival curves of its component groups were so similar that there seemed no point in regarding the two components separately. In both trials all patients received antibiotics, blood transfusions, and other supportive treatment as required.

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